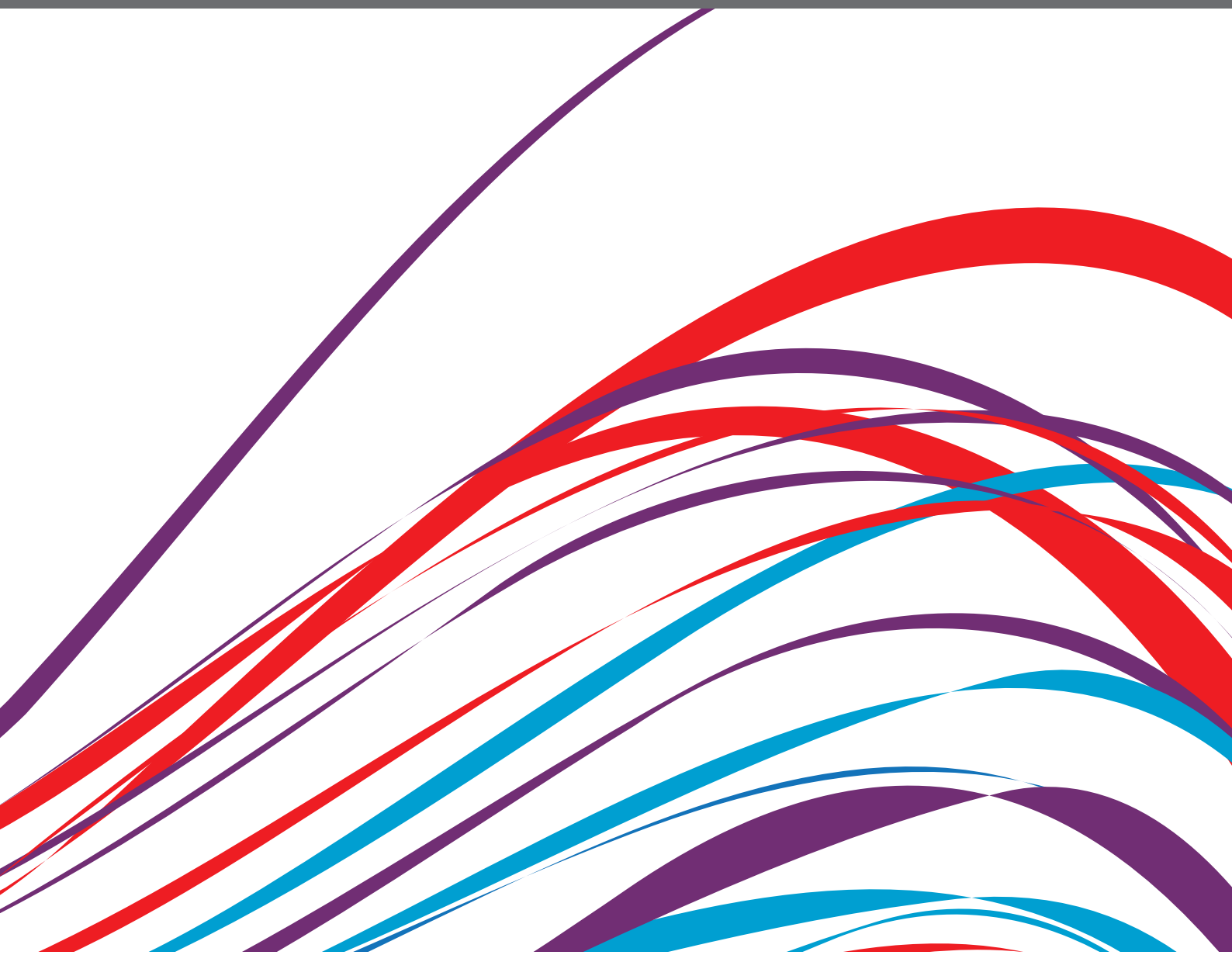
ADVANCES IN THE PREVENTION AND REHABILITATION OF CARDIOVASCULAR DISEASES VIA AEROBIC EXERCISE

EDITED BY: Richard Yang Cao, Jian Yang and Sebastian Kelle
PUBLISHED IN: Frontiers in Cardiovascular Medicine



frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88974-847-1
DOI 10.3389/978-2-88974-847-1

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: frontiersin.org/about/contact

ADVANCES IN THE PREVENTION AND REHABILITATION OF CARDIOVASCULAR DISEASES VIA AEROBIC EXERCISE

Topic Editors:
Richard Yang Cao, Shanghai Xuhui Central Hospital, China
Jian Yang, Fudan University, China
Sebastian Kelle, Deutsches Herzzentrum Berlin, Germany

Citation: Cao, R. Y., Yang, J., Kelle, S., eds. (2022). Advances in The Prevention and Rehabilitation of Cardiovascular Diseases via Aerobic Exercise.
Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88974-847-1

Table of Contents

06 ***Editorial: Advances in the Prevention and Rehabilitation of Cardiovascular Diseases* via *Aerobic Exercise***
Richard Y. Cao, Sebastian Kelle and Jian Yang

10 ***Cardiac Rehabilitation: A Bibliometric Review From 2001 to 2020***
Guozhen Yuan, Jingjing Shi, Qiulei Jia, Shuqing Shi, Xueping Zhu, Yan Zhou, Shuai Shi and Yuanhui Hu

22 ***Impacts of Heart Failure and Physical Performance on Long-Term Mortality in Old Patients With Chronic Kidney Disease***
Shuo-Chun Weng, Yu-Chi Chen, Chiann-Yi Hsu, Chu-Sheng Lin, Der-Cherng Tarng and Shih-Yi Lin

33 ***Translation, Cultural Adaptation, and Reproducibility of the Physical Activity Readiness Questionnaire for Everyone (PAR-Q+): The Brazilian Portuguese Version***
Juliano Schwartz, Paul Oh, Monica Y. Takito, Bryan Saunders, Eimear Dolan, Emerson Franchini, Ryan E. Rhodes, Shannon S. D. Bredin, Josye P. Coelho, Pedro dos Santos, Melina Mazzuco and Darren E. R. Warburton

45 ***Feasibility and Preliminary Effects of the BESMILE-HF Program on Chronic Heart Failure Patients: A Pilot Randomized Controlled Trial***
Xiankun Chen, Wei Jiang, Thomas P. Olson, Cecilia Stålsby Lundborg, Zehuai Wen, Weihui Lu and Gaetano Marrone

56 ***Differential Evaluating Effect on Exercise Capacity of Cardiopulmonary Exercise Testing and Treadmill Exercise Testing in Post-percutaneous Coronary Intervention Patients***
Yifan Gao, Bin Feng, Rong Hu, YingYue Zhang, Yajun Shi, Yong Xu and Jing Ma

63 ***Determinants and Prediction Equations of Six-Minute Walk Test Distance Immediately After Cardiac Surgery***
Basuni Radi, Ade Meidian Ambari, Bambang Dwiputra, Ryan Enast Intan, Kevin Triangto, Anwar Santoso and Budhi Setianto

71 ***Efficacy and Safety of Different Aerobic Exercise Intensities in Patients With Heart Failure With Reduced Ejection Fraction: Design of a Multicenter Randomized Controlled Trial (HF-EI Trial)***
Ting Shen, Xiaoling Liu, Bo Zhuang, Qian Luo, Yishan Jin, Guanghe Li, Yumei Jiang, Dejie Li, Xianchuan Chen, Nuo Tang, Zhimin Xu, Lemin Wang, Liang Zheng and Yuqin Shen

81 ***A Critical Review on New Approaches for Chronic Disease Prevention in Brazil and Canada: From Wholistic Dietary Guidelines to Physical Activity Security***
Juliano Schwartz, Paul Oh, Maira B. Perotto, Ryan E. Rhodes, Wanda Firth, Shannon S. D. Bredin, Alejandro Gaytán-González and Darren E. R. Warburton

94 ***Optimizing Outcomes in Cardiac Rehabilitation: The Importance of Exercise Intensity***
Jenna L. Taylor, Amanda R. Bonikowske and Thomas P. Olson

111 ***Evaluation of the Structure and Health Impacts of Exercise-Based Cardiac and Pulmonary Rehabilitation and Prehabilitation for Individuals With Cancer: A Systematic Review and Meta-Analysis***
Julia N. Rickard, Arun Eswaran, Stephanie D. Small, Alis Bonsignore, Maureen Pakosh, Paul Oh and Amy A. Kirkham

124 ***Treadmill Exercise Attenuates Cerebral Ischemia–Reperfusion Injury by Promoting Activation of M2 Microglia via Upregulation of Interleukin-4***
Juanjuan Lu, Jie Wang, Long Yu, Rong Cui, Ying Zhang, Hanqing Ding and Guofeng Yan

135 ***Regulation of Cardiac-Specific Proteins Expression by Moderate-Intensity Aerobic Exercise Training in Mice With Myocardial Infarction Induced Heart Failure Using MS-Based Proteomics***
Shouling Mi, Hao Jiang, Lei Zhang, Zhonglei Xie, Jingmin Zhou, Aijun Sun, Hong Jin and Junbo Ge

145 ***Differences in Peak Oxygen Uptake in Bicycle Exercise Test Caused by Body Positions: A Meta-Analysis***
Xiaohua Wan, Chang Liu, Thomas P. Olson, Xiankun Chen, Weihui Lu and Wei Jiang

156 ***Exercise-Based Rehabilitation Delivery Models in Comorbid Chronic Pulmonary Disease and Chronic Heart Failure***
Audrey Borghi-Silva, Adriana S. Garcia-Araújo, Eliane Winkermann, Flavia R. Caruso, Daniela Bassi-Dibai, Cássia da Luz Goulart, Snehil Dixit, Guilherme Dionir Back and Renata G. Mendes

165 ***Augmented Cardiac Mitochondrial Capacity in High Capacity Aerobic Running "Disease-Resistant" Phenotype at Rest Is Lost Following Ischemia Reperfusion***
Musaad B. Alsahly, Madaniah O. Zakari, Lauren G. Koch, Steven Britton, Laxmansa C. Katwa, Kelsey Fisher-Wellman and Robert M. Lust

176 ***Acute Hemodynamic Responses to Enhanced External Counterpulsation in Patients With Coronary Artery Disease***
Yahui Zhang, Ziqi Chen, Zhouming Mai, Wenjuan Zhou, Hui Wang, Xiaodong Zhang, Wenbin Wei, Jianhang Du and Guifu Wu

186 ***The Role of 6-Minute Walk Test Guided by Impedance Cardiography in the Rehabilitation Following Knee Arthroplasty: A Randomized Controlled Trial***
Yangyang Lin, Xingwei Hu, Yalin Cao, Xing Wang, Yao Tong, Fengjuan Yao, Peihui Wu and Huiling Huang

195 ***Low Intrinsic Aerobic Capacity Limits Recovery Response to Hindlimb Ischemia***
Elizabeth Granier, Madaniah O. Zakari, Musaad B. Alsahly, Lauren G. Koch, Steven Britton, Laxmansa C. Katwa and Robert M. Lust

204 ***Influence of Intrinsic Aerobic Exercise Capacity and Sex on Cardiac Injury Following Acute Myocardial Ischemia and Reperfusion***
Musaad B. Alsahly, Madaniah O. Zakari, Lauren G. Koch, Steven Britton, Laxmansa C. Katwa and Robert M. Lust

214 ***Effect of Exercise Prescription Implementation Rate on Cardiovascular Events***
Li-Yue Zhu, Min-Yan Li, Kun-Hui Li, Xiao Yang, Yi-Yong Yang, Xiao-Xia Zhao, Ting Yan, Meng-Meng Li, Si-Qi Luo, Mu-Lan Zhang and Jin-Zi Su

223 ***High Intensity Interval Training Leads to Similar Inflammatory Activation as Seen With Traditional Training in Chronic Heart Failure***
Arlana G. Taylor, Andrew I. Ignaszewski, Shannon S. D. Bredin, John S. Hill, Erin M. Shellington and Darren E. R. Warburton

237 ***Effects of Aerobic, Resistance, and Combined Exercise Training on Psychiatric Symptom Severity and Related Health Measures in Adults Living With Schizophrenia: A Systematic Review and Meta-Analysis***
Shannon S. D. Bredin, Kai L. Kaufman, Maddison I. Chow, Donna J. Lang, Nana Wu, David D. Kim and Darren E. R. Warburton

251 ***A Contemporary Review of the Effects of Exercise Training on Cardiac Structure and Function and Cardiovascular Risk Profile: Insights From Imaging***
Waleed Alhumaid, Stephanie D. Small, Amy A. Kirkham, Harald Becher, Edith Pituskin, Carla M. Prado, Richard B. Thompson, Mark J. Haykowsky and D. Ian Paterson

frontiers in Cardiovascular Medicine

EDITORIAL
published: 14 March 2022
doi: 10.3389/fcvm.2022.858785

Editorial: Advances in the Prevention and Rehabilitation of Cardiovascular Diseases *via* Aerobic Exercise

Richard Y. Cao[1]*, *Sebastian Kelle*[2,3,4] *and Jian Yang*[5]*

[1] Department of Cardiology, Shanghai Xuhui Central Hospital, Fudan University, Shanghai, China, [2] Department of Internal Medicine/Cardiology, Deutsches Herzzentrum Berlin, Berlin, Germany, [3] German Centre for Cardiovascular Research (DZHK), Berlin, Germany, [4] Department of Cardiology, Campus Virchow Klinikum, Charité—Universitätsmedizin Berlin, Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany, [5] Department of Rehabilitation, Zhongshan-Xuhui Hospital, Fudan University, Shanghai, China

Keywords: cardiovascular disease, aerobic exercise, cardiac rehabilitation, exercise testing, mechanism

Editorial on the Research Topic

Advances in the Prevention and Rehabilitation of Cardiovascular Diseases *via* Aerobic Exercise

The 21st century is a new era for the rapid development of the cardiac rehabilitation programs. Publications in the field of cardiac rehabilitation research have grown greatly year by year in the past two decades, from <100 per year in 2001–2003 to over 600 in 2019 (Yuan et al.). Cardiac rehabilitation usually involves exercise training, psychological consultation, and lifestyle education to reduce cardiovascular risk factors. Growing evidence demonstrates that aerobic exercise-based cardiac rehabilitation plays an important role in the prevention and management of cardiovascular diseases and is therefore recommended by the American Association of Cardiovascular/Pulmonary Rehabilitation, American Heart Association, American College of Cardiology, as well as the European Society of Cardiology (1).

This Research Topic on "*Advances in the prevention and rehabilitation of cardiovascular diseases via aerobic exercise*" received an overwhelming number of submissions. The final collection brings together 12 original research articles, including five basic and seven clinical studies, three clinical trials containing one trial protocol and two trial reports, and eight review articles. This collection of research aims to reveal appropriate training protocols and evaluation methods to meet the requirements of both clinical and home-based rehabilitation programs. The articles collected under this Research Topic tend to produce high quality and timely articles involving advances in clinical applications and underlying molecular mechanisms from bench to bedside, and beyond, to highlight the underrepresented areas in controlling cardiac risk factors and preventing cardio-metabolic and cardiovascular diseases *via* exercise-based rehabilitation training. These articles represent exceptional research achievements in this field and contribute significantly to cardiovascular medicine and public health.

BASIC SCIENCE IN CARDIAC REHABILITATION

It is important to explore recent basic research in uncovering novel molecular mechanisms and identifying new theories related to cardiovascular pathophysiology in response to aerobic exercise. A research team tested cardiac-specific protein expression after a 4-week exercise using mass spectrometry-based proteomics in a mouse model of ischemia-induced heart failure (Mi et al.). Aerobic exercise-based rehabilitation training significantly up-regulated 597 proteins and down-regulated 707 proteins in comparison to those in the sedentary control group. In which,

OPEN ACCESS

Edited and reviewed by:
Junjie Xiao,
Shanghai University, China

***Correspondence:**
Richard Y. Cao
rycao@scrc.ac.cn
Jian Yang
jyang@scrc.ac.cn

Specialty section:
This article was submitted to General Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

Received: *20 January 2022*
Accepted: *31 January 2022*
Published: *14 March 2022*

Citation:
Cao RY, Kelle S and Yang J (2022) Editorial: Advances in the Prevention and Rehabilitation of Cardiovascular Diseases via Aerobic Exercise. Front. Cardiovasc. Med. 9:858785. doi: 10.3389/fcvm.2022.858785

numerous proteins such as pyruvate dehydrogenase complex E1 component subunit alpha and subunit beta, pyruvate dehydrogenase kinase 2 and 4, and poly [ADP-ribose] polymerase 3 were associated with mitochondrial energy regulation, indicating that aerobic exercise might influence energy metabolism in heart failure mice. Another research team found that cardiac mitochondrial function in high aerobic capacity disease resistant phenotype was lost after ischemia-reperfusion insult in a rat model of coronary artery occlusion injury (Alsahly-a et al.). These studies propose potential molecular targets regarding mitochondrial regulation and function for future mechanism exploration. It was demonstrated that low capacity running rats had increased risk for ischemic injury characterized by high expression of vascular endothelial growth factor, endothelial nitric oxide synthase, and angiopoietin 2 after hind limb ischemia occlusion (Granier et al.). Therefore, high intrinsic aerobic capacity is essential for adaptive response to ischemic stress, though it may be influenced by gender differences (Alsahly-b et al.). Another study evaluated the influence of treadmill exercise on microglia polarization in a rat model of cerebral ischemia-reperfusion injury and found that exercise improved neurobehavioral outcomes, reduced infarct volumes, and increased interleukin-4 expression, which promoted M2 microglia activation along with the increasing of p-JAK1 and p-STAT6 expressions (Lu et al.). In a few words, the above-mentioned research demonstrates that aerobic exercise is beneficial for cardiac and cerebral vascular health, evidenced by using mice and rats as animal models.

CLINICAL PRACTICE IN CARDIAC REHABILITATION

International collaborations promote the development of the Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) from a concept to an evidence-based document for safe engagement in the physical activity and fitness assessment (2). Now PAR-Q+ is the gold standard in clinical practice for pre-participation risk stratification and screening globally. The translation, cultural adaptation, and reproducibility of the new version of PAR-Q+ in the Brazilian Portuguese language may facilitate a large number of Brazilians to participate in safer physical activity (Schwartz, Oh, Takito et al.). The same research team undertook in a critical review that also interprets and synthesizes current approaches for the prevention of chronic conditions such as being overweight and obesity with regard to dietary guidelines and physical activity security, which will enable a healthier and more active lifestyle for people in Brazil and Canada (Schwartz, Oh, Perotto et al.).

Currently, cardiopulmonary exercise testing (CPET) is the gold standard for the measurement and evaluation of the cardiorespiratory system in response to stress during exercise but requires costly instruments and well-trained technicians. Some easy-to-handle methods such as the six-min walk test (6MWT) and treadmill exercise testing (TET) are used as alternative solutions to measure cardiopulmonary capacities. Thus, it may open a door to develop additional methods besides CPET for evaluating cardiopulmonary capacities before and after rehabilitation training. For instance, researchers identified determinants using 6MWT and generated two reference equations for predicting 6MWT distance in patients immediately after coronary artery bypass and valve surgery (Radi et al.). Moreover, the role of 6MWT guided by impedance cardiography during rehabilitation in patients with knee arthroplasty was proven to be effective in evaluating the recovery of lower limb function and the improvement of exercise capacity in a randomized controlled trial (Lin et al.). While other scientists showed that TET was also able to assess exercise capacity accurately besides CPET (Gao et al.). The maximum exercise capacity measured by TET was negatively correlated with the waist-hip ratio, implying that TET could represent physical status. Thus, in addition to CPET, measurements of 6MWT and TET are valuable methods for the evaluation of exercise capacity in clinical practice. However, body positions may alter measurements; for example, peak oxygen uptake in the upright position is higher than that in the supine position and such differences need further verification for clinical significance (Wan et al.). Furthermore, the effects of exercise training on cardiac structure, cardiac function, and cardiovascular risk profiles can also be characterized by imaging metrics, including parameters derived from echocardiography, magnetic resonance, and Doppler ultrasound (Alhumaid et al.).

In addition to evaluation methods and measurements, exercise intensity is also an important component in optimizing outcomes in cardiac rehabilitation. A research group reviewed and compared evidence for prescribing moderate-vigorous intensity aerobic exercise and high intensity interval training in cardiac rehabilitation programs and found that higher intensity exercise contributed to greater improvements in peak oxygen uptake than low-moderate intensity exercise; however, there was no one-size-fits-all model for high intensity interval training (Taylor J. L. et al.). The gradual introduction and progression of higher intensity exercise can maximize an individual's safety, adherence, and physiological outcomes. In addition, exercise prescription implementation rate may also have significant effects on cardiovascular outcomes (Zhu et al.).

Enhanced external counterpulsation is a non-invasive procedure that alleviates symptoms of angina and reduces myocardial ischemia in patients with coronary artery disease (3). A recent meta-analysis confirmed that enhanced external counterpulsation could improve exercise capacity in patients with chronic heart failure resulting from randomized controlled trials (4). An original study explored acute hemodynamic responses to enhanced external counterpulsation in patients with coronary artery disease. They found that enhanced external counterpulsation induced more significant acute responses of vascular and blood flow characteristics in carotid arteries than that in peripheral arteries with a gender difference, in which acute improvement of flow rate in the brachial artery was only shown in male participants and resistance index in carotid arteries was only changed in female participants (Zhang et al.). These results suggest that enhanced external counterpulsation can regulate the vascular and blood flow characteristics of conduit arteries and further ameliorate the carotid and probably

peripheral vascular function in patients with coronary artery disease but the gender difference remains to be elucidated.

Heart failure, the terminal stage of several cardiovascular diseases with poor quality of life, is the major cause of morbidity and mortality globally (5). Exercise-based rehabilitation training has also been demonstrated to be suitable for heart failure patients. A group of scientists showed that high intensity interval training led to a similar inflammatory response as seen with traditional training in patients with chronic heart failure (Taylor A. G. et al.). A pilot randomized controlled trial of the *Baduanjin* Eight-Silken-Movements with Self-Efficacy was conducted in patients with chronic heart failure and proved to be feasible and effective (Chen et al.). Moreover, other clinician scientists designed a multicenter randomized controlled trial to test the efficacy and safety of different aerobic exercise intensities in heart failure patients with reduced ejection fraction (Shen et al.). The successful completion of this trial could potentially provide a basis for formulating appropriate exercise prescriptions for this patient population.

REHABILITATION IN PATIENTS WITH COMPLICATED CONDITIONS

Exercise-based rehabilitation is beneficial for not only cardiovascular diseases but also other disorders. Low physical performance in patients with chronic kidney disease concomitant with heart failure was found to be associated with long-term mortality in a retrospective longitudinal study (Weng et al.). Moreover, the prevalence of chronic obstructive pulmonary disease coexistence in patients with chronic heart failure is challenging in developed countries with a large aging population because patients with coexistence of these two diseases present a further impaired exercise capacity, daily life activity, and health status. It showed that in addition to the pharmacological approach, cardiopulmonary rehabilitation, which could improve aerobic capacity, respiratory and peripheral muscle strength, was an optimized scheme to reduce hospital re-admission, morbidity, and mortality for these patients in comorbid chronic pulmonary disease and chronic heart failure (Borghi-Silva et al.). A systematic review and meta-analysis evaluated the structure and format of all kinds of exercise-based, multimodal rehabilitation programs used in individuals with cancer and showed that exercise-based rehabilitation could promote cardiopulmonary fitness, improve the cancer-specific quality of life, and reduce cardiovascular risk among cancer survivors (Rickard et al.). Moreover, another systematic review and meta-analysis supported the importance of exercise participation with both aerobic and resistance training in adults living with schizophrenia (Bredin et al.). Although disputed results of combination training exist in the above study, physical activity is still a real-world therapy to boost physical and psychological health for persons with schizophrenia, cancer survivors, and heart failure patients concomitant with chronic kidney disease or chronic obstructive pulmonary disease, and probably individuals with other chronic conditions who need ongoing healthcare and medical attention.

CONCLUSIONS AND FUTURE PERSPECTIVES

The collection of articles in this Research Topic examines the effects of aerobic exercise in the prevention and rehabilitation of cardiovascular diseases with/without some concomitant chronic conditions. These studies elucidate not only the latest accomplishments in the field but also the unmet challenges in current clinical practice. Despite significant evidence of the benefits of exercise-based cardiac rehabilitation, controversial results of exercise still exist and key elements of exercise intensity, training duration, and evaluation methods remain to be illustrated. In addition, further understanding of the underlying molecular mechanisms of aerobic exercise in the prevention of cardiovascular diseases through basic science is desperately needed to optimize current rehabilitation programs. Since research has become a team sport more than ever before, we sincerely hope that researchers all over the world can work together to address these challenges and move the field of exercise-based cardiac rehabilitation forward through translational achievements in the near future.

AUTHOR CONTRIBUTIONS

RC drafted the editorial in consultation with JY and SK edited it. All authors approved it for publication.

FUNDING

RC was supported by the National Natural Science Foundation of China (Grant number 81672260). JY was supported by Shanghai Municipal Health Commission (Grant number ZK 2019A10). SK received support from the DZHK (German Center for Cardiovascular Research). Partner Site Berlin was supported by an unrestricted research grant from Philips Healthcare.

ACKNOWLEDGMENTS

We would like to thank Siyu Liu for her generous contribution to this Research Topic.

REFERENCES

1. American Association of Cardiovascular and Pulmonary Rehabilitation; American College of Cardiology Foundation; American Heart Association Task Force on Performance Measures (Writing Committee to Develop Clinical Performance Measures for Cardiac Rehabilitation), Thomas RJ, King M, Lui K, et al. AACVPR/ACCF/AHA 2010 update: performance measures on cardiac rehabilitation for referral to cardiac rehabilitation/secondary prevention services endorsed by the American College of Chest Physicians, the American College of Sports Medicine, the American Physical Therapy

Association, the Canadian Association of Cardiac Rehabilitation, the Clinical Exercise Physiology Association, the European Association for Cardiovascular Prevention and Rehabilitation, the Inter- American Heart Foundation, the National Association of Clinical Nurse Specialists, the Preventive Cardiovascular Nurses Association, and the Society of Thoracic Surgeons. *J Am Coll Cardiol.* (2010) 56:1159–67. doi: 10.1016/j.jacc.2010.06.006

2. Warburton DER, Gledhill N, Jamnik VK, Bredin SSD, McKenzie DC, Stone J, et al. International launch of the PAR-Q+ and ePARmed-X. The physical activity readiness questionnaire (PAR-Q+) and electronic physical activity readiness medical examination (ePARmed-X+): summary of consensus panel recommendations. *Health Fitness J Can.* (2011) 4:26–37. doi: 10.14288/hfjc.v4i2.103
3. Bonetti PO, Holmes DR, Lerman A, Barsness GW. Enhanced external counterpulsation for ischemic heart disease. *J Am Coll Cardiol.* (2003) 41:1918–25. doi: 10.1016/S0735-1097(03)00428-5
4. Zhou ZF, Wang DJ, Li XM, Zhang CL, Wu CY. Effects of enhanced external counterpulsation on exercise capacity and quality of life in patients with chronic heart failure: a meta-analysis. *Medicine (Baltimore).* (2021) 100:e26536. doi: 10.1097/MD.0000000000026536
5. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. *Eur J Heart Fail.* (2020) 22:1342–56. doi: 10.1002/ejhf.1858

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Cardiovascular Medicine

REVIEW
published: 31 May 2021
doi: 10.3389/fcvm.2021.672913

Cardiac Rehabilitation: A Bibliometric Review From 2001 to 2020

Guozhen Yuan[1†], *Jingjing Shi*[1†], *Qiulei Jia*[1], *Shuqing Shi*[1], *Xueping Zhu*[1], *Yan Zhou*[1], *Shuai Shi*[2] *and Yuanhui Hu*[1*]

[1] Department of Cardiovascular Diseases, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China, [2] Department of General Internal Medicine, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China

Cardiovascular disease (CVD) is a serious threat to global public health due to its high prevalence and disability rate. Meanwhile, cardiac rehabilitation (CR) has attracted increasing attention for its positive effects on the cardiovascular system. There is overwhelming evidence that CR for patients with CVD is effective in reducing cardiovascular morbidity and mortality. To learn more about the development of CR, 5,567 papers about CR and related research were retrieved in the Web of Science Core Collection from 2001 to 2020. Then, these publications were scientometrically analyzed based on CiteSpace in terms of spatiotemporal distribution, author distribution, subject categories, topic distribution, and references. The results can be elaborated from three aspects. Firstly, the number of annual publications related to CR has increased year by year in general over the past two decades. Secondly, a co-occurrence analysis of the output countries and authors shows that a few developed countries such as the United States, Canada, and the UK are the most active in carrying out CR and where regional academic communities represented by Sherry Grace and Ross Arena were formed. Thirdly, an analysis of the subject categories and topic distribution of the papers reveals that CR is a typical interdiscipline with a wide range of disciplines involved, including clinical medicine, basic medicine, public health management, and sports science. The research topics cover the participants and implementers, components, and the objectives and requirements of CR. The current research hotspots are the three core modalities of CR, namely patient education, exercise training and mental support, as well as mobile health (mHealth) dependent on computer science. In conclusion, this work has provided some useful information for acquiring knowledge about CR, including identifying potential collaborators for researchers interested in CR, and discovering research trends and hot topics in CR, which can offer some guidance for more extensive and in-depth CR-related studies in the future.

Keywords: cardiac rehabilitation, cardiovascular disorders, COVID-19, mapping knowledge domains, CiteSpace

OPEN ACCESS

Edited by:
Jian Yang,
Fudan University, China

Reviewed by:
Han Xiao,
Peking University Third Hospital, China
Richard Yang Cao,
Shanghai Xuhui Central Hospital, China

****Correspondence:***
Yuanhui Hu
huiyuhui55@sohu.com

[†]These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to General Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

Received: *26 February 2021*
Accepted: *26 April 2021*
Published: *31 May 2021*

Citation:
Yuan G, Shi J, Jia Q, Shi S, Zhu X, Zhou Y, Shi S and Hu Y (2021) Cardiac Rehabilitation: A Bibliometric Review From 2001 to 2020. Front. Cardiovasc. Med. 8:672913. doi: 10.3389/fcvm.2021.672913

INTRODUCTION

Cardiovascular disease (CVD) is prevalent and is causing deaths worldwide, whether in developed or developing countries. It was reported that about 485.6 million people suffered from CVD, and 17.8 million deaths were attributed to it in 2017 globally, an increase of 21.1 and 28.5% compared with a decade ago, respectively (1). What is worse is that CVD is expected to account for >22.2

million deaths by 2030 (2). In the United States, the overall prevalence of CVD (comprising coronary heart disease, heart failure, stroke, and hypertension) in adults ≥20 years of age is 48.0% in 2013 and 2016 (3). In China, according to the latest estimate of the National Center for Cardiovascular Diseases, there are 330 million CVD cases, resulting in 40% of the deaths in the nation (4). On the other hand, advances in medical technology and a younger age of onset have made a sharp increase in cases surviving with CVD. All in all, non-communicable diseases represented by CVDs, especially ischemic heart disease, have become the leading cause of the growing global disease burden in the past 30 years (5). Therefore, preventing the occurrence and recurrence of CVD is a great challenge for the public health systems worldwide. Hopefully, mounting scientific evidences show that cardiac rehabilitation (CR) plays a positive role in the secondary prevention of CVD, including lowering cardiovascular risk and mortality, reducing relapse and hospital admissions, and improving cardiopulmonary functions, quality of life, and prognosis (6–12). CR has been an indispensable part of modern cardiology, endorsed and recommended by some authoritative organizations, such as the American Heart Association (AHA), American College of Cardiology, and the European Society of Cardiology (13, 14).

Actually, the development of CR is out of balance in different regions and countries. According to a survey of global CR availability and density, CR is available in only half of the countries around the world, and the capacity is grossly insufficient, where offered (15). Although it is difficult to conduct a systematic epidemiological investigation on the current situation of CR around the world, it does not mean we cannot maximize knowledge gain about CR, nevertheless. Visual analytics of the literature offers a valuable, timely, repeatable, and flexible approach besides traditional systematic reviews so as to track the new emerging trends and identify critical evidence (16). In this review, visual analysis based on CiteSpace is applied in published literatures on the topic of CR in the last 20 years to help learn the trends of this old and young discipline in the new century and to promote extensive application in CVD patients.

MATERIALS AND METHODS

Data Source and Search

The publications were obtained from the Core Collection database of Web of Science (WoS) (http://apps.webofknowledge.com) because it is considered the most prominent database of scientific publications on many research topics. The strategy used during the search was [TS = ("cardiac rehabilitation" OR "heart rehabilitation")] AND [Language = (English)]. A total of 7,678 results were found from 2001 to 2020 (retrieved on November 19, 2020). Then, the exclusion of publications was performed according to document type; therefore, only 5,567 records (4,721 articles and 846 reviews) were used in the final database. All the records, including the titles, authors, abstracts, keywords, cited references, and so on, were then imported to CiteSpace5.7. R2, a knowledge mapping tool based on Java to visualize the patterns and trends in scientific literature (17, 18).

Scientometric Analysis Methods

CiteSpace, a freely available Java-based application, was designed to analyze and visualize trends and patterns in scientific literature, presenting the structure and distribution of scientific knowledge. It focuses on finding critical points in the development of a field or a domain, especially intellectual turning points and pivotal points (17). Once the literature has been imported into CiteSpace, the first step is data cleaning. If there are no duplicates, the original data can be used directly; otherwise, the repeat ones should be removed before subsequent analysis. CiteSpace supports structural and temporal analyses of a range of networks derived from scientific publications, including collaboration networks, co-occurrence networks, and co-citation networks, and it also supports networks of hybrid node types such as terms, authors, and countries. The results are displayed in the form of visual graphs where nodes represent research items; the more frequently the item appears or is cited, the larger is the size of the node. Links between nodes describe a co-occurrence or a co-citation between these nodes, and their thickness indicates the strength of these correlations: the thicker the line, the closer is the connection between them. The shade or tone of the node and link color indicates the chronological order of occurrence of the item (16). Burst detection is also one of the features of CiteSpace, and a positive node after burst detection means a sharp change in its frequency in a short period of time (19). Such nodes usually suggest a shift in a certain field of research and are shown in red in the knowledge map. In addition, CiteSpace also introduces some common network topology parameters to describe the structure of complex networks, such as betweenness centrality (BC) put forward by the American sociologist Linton Freeman. The BC of node X represents the ratio of the shortest paths between any two different nodes through node X in all the shortest paths of these two nodes in a fully connected network (20). At the documental level, the betweenness centrality metric can be used to partially assess the importance of each node in the network (21). A node with BC >0.1 is displayed in terms of a purple ring. The thickness of the purple ring increases as the degree of its BC rises, which is a measure associated with the transformative potential of a scientific contribution (16). What is more is that cluster analysis is another important way of analyzing knowledge networks easily in CiteSpace. More specifically, terms in the literature are classified based on their similarity and are scored by some specific algorithms, and then the term with the highest score of each cluster is selected as the representative, that is, the label of the cluster. The size of the cluster is the number of grouped objects. CiteSpace distributes the ID #0 to the largest cluster formed, the ID #1 to the second largest, and so on (22). It should be noted that all running parameters were set as defaults for the following analysis, except for the time slice setting of 2 years.

RESULTS AND DISCUSSION

Annual Quantitative Distribution of Publications

The annual number of published papers reflects the pace of subject knowledge and is a significant indicator for studying the

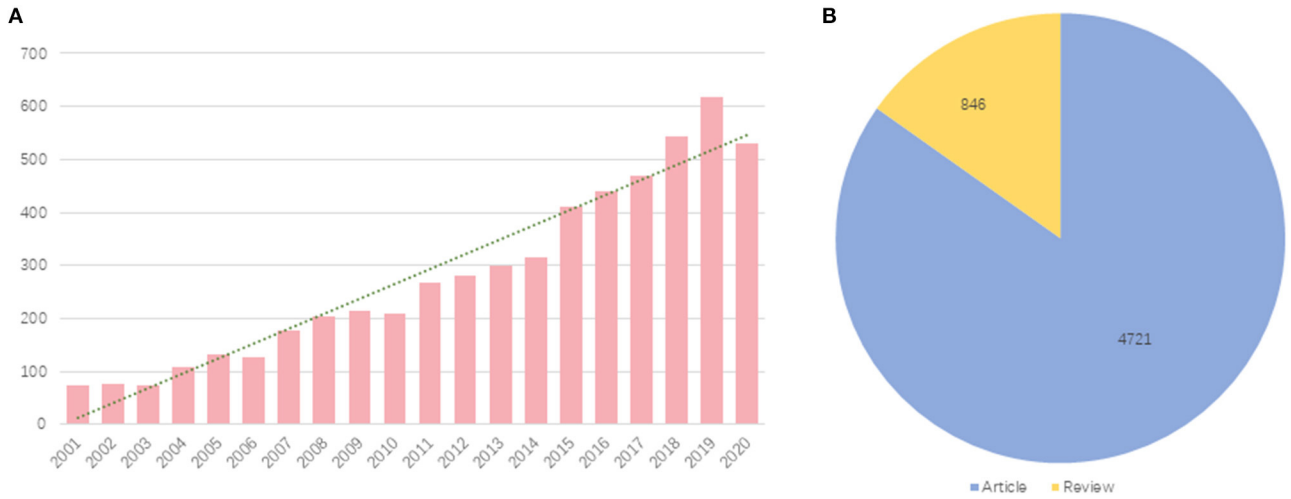


FIGURE 1 | Yearly quantity and document type of publications about cardiac rehabilitation (CR) and related research. **(A)** Annual quantitative distribution. **(B)** Document type. *Blue* represents articles and *yellow* represents reviews.

trends in the field (23). The yearly quantity and the document type of publications of research on CR are visually displayed in **Figure 1**. We can draw directly that the number of CR-related literature has increased year by year on the whole between 2001 and 2020, except for a slight decrease in 2006 and 2010 (**Figure 1A**), indicating a steady development of CR. Especially since the last 5 years, CR has stepped into a period of rapid development, with the quantity of papers growing much faster than that in the previous decade, which shows that CR is getting more and more attention. It may be attributed to the worldwide increase in CVD patients on the one hand and, on the other hand, perhaps implies that the concept of CR is popularizing from local to global. Furthermore, articles account for about 85% in terms of document type (**Figure 1B**), which indicates the greater emphasis paid on clinical practice and that original studies such as case report and clinical trials are the mainstream in the area of CR.

Country Ranking and Co-author Analysis

Visualized knowledge mapping can provide information on influential research teams and potential collaborators and help researchers establish collaborative relationships (24). An analysis of the country distribution of these publications shows that the United States, Canada, and England are the most noticeable countries for co-authored papers, not only for the largest number of articles written in collaboration but also for the highest betweenness centrality (**Table 1**), revealing that these countries are highly outstanding in CR research, both quantitatively and qualitatively. Indeed, it was these countries that were among the first to focus on and implement CR, and several academic communities active in CR have been formed in these countries. Sherry L. Grace, full professor in the Faculty of Health at York University of Canada, is one of the representative figures. Professor Grace's research centers on optimizing post-acute cardiovascular care globally, as well as outcomes (including mental health). As the most prolific co-author who has made an important contribution to the field of CR (**Table 1**), she authored clinical practice guidelines internationally (25, 26) and led the development of the Canadian quality indicators for CR (27, 28), as well as policy positions on systematic referral and utilization (29). In the United States, Professor Ross Arena from the University of Illinois at Chicago is a moving force in the world of cardiovascular rehabilitation. He is devoted to exercise testing and training in patients diagnosed with cardiopulmonary dysfunction, as well as healthy living initiatives and policies that promote the healthspan (30–32). More importantly, he has conceived of and oversaw the successful implementation of several innovative healthy living initiatives in the academic, clinical, and community settings (33). We can see that, however,

TABLE 1 | Top 5 productive countries and top 10 productive authors of publications about cardiac rehabilitation (CR) and related research.

Rank	Country/author	Publication frequency	Burst	BC
1	USA	1,529	8.51	0.24
2	Canada	747	–	0.24
3	England	588	5.96	0.22
4	Australia	532	–	0.17
5	Italy	385	–	0.18
1	Sherry L. Grace	158	–	0.05
2	Paul Oh	80	6.05	0.01
3	Ross Arena	69	5.03	0.02
4	Randal J. Thomas	66	4.45	0.05
5	Carl J. Lavie	65	3.36	0.02
6	Patrick Doherty	62	8.27	0.02
7	Rod S. Taylor	56	3.67	0.05
8	Philip A. Ades	56	6.14	0.01
9	Susan Marzolini	46	–	0
10	Anndorthe Zwisler	46	4.31	0.02

BC, betweenness centrality.

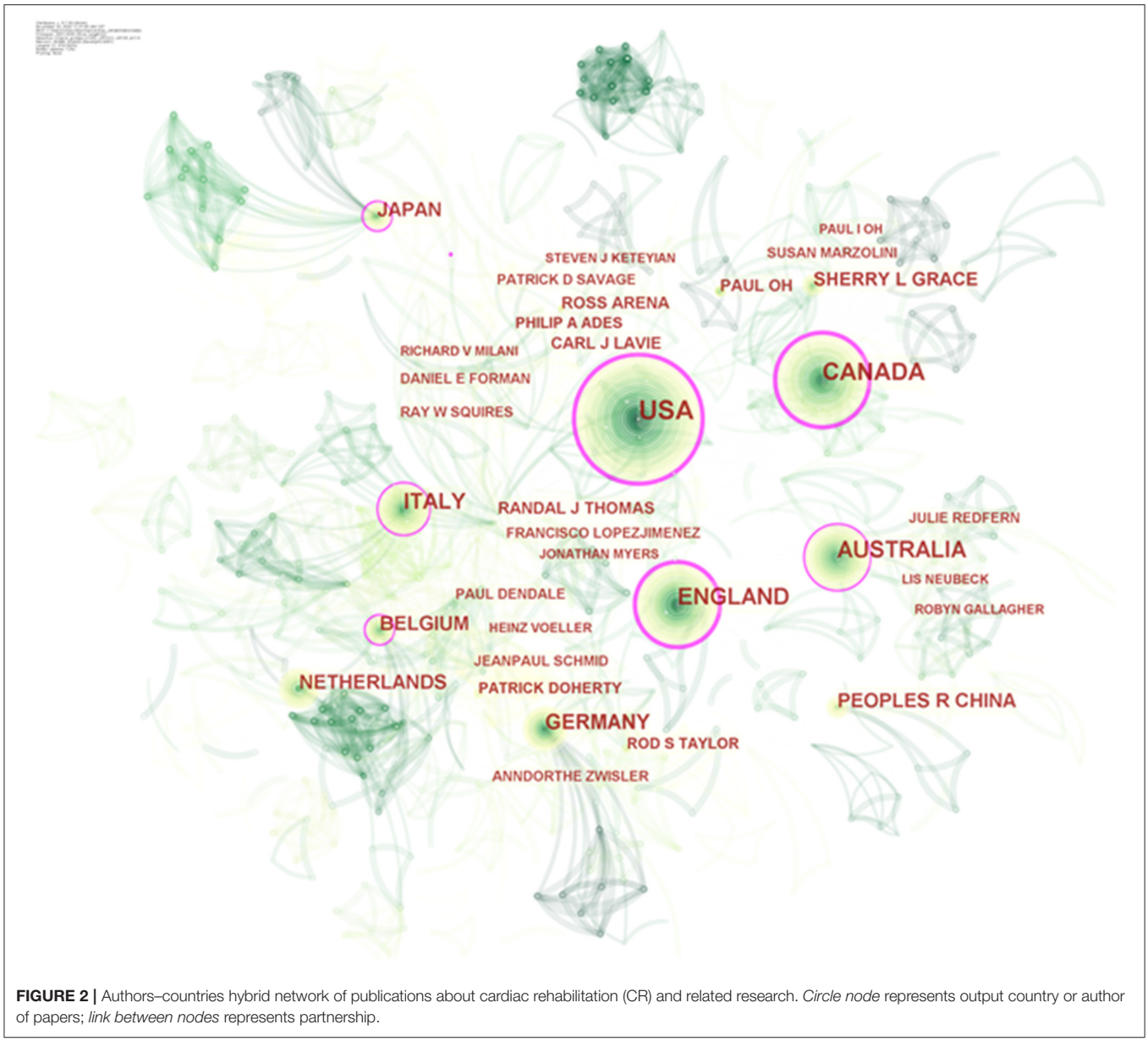


FIGURE 2 | Authors–countries hybrid network of publications about cardiac rehabilitation (CR) and related research. *Circle node* represents output country or author of papers; *link between nodes* represents partnership.

there are far more links between the nodes representing authors than between the nodes representing countries in **Figure 2**, which means that the interaction and the corporation between countries in the field of CR are relatively poor, and the form of partnership is still dominated by corporation within academic teams in each country.

Subject Categories Co-occurrence Analysis

The subject category (SC) in the Web of Science is based on journal–journal citation patterns and the judgment of domain experts, and then it is assigned to periodical, and finally, the papers included in the journal will be classified into the SC of the journal. Although this classification is controversial (34), we still use the subject co-occurrence function of CiteSpace to analyze the fields as SC in the literature due to its wide application and easy access (35), which contributes to constructing a correlation network of CR that demonstrates the interconnectedness of the disciplines and identifying high-impact disciplinary categories at the meso level. CR, a typical interdiscipline, is a comprehensive project for patients with CVDs (36), which is corroborated by disciplinary co-occurrence analysis. The results show varying degrees of interrelatedness between CR and lots of disciplines, and the involvement and utilization are the highest in clinical medicine, followed by public health management. Interestingly, CR also shows a strong crossover with sports science, a non-medical discipline (**Figure 3** and **Table 2**). In **Figure 3**, the nodes denoting cardiology, public, environmental, and occupational health, and psychology are labeled with purple circles, namely with good betweenness centrality (BC > 0.1), suggesting that they

FIGURE 3 | Subject category co-occurrence of publications about cardiac rehabilitation (CR) and related research. *Circle node* represents subject category; *link between nodes* represents interdisciplinary interaction of the literature.

are more impactful disciplines. The red nodes with positive burst detection are popular subjects for a certain period of time. For example, exercise prescription is a key component of CR, but clinicians experience difficulties in how to optimally prescribe exercise for patients with different cardiovascular disease risk factors (37), which requires sports medicine specialists to get involved in order to develop a personalized exercise program tailored to the needs of CVD patients. People with CVD are often accompanied by mental disorders, such as stress, anxiety, and depression, and it is a major challenge for heart rehabilitation (38–40). For such patients, the intervention of a professional psychologist or psychiatrist is urgently needed. In a word, CR has a comprehensive goal to aim for the optimal recovery of CVD patients physically, mentally, and socially. An ideal CR therapy demands multidisciplinary cooperation and integrative intervention, including medicine, exercise, nutrition, education, and psychological and social support, thus posing a huge challenge to interdisciplinary collaboration around CR. To obtain better development and application of CR, what need to be strengthened are breaking down the barriers between disciplines as well as accelerating the integration of transdisciplinary intelligence.

TABLE 2 | Top 15 subject categories of publications about cardiac rehabilitation (CR) and related research.

Rank	Subject category	Frequency	Burst	BC
1	Cardiovascular system and cardiology	2,611	–	0.21
2	General and internal medicine	562	–	0.1
3	Nursing	516	–	0.07
4	Rehabilitation	490	–	0.07
5	Sport sciences	331	4.58	0.05
6	Public, environmental, and occupational health	330	–	0.44
7	Psychology	292	14.84	0.19
8	Health care sciences and services	248	–	0.06
9	Peripheral vascular disease	185	–	0.03
10	Geriatrics and gerontology	130	–	0.06
11	Psychiatry	130	8.34	0.02
12	Research and experimental medicine	116	6.91	0.08
13	Respiratory system	115	6.87	0.02
14	Physiology	84	–	0.1
15	Psychology, clinical	77	–	0.01

BC, betweenness centrality.

Topic Distribution Analysis Based on Keywords

If subject co-occurrence is to explore research topics in a field at a meso level, keyword co-occurrence is to answer the specific questions in the subject from a micro perspective. As a highly condensed version of the paper's content, to some extent, keywords are able to summarize the theme of the paper simply and directly. The keyword co-occurrence network is a text content-based analytical approach. It sorts out the connections

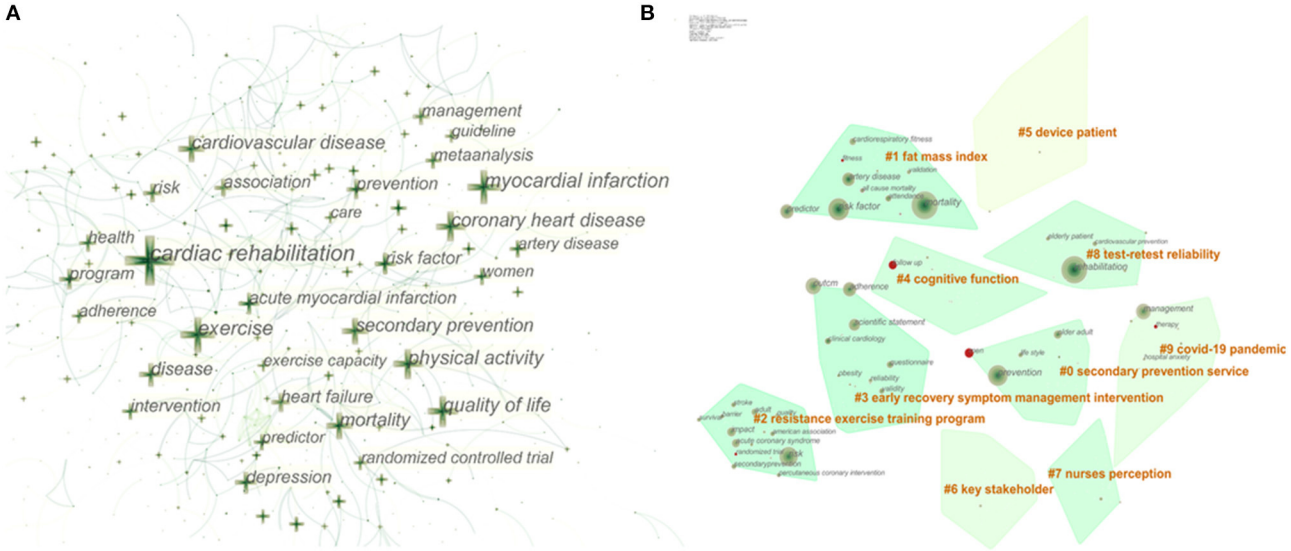


FIGURE 4 | Keyword co-occurrence and clustering. **(A)** Network of the main keywords in publications about cardiac rehabilitation (CR) and related research. **(B)** Top 10 keyword clusters.

between the different topics in the discipline and helps readers get more acquainted with it through analyzing the co-occurring forms of keyword pairs in the same text. The co-occurrence results of the keywords in publications of CR and related research can be seen in **Figure 4**. The cross in **Figure 4A** indicates the keyword; the larger the size of the cross, the higher the frequency of the keyword. In fact, when the number of keywords is too large, it is difficult for us to generalize the research topics they belong to, and cluster analysis could assist with this problem. **Figure 4B** shows the top 10 keywords clustering based on the log-likelihood rate (LLR) algorithm. They encompass plenty of concerns in the field of CR, comprising participant (#5device patient, #6stakeholder), implementer (#7Nurses perception), content (#1 Fat mass index, #2 Resistance exercise training program, and #4 Cognitive function), purpose (#0 Secondary prevention service), requirements (#8 Test–retest reliability), and indications of CR (#9 COVID-19 pandemic).

The primary item that must be mentioned is the coronavirus disease 2019 (COVID-19) pandemic (cluster #9), which continues to attract global eyes throughout 2020 and will last for some time. As the pandemic is spreading all over the world, there are increasing reports of cardiac system damage and cardiovascular sequelae caused by COVID-19 (41, 42). Obviously, CR can play a significant role in the fight against this catastrophe, beneficial for patients with aggravation of preexisting CVD or secondary cardiovascular impairment due to COVID-19 (43). Secondly, most of the clusters involve the core components of CR, also known as prescription for CR, containing management of risk factors like overweight and obesity (cluster #1), psychosocial support (cluster #3), and exercise training (cluster #2), all of which are core modalities of CR recommended by international guidelines (36, 44). Last but not least, it is the evaluation of tests used for CR to ensure the reliability, stability, and consistency of the test results, such as the 6-min walk test, the 10-m incremental shuttle walk test, and other common outcome measurements in CR, which is crucial for the long-term validity of the tests for CR (45, 46). At the same time, screening out tests with high retest reliability makes it possible to compare and evaluate the efficacy in large clinical populations of CVD after recovery in the future. In brief, clustering based on keywords reveals the hot issues of CR microcosmically and helps us have a better sense of the topic distribution in the field of CR.

Reference Co-citation Analysis

Co-citation analysis was put forward by Small and Marshakova in 1973 and later introduced into the analysis of co-citation of references, a phenomenon of two or more references being cited in the same literature (47, 48). By analyzing the clusters and pivotal nodes in the co-citation network, the knowledge structure of a research area and its changes can be uncovered. **Figure 5** shows the co-citation network and timeline view of references on CR and related studies. The circular node in **Figure 5A** represents the reference, and the larger the size of the node, the higher is the citation frequency of the reference. Obviously, there are three nodes with a purple circle in the network; that is, the BC of the nodes is >0.1, which indicates that they are the critical turning points driving the development of CR. The first turning point occurred in 2003. A guideline jointly released by two subcommittees of AHA provides a clear definition of physical activity and exercise as well as their dose and intensity, and a comprehensive summary of prospective epidemiologic studies showing that physical activity could reduce the incidence of CAD events over the past half century (49). Therefore, it can provide clinicians with direct and detailed guidance when prescribing exercise to patients

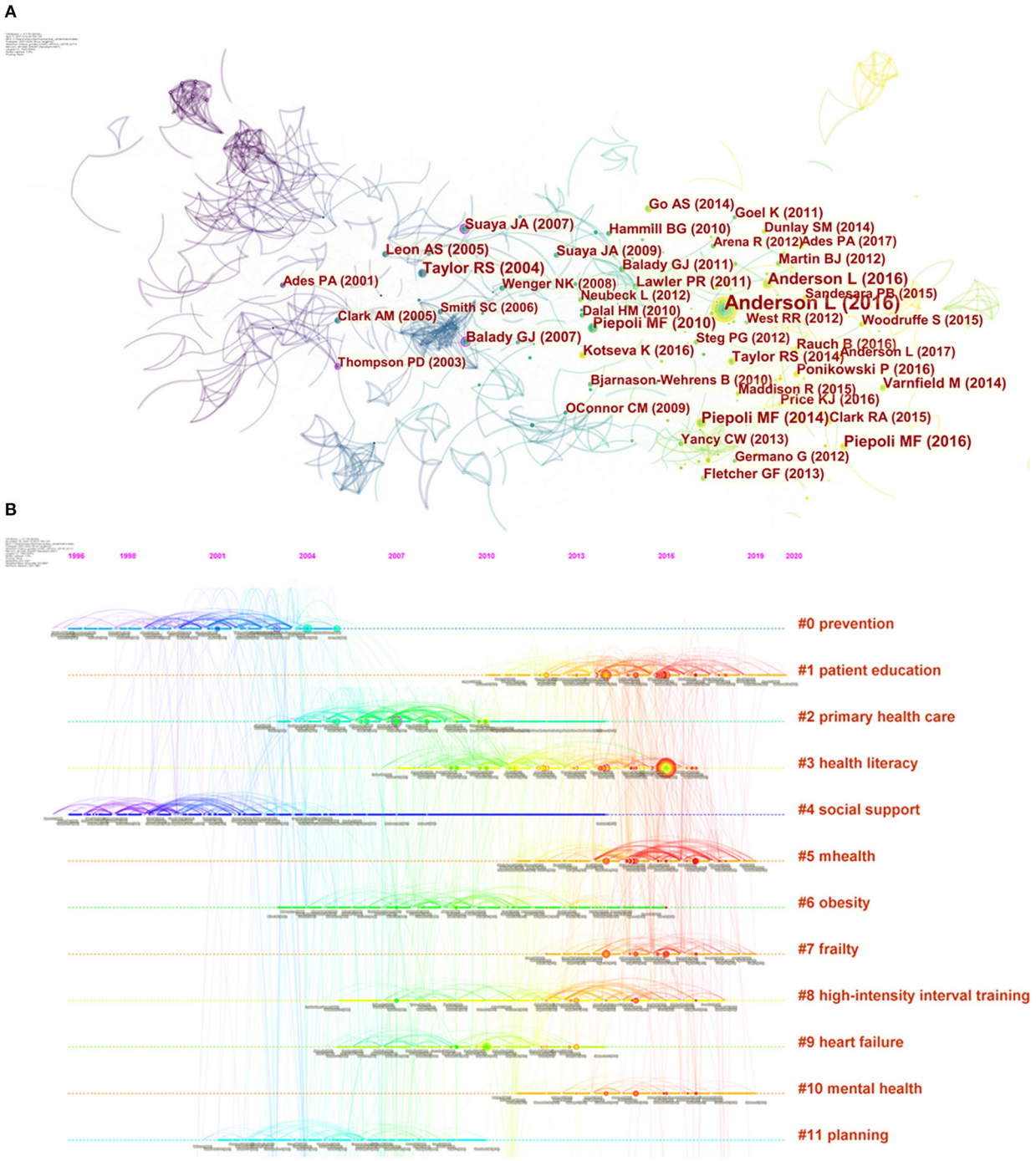


FIGURE 5 | Co-citation network and timeline view of references cited by publications about cardiac rehabilitation (CR) and related research. **(A)** References co-citation network. *Circle node* represents reference; the *line between the nodes* indicates the frequency of the two references being cited at the same time. The betweenness centrality of the nodes with *purple circle* is >0.1. **(B)** Timeline view of references. Each *horizontal line* represents a cluster; the *circular nodes on the line* represent the top three most cited references in this time slice. The timeline is shown at the *top of the figure*, and the year corresponding to the node is its publication time. *Link between nodes* represents the co-citation relationship.

with atherosclerotic cardiovascular disease (ACD). This guideline broke the dilemma of having no guideline for prescribing exercise for adults with ACD and greatly improved the status of exercise in the prevention and treatment of CVD and the management of its risk factors, laying a solid evidence-based medical foundation for later recommending exercise as one of the core modalities of CR.

The next two turning points both came in 2007. The former, again a guideline, was jointly released by the AHA and the American Association of Cardiovascular and Pulmonary Rehabilitation (AACPR). This update presented the latest information on the evaluation, interventions, and expected outcomes in each of the core components of CR/secondary prevention programs at that time, including baseline patient assessment, nutritional counseling, risk factor management, psychosocial interventions, and physical activity counseling and exercise training (36). Its content is more abundant and systematic than that of the guideline in 2003, providing more comprehensive guidance for the application of CR. The latter is a study that uses Medicare claims to evaluate national use patterns and predictors of CR use. The results directly reveal the underutilization and regional imbalance of CR in the United States, even though it is one of the countries with the most advanced CR referral system (50). To some extent, this survey served as a warning to healthcare policy makers that accelerating the widespread and balanced development of CR is imperative. In a word, these three crucial turnarounds could be considered as landmark events in the field of CR and have a profound impact on it.

CiteSpace also visualizes the research frontiers, knowledge base and their time span, as well as the literature that has played a key role in the evolution, in a unique way with a timeline view. The timeline view is a visualization method that combines the clustering and time slicing techniques. Items are ranked according to their early or late appearance after clustering, which both exhibit the topic distribution in the field and depict the trends and interconnections of the research topics over time. In **Figure 5B**, the cool-toned nodes (blue and green ones) represent earlier literature and the warm-toned nodes (yellow and red ones) represent more recent literature, with the earliest one dating back to 1996. A straight line at the same horizontal position indicates the set of all references belonging to the cluster, and the label of the cluster is located at the rightmost end of the line. The integrated network is divided into co-citation clusters of references. Citers to these references are considered as the research fronts associated with these clusters. Each cluster represents the knowledge fundamental of the underlying specialty. As can be seen in **Figure 5B**, in the early stage, CR-related research was dominated by exploration of its cardiovascular prevention and the importance of social support (cluster #0 and cluster #4). As strong evidence accumulated, these two questions were largely answered (51–53), so the research focus of CR had shifted to other aspects.

Despite overwhelming evidence that CR reduces risks and improves the quality of life and prognosis of CVD patients, the uptake and adherence to such programs among CVD patients remain below the recommended levels (54). Naturally, primary health care, planned CR intervention, and so on were immediately on the agenda (cluster #2 and cluster #11), and their implementation contributed to promoting patient participation and compliance in CR. Meanwhile, completing the prescription content of CR, such as the management of obesity and other risk factors (cluster #6), and tailoring rehabilitation programs for patients with heart failure were also the hot spots in this period (cluster #9). As stated in international guidelines and expert consensus, education, exercise training, and psychological support are three core modalities of CR (55). These core components are the current hot topics (cluster #1, cluster #3, cluster #4, cluster #8, and cluster #10), which are of great significance to improve CR prescription and promote the effective implementation of CR in the long run in this field. In addition, with advances in Internet technology and ubiquity of smart mobile devices, the availability of mobile health (mHealth) application that provides medical information and services via mobile devices such as pads and smart phones for CVD patients has markedly increased in recent years. There is no doubt that the elderly or mobility-impaired patients with CVD have the potential to benefit considerably from interventions that utilize mHealth (cluster #5 and #7). mHealth is extremely likely to be a complement or even an alternative to the traditional facility-based CR that is underutilized, and without much concern, there is also evidence that older patients may be willing to adopt these trendy technologies (56, 57).

In other aspects, the identification of core literature in a certain field generally depends on the frequency of citations, and references with the highest cited frequency, namely high-impact literature, are usually the main focus of the researchers. **Table 3** shows the top 15 cited references with the highest frequency; their approximate content can be inferred from the titles. It is not difficult to find that the content of these most cited references is almost all centered on the clinical application of CR, and their types are mainly systematic review and meta-analysis and practice guideline or scientific statement. These high-quality systematic reviews provide important data and scientific evidence for the use of CR, especially exercise-based CR, in the CVD population, and they confirm that exercise-based CR lowers cardiovascular risk and mortality (6–8) and decreases reinfarction after myocardial infarction and heart failure-related hospital admissions (9, 10). Moreover, practice guidelines and scientific statements drafted by experts also provide practical advice and detailed guidance for the safe and effective application of CR and its effectiveness evaluation (13, 14, 36, 58–60). Clinical trial is one of the most important approaches of medical research, such as randomized controlled trial and cross-sectional study, assessing the participation, adherence, completion, and the effectiveness of CR in order to offer useful information and guidance for the long-term effective application of CR in the future (61, 62). In short, the co-citation analysis of CR-related references provides us with rich and valuable information to learn more about the evolution of the knowledge structure and changes of research hot spots in CR and helps to discover the core topic and key focus in this area.

CONCLUSIONS

With the accelerated aging of the global population and the dramatic increase in the number of patients surviving with CVD, how to reduce the risk of relapse and improve the prognosis of CVD patients is a major test for health care systems in all countries. CR is a shift from the traditional disease-centered model to a patient-centered biopsychosocial model, and its

TABLE 3 | Top 15 most cited references of publications about cardiac rehabilitation (CR) and related research.

Rank	Article title	Year	Total cited frequency	Average per year
1	Exercise-Based Cardiac Rehabilitation for Coronary Heart Disease	2016	675	168.75
2	Exercise-Based Cardiac Rehabilitation for Coronary Heart Disease: Cochrane Systematic Review and Meta-analysis	2016	172	43.00
3	Exercise-Based Rehabilitation for Patients with Coronary Heart Disease: Systematic Review and Meta-analysis of Randomized Controlled Trials	2004	149	9.31
4	Secondary Prevention in the Clinical Management of Patients with Cardiovascular Diseases. Core Components, Standards and Outcome Measures for Referral and Delivery: A Policy Statement from the Cardiac Rehabilitation Section of the European Association for Cardiovascular Prevention and Rehabilitation. Endorsed by the Committee for Practice Guidelines of the European Society of Cardiology	2014	148	24.67
5	2016 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention and Rehabilitation (EACPR)	2016	140	35.00
6	Secondary Prevention through Cardiac Rehabilitation: From Knowledge to Implementation. A position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation	2010	124	12.40
7	Smartphone-Based Home Care Model Improved Use of Cardiac Rehabilitation in Postmyocardial Infarction Patients: Results from a Randomized Controlled Trial	2014	103	17.17
8	2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC	2016	103	25.75
9	Cardiac Rehabilitation and Secondary Prevention of Coronary Heart Disease: An American Heart Association Scientific Statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity), in collaboration with the American Association of Cardiovascular and Pulmonary Rehabilitation	2005	99	6.60
10	Use of Cardiac Rehabilitation by Medicare Beneficiaries after Myocardial Infarction or Coronary Bypass Surgery	2007	99	7.62
11	Core Components of Cardiac Rehabilitation/Secondary Prevention Programs: 2007 Update: A Scientific Statement from the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical Activity, and Metabolism; and the American Association of Cardiovascular and Pulmonary Rehabilitation	2007	97	7.46
12	Exercise Based Rehabilitation for Heart Failure	2014	96	16.00
13	Efficacy of Exercise-Based Cardiac Rehabilitation Post-myocardial Infarction: A Systematic Review and Meta-analysis of Randomized Controlled Trials	2011	94	10.44
14	EUROASPIRE IV: A European Society of Cardiology Survey on the Lifestyle, Risk Factor and Therapeutic Management of Coronary Patients from 24 European Countries	2016	86	21.50
15	Heart Disease and Stroke Statistics—2014 Update: A Report from the American Heart Association	2014	82	13.67

emergence is of great significance to patients with CVD. The visual analytic tool we utilized in this review plays an active role in supplementing traditional review and survey articles, and they are valuable in finding critical developments in the vast number of published studies.

In this review, our visual analysis of the literature on CR and related research over the last two decades has shown that CR has generally had a steady development during this period, but its development is quite unbalanced between areas and countries. Only a few developed Western countries such as Canada, the United States, and the UK have developed systematic and standardized CR models, as well as mature and well-established CR referral systems; awareness of and participation in CR are both insufficient in the vast majority of developing countries and regions. Correspondingly, several of the most active academic communities in CR have been formed in these countries, such as Professor Sherry Grace's team at York University in Canada and Professor Ross Arena's team at the University of Illinois in the United States. However, the interaction and collaboration around CR are poor among these leading countries and academic communities. In order for a balanced and widespread development of CR globally, it is urgent to strengthen transnational and cross-team cooperation, which requires the involvement of more international organizations specialized in CR. In addition, CR has a typical interdisciplinary characteristic, and its long-term and healthy development cannot be achieved without the coordinated development and mutual integration of clinical medicine, basic medicine, psychology, public health management, sports science, and even computer science. It means that more attention should be paid to the cultivation of compound talents with medical background in future medical education.

The keyword clustering analysis of the original documents and the co-citation analysis of the references reflect the trends and hot spots of CR. Early CR-related studies mainly focused on its cardiovascular prevention and social support, followed by primary health care and planned CR interventions to refine the social support for CR at the institutional and methodological

levels. Then came the focus on specific populations, such as patients with obesity or heart failure, emphasizing the individualization of CR programs. The current hot spots are the three core modalities of CR, namely education, exercise training, and psychological support, particularly centering at exercise prescription for CR, including weight management, resistance exercise training program, and high-intensity interval training. At the same time, mHealth, born from the wave of Internet popularity, has started to emerge and become popular. There is no doubt that this trend of "Internet plus healthcare" will continue to prevail. Besides, it must be mentioned that CR is likely to play a critical role in improving cardiovascular damage and sequelae caused by COVID-19 as it continues to spread worldwide. Finally, there were three pivotal turning points that had driven the development of CR. The first was the guideline on physical activity and exercise in patients with ACD published by the AHA in 2003, followed by the systematic guideline on CR jointly issued by AHA and AACPR in 2007, and the last one is a study on the prediction of CR utilization. They have gradually contributed to the development of CR.

In conclusion, this work has provided some useful information for obtaining knowledge about CR as a long-established and innovative interdiscipline, identified potential collaborators for researchers interested in CR, and discovered research trends and hot topics. At the same time, we expect that our work will help more medical practitioners and patients with CVD, especially those in developing countries and regions where heart rehabilitation still lags behind. A deeper understanding of CR can inspire people's interest in it, which will be beneficial to the treatment and prognosis of the hundreds of millions of populations suffering from CVD worldwide.

AUTHOR CONTRIBUTIONS

YHH, GZY, and JJS devised the research plan and established the methodology. GZY, JJS, QLJ, SQS, and YHH wrote the original draft. XPZ, YZ, and SS were in charge of software, literature retrieval, and visualization. YHH, GZY, and JJS modified and polished the manuscript. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

We wish to thank Professor Chaomei Chen for developing CiteSpace and making it freely available to the public.

REFERENCES

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. (2018) 392:1789–858. doi: 10.1016/S0140-6736(18)32279-7
2. *Global Status Report on Noncommunicable Diseases 2014*. Geneva: World Health Organization (2014). Available online at: http://apps.who.int/iris/bitstream/10665/148114/1/9789241564854_eng.pdf (accessed January 21, 2003).
3. National Center for Health Statistics. *National Health and Nutrition Examination Survey (NHANES) Public Use Data Files*. Centers for Disease Control and Prevention Website. Available online at: https://www.cdc.gov/nchs/nhanes/ (accessed January 21, 2003).
4. National Center for Cardiovascular Diseases. *Annual Report on Cardiovascular Health and Diseases in China 2019,* 1st edn. Beijing: Science Press (2020).
5. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. (2020) 396:1204–22. doi: 10.1016/S0140-6736(20)30925-9
6. Anderson L, Thompson DR, Oldridge N, Zwisler AD, Rees K, Martin N, et al. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev.* (2016) 2016:CD001800. doi: 10.1002/14651858.CD001800.pub3
7. Anderson L, Oldridge N, Thompson DR, Zwisler AD, Rees K, Martin N, et al. Exercise-based cardiac rehabilitation for coronary heart disease: cochrane systematic review and meta-analysis. *J Am Coll Cardiol.* (2016) 67:1–12. doi: 10.1016/j.jacc.2015.10.044
8. Taylor RS, Brown A, Ebrahim S, Jolliffe J, Noorani H, Rees K, et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *Am J Med.* (2004) 116:682–92. doi: 10.1016/j.amjmed.2004.01.009
9. Davies EJ, Moxham T, Rees K, Singh S, Coats AJ, Ebrahim S, et al. Exercise based rehabilitation for heart failure. *Cochrane Database Syst Rev*. (2010) CD003331. doi: 10.1002/14651858.CD003331.pub3
10. Lawler PR, Filion KB, Eisenberg MJ. Efficacy of exercise-based cardiac rehabilitation post-myocardial infarction: a systematic review and meta-analysis of randomized controlled trials. *Am Heart J.* (2011) 162:571–84.e2. doi: 10.1016/j.ahj.2011.07.017
11. Taylor RS, Walker S, Ciani O, Warren F, Smart NA, Piepoli M, et al. Exercise-based cardiac rehabilitation for chronic heart failure: the EXTRAMATCH II individual participant data meta-analysis. *Health Technol Assess.* (2019) 23:1–98. doi: 10.3310/hta23250
12. Cao RY, Zheng H, Hong Y, Zheng Y, Ding Y, Zhao L, et al. Cardiac rehabilitation with targeted intensity improves cardiopulmonary functions accompanying with reduced copeptin level in patients with coronary artery disease. *J Cardiovasc Transl Res.* (2021) 14:317–26. doi: 10.1007/s12265-020-10055-y
13. Piepoli MF, Corrà U, Benzer W, Bjarnason-Wehrens B, Dendale P, Gaita D, et al. Secondary prevention through cardiac rehabilitation: from knowledge to implementation. A position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation. *Eur J Cardiovasc Prev Rehabil.* (2010) 17:1–17. doi: 10.1097/HJR.0b013e3283313592
14. Leon AS, Franklin BA, Costa F, Balady GJ, Berra KA, Stewart KJ, et al. Cardiac rehabilitation and secondary prevention of coronary heart disease: an American Heart Association (AHA) scientific statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity), in collaboration with the American association of Cardiovascular and Pulmonary Rehabilitation. *Circulation.* (2005) 111:369–76. doi: 10.1161/01.CIR.0000151788.08740.5C
15. Turk-Adawi K, Supervia M, Lopez-Jimenez F, Pesah E, Ding R, Britto RR, et al. Cardiac rehabilitation availability and density around the globe. *E Clin Med.* (2019) 13:31–45. doi: 10.1016/j.gheart.2018.09.026
16. Chen CM, Hu Z, Liu S, Tseng H. Emerging trends in regenerative medicine: a scientometric analysis in CiteSpace. *Expert Opin Biol Ther.* (2012) 12:593–608. doi: 10.1517/14712598.2012.674507

17. Chen CM. Searching for intellectual turning points: progressive knowledge domain visualization. *Proc Natl Acad Sci U S A*. (2004) 101(Suppl 1):5303–10. doi: 10.1073/pnas.0307513100
18. Chen CM. CiteSpace II: detecting and visualizing emerging trends and transient patterns in scientific literature. *J Am Soc Inf Sci Technol.* (2006) 57:359–77. doi: 10.1002/asi.20317
19. Kleinberg J. Bursty and hierarchical structure in streams. In: *Proceedings of the Eighth ACM SIGKDD International Conference on Knowledge Discovery and Data Mining*. New York, NY: Association for Computing Machinery (2002). p. 91–101.
20. Freeman LC. Centrality in social networks: conceptual clarification. *Soc Netw.* (1979) 1:215–39. doi: 10.1016/0378-8733(78)90021-7
21. Ouyang W, Wang Y, Lin C, He M, Hao F, Liu H, et al. Heavy metal loss from agricultural watershed to aquatic system: a scientometrics review. *Sci Total Environ.* (2018) 637–638:208–20. doi: 10.1016/j.scitotenv.2018.04.434
22. Chen CM. *The CiteSpace Manual*. Available online at: http://cluster.ischool.drexel.edu/~cchen/citespace/CiteSpaceManual.pdf (accessed December 20, 2020).
23. Qin Y, Zhang Q, Liu Y. Analysis of knowledge bases and research focuses of cerebral ischemia-reperfusion from the perspective of mapping knowledge domain. *Brain Res Bull.* (2020) 156:15–24. doi: 10.1016/j.brainresbull.2019.12.004
24. Liang YD, Li Y, Zhao J, Wang XY, Zhu HZ, Chen XH. Study of acupuncture for low back pain in recent 20 years: a bibliometric analysis via CiteSpace. *J Pain Res.* (2017) 10:951–64. doi: 10.2147/JPR.S132808
25. Grace SL, Turk-Adawi KI, Contractor A, Atrey A, Campbell N, Derman W, et al. Cardiac rehabilitation delivery model for low-resource settings. *Heart.* (2016) 102:1449–55. doi: 10.1136/heartjnl-2015-309209
26. Grace SL, Turk-Adawi KI, Contractor A, Atrey A, Campbell NR, Derman W, et al. Cardiac rehabilitation delivery model for low-resource settings: an International Council of Cardiovascular Prevention and Rehabilitation Consensus Statement. *Prog Cardiovasc Dis.* (2016) 59:303–22. doi: 10.1016/j.pcad.2016.08.004
27. Grace SL, Poirier P, Norris CM, Oakes GH, Somanader DS, Suskin N, et al. Pan-Canadian development of cardiac rehabilitation and secondary prevention quality indicators. *Can J Cardiol.* (2014) 30:945–8. doi: 10.1016/j.cjca.2014.04.003
28. Grace SL, Tan Y, Oh P, Aggarwal S, Unsworth K, Suskin N. Feasibility of assessing 2 cardiac rehabilitation quality indicators. *J Cardiopulm Rehabil Prev.* (2016) 36:112–6. doi: 10.1097/HCR.0000000000000136
29. Grace SL, Bennett S, Ardern CI, Clark AM. Cardiac rehabilitation series: Canada. *Prog Cardiovasc Dis.* (2014) 56:530–5. doi: 10.1016/j.pcad.2013.09.010
30. Lavie CJ, Arena R, Swift DL, Johannsen NM, Sui X, Lee DC, et al. Exercise and the cardiovascular system: clinical science and cardiovascular outcomes. *Circ Res.* (2015) 117:207–19. doi: 10.1161/CIRCRESAHA.117.305205
31. Lavie CJ, Ozemek C, Arena R. Bringing cardiac rehabilitation and exercise training to a higher level in heart failure. *J Am Coll Cardiol.* (2019) 73:1444–6. doi: 10.1016/j.jacc.2018.12.073
32. Fletcher GF, Landolfo C, Niebauer J, Ozemek C, Arena R, Lavie CJ. Promoting physical activity and exercise: JACC health promotion series. *J Am Coll Cardiol.* (2018) 72:1622–39. doi: 10.1016/j.jacc.2018.08.2141
33. Strieter L, Laddu DR, Sainsbury J, Arena R. The importance of school-based healthy living initiatives: introducing the Health and Wellness Academy Concept. *Prog Cardiovasc Dis.* (2019) 62:68–73. doi: 10.1016/j.pcad.2018.08.005
34. Pudovkin A I, Garfield E. Algorithmic procedure for finding semantically related journals. *J Am Soc Inf Sci Technol.* (2002) 53:1113–19. doi: 10.1002/asi.10153
35. Rafols I, Porter AL, Leydesdorff L. Science overlay maps: a new tool for research policy and library management. *J Am Soc Inf Sci Technol.* (2010) 61:1871–87. doi: 10.1002/asi.21368
36. Balady GJ, Williams MA, Ades PA, Bittner V, Comoss P, Foody JM, et al. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update: a scientific statement from the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical Activity, and Metabolism; and the American Association of Cardiovascular and Pulmonary Rehabilitation. *Circulation.* (2007) 115:2675–82. doi: 10.1161/CIRCULATIONAHA.106.180945
37. Hansen D, Niebauer J, Cornelissen V, Barna O, Neunhäuserer D, Stettler C, et al. Exercise prescription in patients with different combinations of cardiovascular disease risk factors: a consensus statement from the EXPERT Working Group. *Sports Med.* (2018) 48:1781–97. doi: 10.1007/s40279-018-0930-4
38. Tully PJ, Cosh SM, Baumeister H. The anxious heart in whose mind? A systematic review and meta-regression of factors associated with anxiety disorder diagnosis, treatment and morbidity risk in coronary heart disease. *J Psychosom Res.* (2014) 77:439–48. doi: 10.1016/j.jpsychores.2014.10.001
39. Lichtman JH, Froelicher ES, Blumenthal JA, Carney RM, Doering LV, Frasure-Smith N, et al. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: systematic review and recommendations: a scientific statement from the American Heart Association. *Circulation.* (2014) 129:1350–69. doi: 10.1161/CIR.0000000000000019
40. Chauvet-Gelinier JC, Bonin B. Stress, anxiety and depression in heart disease patients: a major challenge for cardiac rehabilitation. *Ann Phys Rehabil Med.* (2017) 60:6–12. doi: 10.1016/j.rehab.2016.09.002
41. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA.* (2020) 323:1061–9. doi: 10.1001/jama.2020.1585
42. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. *JAMA Cardiol.* (2020) 5:831–40. doi: 10.1001/jamacardio.2020.1286
43. Barker-Davies RM, O'Sullivan O, Senaratne KPP, Baker P, Cranley M, Dharm-Datta S, et al. The Stanford Hall consensus statement for post-COVID-19 rehabilitation. *Br J Sports Med.* (2020) 54:949–59. doi: 10.1136/bjsports-2020-102596
44. Cowie A, Buckley J, Doherty P, Furze G, Hayward J, Hinton S, et al. Standards and core components for cardiovascular disease prevention and rehabilitation. *Heart.* (2019) 105:510–5. doi: 10.1136/heartjnl-2018-314206
45. Berghmans DD, Lenssen AF, Bastiaenen CH, Ilhan M, Lencer NH, Roox GM. Reliability, agreement, and responsiveness of a 6-minute walk/run test in patients with heart disease. *Eur J Prev Cardiol.* (2013) 20:135–41. doi: 10.1177/2047487312437038
46. Hanson LC, Taylor NF, McBurney H. The 10m incremental shuttle walk test is a highly reliable field exercise test for patients referred to cardiac rehabilitation: a retest reliability study. *Physiotherapy.* (2016) 102:243–8. doi: 10.1016/j.physio.2015.08.004
47. Small H. Co-citation in the scientific literature: a new measure of the relationship between two documents. *J Am Soc Info Sci.* (1973) 24:265–9 doi: 10.1002/asi.4630240406
48. Marshoakova IV. System of document connections based on references (in Russian). *Nauchn-Techn Inform.* (1973) 2:3–8.
49. Thompson PD, Buchner D, Pina IL, Balady GJ, Williams MA, Marcus BH, et al. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). *Circulation.* (2003) 107:3109–16. doi: 10.1161/01.CIR.0000075572.40158.77
50. Suaya JA, Shepard DS, Normand SL, Ades PA, Prottas J, Stason WB. Use of cardiac rehabilitation by Medicare beneficiaries after myocardial infarction or coronary bypass surgery. *Circulation.* (2007) 116:1653–62. doi: 10.1161/CIRCULATIONAHA.107.701466
51. Rees K, Taylor RS, Singh S, Coats AJ, Ebrahim S. Exercise based rehabilitation for heart failure. *Cochrane Database Syst Rev*. (2004) CD003331. doi: 10.1002/14651858.CD003331.pub2
52. Dendale P, Berger J, Hansen D, Vaes J, Benit E, Weymans M. Cardiac rehabilitation reduces the rate of major adverse cardiac events after percutaneous coronary intervention. *Eur J Cardiovasc Nurs.* (2005) 4:113–6. doi: 10.1016/j.ejcnurse.2004.11.003
53. Shen BJ, McCreary CP, Myers HF. Independent and mediated contributions of personality, coping, social support, and depressive symptoms to physical functioning outcome among patients in cardiac rehabilitation. *J Behav Med.* (2004) 27:39–62. doi: 10.1023/B:JOBM.0000013643.36767.22

54. Karmali KN, Davies P, Taylor F, Beswick A, Martin N, Ebrahim S. Promoting patient uptake and adherence in cardiac rehabilitation. *Cochrane Database Syst Rev*. (2014) CD007131. doi: 10.1002/14651858.CD007131.pub3
55. Anderson L, Brown JP, Clark AM, Dalal H, Rossau HK, Bridges C, et al. Patient education in the management of coronary heart disease. *Cochrane Database Syst Rev*. (2017) 6:CD008895. doi: 10.1002/14651858.CD008895.pub3
56. MacKinnon GE, Brittain EL. Mobile health technologies in cardiopulmonary disease. *Chest*. (2020) 157:654–64. doi: 10.1016/j.chest.2019.10.015
57. Bostrom J, Sweeney G, Whiteson J, Dodson JA. Mobile health and cardiac rehabilitation in older adults. *Clin Cardiol*. (2020) 43:118–26. doi: 10.1002/clc.23306
58. Piepoli MF, Corrà U, Adamopoulos S, Benzer W, Bjarnason-Wehrens B, Cupples M, et al. Secondary prevention in the clinical management of patients with cardiovascular diseases. Core components, standards and outcome measures for referral and delivery: a policy statement from the cardiac rehabilitation section of the European Association for Cardiovascular Prevention & Rehabilitation. Endorsed by the Committee for Practice Guidelines of the European Society of Cardiology. *Eur J Prev Cardiol*. (2014) 21:664–81. doi: 10.1177/2047487312449597
59. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. (2016) 37:2315–81. doi: 10.1093/eurheartj/ehw106
60. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis treatment of acute chronic heart failure: The Task Force for the diagnosis treatment of acute chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. (2016). 37:2129–200. doi: 10.1093/eurheartj/ehw128
61. Varnfield M, Karunanithi M, Lee CK, Honeyman E, Arnold D, Ding H, et al. Smartphone-based home care model improved use of cardiac rehabilitation in postmyocardial infarction patients: results from a randomised controlled trial. *Heart*. (2014) 100:1770–9. doi: 10.1136/heartjnl-2014-305783
62. Kotseva K, Wood D, De Bacquer D, De Backer G, Rydén L, Jennings C, et al. EUROASPIRE IV: a European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. *Eur J Prev Cardiol*. (2016) 23:636–48. doi: 10.1177/2047487315569401

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 04 June 2021
doi: 10.3389/fcvm.2021.680098

Impacts of Heart Failure and Physical Performance on Long-Term Mortality in Old Patients With Chronic Kidney Disease

Shuo-Chun Weng[1,2], *Yu-Chi Chen*[3], *Chiann-Yi Hsu*[4], *Chu-Sheng Lin*[5], *Der-Cherng Tarng*[1,6,7,8] *and Shih-Yi Lin*[1,9]*

[1] *Institute of Clinical Medicine, School of Medicine, College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan,* [2] *Division of Nephrology, Department of Internal Medicine, Center for Geriatrics and Gerontology, Taichung Veterans General Hospital, Taichung, Taiwan,* [3] *Institute of Clinical Nursing, College of Nursing, National Yang Ming Chiao Tung University, Taipei, Taiwan,* [4] *Biostatistics Task Force of Taichung Veterans General Hospital, Taichung, Taiwan,* [5] *Department of Family Medicine, Center for Geriatrics and Gerontology, Taichung Veterans General Hospital, Taichung, Taiwan,* [6] *Department and Institute of Physiology, National Yang Ming Chiao Tung University, Taipei, Taiwan,* [7] *Division of Nephrology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan,* [8] *Department of Biological Science and Technology, Center for Intelligent Drug Systems and Smart Bio-Devices (IDS2B), College of Biological Science and Technology, National Yang Ming Chiao Tung, Hsinchu, Taiwan,* [9] *Division of Endocrinology and Metabolism, Department of Internal Medicine, Center for Geriatrics and Gerontology, Taichung Veterans General Hospital, Taichung, Taiwan*

OPEN ACCESS

Edited by:
Sebastian Kelle,
Deutsches Herzzentrum Berlin, Germany

Reviewed by:
Lígia Mendes,
Hospital da Luz Setúbal, Portugal
Djawid Hashemi,
Charité–Universitätsmedizin Berlin, Germany

***Correspondence:**
Shih-Yi Lin
sylin@vghtc.gov.tw

Specialty section:
This article was submitted to General Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

Received: *13 March 2021*
Accepted: *27 April 2021*
Published: *04 June 2021*

Citation:
Weng S-C, Chen Y-C, Hsu C-Y, Lin C-S, Tarng D-C and Lin S-Y (2021) Impacts of Heart Failure and Physical Performance on Long-Term Mortality in Old Patients With Chronic Kidney Disease. Front. Cardiovasc. Med. 8:680098. doi: 10.3389/fcvm.2021.680098

Background: In patients with chronic kidney disease (CKD), physical functional limitations and heart failure (HF) are common, and each is associated with adverse outcomes. However, their joint effects on mortality are not clear.

Design and Methods: Using administration data from the geriatric department in a tertiary hospital, retrospective longitudinal analyses of patients aged ≥65 years with CKD were consecutively enrolled from February 2010 to November 2015. Baseline CKD stages, HF with reduced and preserved ejection fraction (HFrEF and HFpEF), Rockwood frailty index, handgrip strength (HGS), 6-m walking speed, and timed up-and-go test were used to predict the prevalence of frailty, physical disability, and all-cause mortality.

Results: Among 331 old patients with CKD, their mean age was 81.3 ± 6.6 years. CKD stages showed the following distributions: stage 3, 74.9%; stage 4, 15.7%; stage 5, 9.4%. The prevalence of HF was 23.3%, and Rockwood frailty was 74.3%. Rockwood frailty and HF were both significantly associated with CKD stages. After a mean follow-up period of 3.1 ± 2.1 years, 44 patients died, and a crude analysis showed that stage 4, stage 5 CKD, low HGS, and Rockwood frailty index were associated with mortality. Regarding the survival of these patients, the adjusted mortality hazard ratio for CKD stage 5 was 3.84 against stage 3A [95% confidence interval (CI) 1.51–9.75], 1.04 (95% CI 1.01–1.07) for higher Rockwood frailty score, 4.78 (95% CI 1.26–18.11) for HFrEF, and 3.47 (95% CI 1.15–10.42) for low HGS. Survival analysis using Kaplan–Meier survival plots showed that patients with both HF and poor HGS had the poorest survival.

Conclusions: Our study shows that both low physical performance and HF were common in old CKD patients and were associated with CKD stages. HF, frailty, and HGS all independently predicted the mortality of these CKD patients. The mortality is especially high amongst individuals with both HF and decreased HGS.

Keywords: comprehensive geriatric assessment, ejection fraction, handgrip strength, mortality, physical functionality, timed up-and-go test

INTRODUCTION

Chronic kidney disease (CKD) is a public health problem worldwide, especially in older populations. CKD has prevalence ranging from 23.4 to 35.8% based on a systematic review of population-based studies (1). The National Health and Nutrition Examination Survey (NHANES 2007–2012) reported a CKD prevalence of 33.2% for those aged ≥60 years (2). Individuals with CKD have a mortality rate double that of the general population, and more than half of the deaths in these patients are from cardiovascular disease (CVD). CVD in CKD patients includes the following: coronary artery disease (CAD), acute myocardial infarction (MI), heart failure (HF), valvular heart disease, cerebrovascular accidents (CVA), peripheral artery disease (PAD), thromboembolic disease, and sudden cardiac death with HF being the leading cause (3). The study on Atherosclerosis Risk in Communities (ARIC) reports a threefold higher risk of incident HF in those with estimated glomerular filtration rate (eGFR) <60 mL/1.73m^2/min compared with those with eGFR >90 mL/min/1.73m^2. Both the prevalence and incidence of HF also increase with the severity of CKD. CKD patients develop HF with reduced (HFrEF) and preserved ejection fraction (HFpEF), but HFpEF is more common (4, 5).

It has been proposed that there is close interdependence between CKD and chronic HF (CHF), and their common pathophysiologic pathways can lead to function deterioration and lower life expectancy (6, 7). Our previous study reports that low eGFR is potentially and highly capable of distinguishing between deaths in all patients and deaths in HF patients (8). Based on the close relationship between CHF and CKD, individualized treatments for patients with chronic systolic HF are applied according to different stages of CKD (6). In addition to HF, CKD also has a negative impact on physical functions and frailty. Dalrymple et al. report a 24% prevalent frailty in those patients with eGFR <45 mL/1.73 m^2/min (9). In dialysis-dependent CKD patients, the frailty prevalence is >60%, which is independently linked with adverse clinical outcomes, including mortality and repetitive hospitalization for all stages of CKD (9).

Comprehensive geriatric assessment (CGA), a multidimensional diagnostic tool for determining the medical, psychological, and functional capabilities in the frail population, can predict prognosis for hospitalized old patients with HF (10). Apart from these, walking speed (WS) (11) and the timed up-and-go (TUG) test, the other two indicators for frailty, are associated with quality of life and progress of NYHA functional class in patients with congestive HF (12). Only a few studies have yet investigated the joint effects of physical disability and HF on outcomes in old patients with CKD (13).

Given the close relationship and adverse outcomes of CHF and frailty in CKD, a better understanding of their individual and combined impacts is important for planning interventions to improve prognosis and reduce healthcare costs. In our present study on old patients with CKD, we aimed to use CGA to evaluate the prevalence of frailty and determine the independent and composite prognostic effects of physical functions, HFpEF, and HFrEF on all-cause mortality in old patients with CKD.

MATERIALS AND METHODS

Study Participants

Our study was conducted in a medical center Taichung Veterans General Hospital (TCVGH), between February 2, 2010, and November 26, 2015, based on the records of the case management care system of the Hospital's Center for Geriatrics and Gerontology. The study was approved by the institutional review board of TCVGH (No.CF20293). Participating patients were eligible if they had visited the inpatient and outpatient clinics of the geriatric department. The inclusion criteria were age ≥65 years, without complicated neurologic disorders, with a diagnosis of CKD with or without HF. After enrollment, medical history, including basic personal information (age, gender, history of chronic illness, education, and source of referral) was recorded.

Diagnosis of HF and CKD

CHF was defined by the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes (428.0-428.9, 402.91). Besides this, a 2-D echocardiogram (ECHO) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were obtained to diagnose and differentiate HFpEF and HFrEF under a standard protocol (ASE or EACVI protocol) (14–16). By 2-D ECHO, LVEF ≥ 50% was defined as HFpEF and <50% as HFrEF according to the American College of Cardiology Foundation/American Heart Association guideline (17). Other codes for relevant diseases were atrial fibrillation (AF) 427.31, cardiac arrhythmia 427.0–427.9, and CKD 585.XX.

CKD patients were confirmed by the following criteria: eGFR <60 ml/1.73m^2/min, urine albumin/creatinine ratio (ACR) >30 mg/g (18), urine protein/creatinine (PC) ratio >0.2 mg/g (19), or showing abnormal kidney images. Concomitant medication data associated with HF were extracted according to the anatomic therapeutic chemical (ATC) codes. Comorbid conditions were measured using the Charlson comorbidity index (CCI), which includes 19 chronic diseases weighted based on their associations with mortality (20) but with some modifications as neither HF nor CKD are considered within the CCI (10). Finally, clinical

records were selected for the 331 enrolled patients concurrent with 2-D ECHO examinations (254 non-HF and 77 HF patients with 45 HFpEF and 32 HFrEF) and CKD (147 stage 3A, 101 stage 3B, 52 stage 4, and 31 stage 5 CKD patients).

CGA and Evaluation of Physical Functionality

Trained research nurses administered a CGA with standardized measures, of which the components were previously described (21), including the mini-nutritional assessment (MNA) used to identify old adults at risk for malnutrition (22). HGS was measured by a dynamometer (Smedley's Dynamometer, TTM, Tokyo, Japan), and slowness was measured by the 6-m WS (6MW). For the TUG test, participants were to stand up from a 46-cm-high armchair with back support, walk in a straight line for 3 m, turn around, walk back to the chair, and sit down as quickly and safely as possible (23). The timing started when the investigator said "go" and stopped when the participant sat back down on the chair. Arbitrary cutoff points instead of traditional values were used to define frailty parameters, including TUG, HGS, and 6MW (8, 24). TUG values were separated into quartiles, and the Chi-square test was used to determine the appropriateness of 24 s. The HGS values were divided into tertiles, and the cutoff point was 20.4 kg for men and 15.435 kg for women. Values of 6MW were calculated as deciles with a cutoff point of 22 s for men and 30 s for women.

Frailty Index

Frailty was defined according to the Asia-Pacific clinical practice guideline (24). A modified Rockwood frailty index (25) was used to measure frailty by utilizing health deficits collected in health assessments, including 11 chronic diseases, four items (MNA-SF, TUG, HGS, 6MW) of CGA, and five abnormal laboratory data. Categories were generated according to established cutoffs in community-dwelling cohorts to match the Fried physical phenotype: non-frail (0–0.1), pre-frail (>0.1–0.21), and frail (>0.21) (26, 27).

Study Outcome and Follow-Up

The index date was the date of HF and CKD diagnosis. CGA and 2-D ECHO were completed around the time of HF diagnosis. The patient outcome was all-cause mortality obtained from the Clinical Information Research and Development Center, TCVGH, and the accuracy of death was validated by Taiwan's National Death Registry according to the ICD-9 (ICD9 001.x-999.x) or ICD10 (A00.x-Z99.x). All participants were followed up until death or June 19, 2018, to prevent lead-time bias.

Statistical Analyses

For continuous variables, we used the Kolmogorov–Smirnov test to test the normality of sample distributions. Continuous variables were analyzed by the Kruskal–Wallis (more than a dichotomy) and Mann–Whitney *U* (dichotomy) tests, generating the median and interquartile range (IQR). Categorical variables, expressed as percentages, were tested by chi-square or Fisher's exact test. All-cause mortality was delineated based on previously defined high or low functioning status, the severity of HF, and stages of CKD. Then, Cox proportional hazard models were finally applied in the multivariate analyses to estimate the hazard ratios of study outcomes after adjusting for age and gender. To determine cumulative effects of HF with preserved or reduced EF, Rockwood frailty, and physical functionality (HGS, TUG, 6MW) on survival, they were stratified into subgroups according to the cutoff values (8). Kaplan–Meier (KM) plots were generated to estimate the cumulative survival rate in different subgroups by log rank (Mantel–Cox) and pairwise comparison to judge which entity displayed significance; *p*-values for non-linearity were calculated using the null hypothesis test. Statistical significance was set at $p < 0.05$. Statistical analyses were performed with the SPSS for Windows version 22.0 (SPSS Institute Inc., Chicago, USA).

RESULTS

Clinical Characteristics of Patients

The mean age of the 331 CKD patients was 81.3 ± 6.6 years with a mean follow-up period of 3.1 ± 2.1 years. The percentage of CKD stage 3, 4, or 5 was 74.9, 15.7, or 9.4%, respectively. Among them, patients from CKD stage 3A to 5 had similar distributions for the following: gender, body mass index (BMI), CCI, LVEF, cardiac arrhythmia, β-blocker, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blockers (ARB), and digoxin except for distribution of age, HF, HFpEF, HFrEF, NT-proBNP, low-density lipoprotein (LDL), albumin, glycated hemoglobin (Hba1c), eGFR, proteinuria, mineralocorticoid receptor antagonist (MRA), and anticoagulants (**Table 1**).

Frailty and Physical Performance in CKD Patients

The Rockwood frailty assessment showed 74.3% of CKD patients were frail. Compared with patients of CKD stages 3A and 3B, CKD patients with stages 4 and 5 showed lower scores of MNA-short form (MNA-SF) but higher scores on the Rockwood index and showed no differences with the TUG and HGS. The Rockwood frailty index was significantly associated with CKD stages (**Table 2**).

Heart Failure, HFpEF, and HFrEF in the CKD Patients

In all these patients, the prevalence of HF, HFpEF, and HFrEF were 23.3, 13.6, and 9.7%, respectively. Compared with non-HF patients, HF patients in the CKD cohort had higher percentages in the following: CVD, AF, MI, cardiac arrhythmia, lower LVEF, and lower eGFR (data not shown). Patients with HF and CKD had significantly high Rockwood frailty scores ($p < 0.001$) but a marginally higher percentage of longer TUG test with cutoff ≥24 s ($p = 0.065$).

Due to possibly mixing HFpEF and HFrEF in a mutual effect on the endpoints, we differentiated between these two entities (**Table 3**). In the geriatric assessment, lower HGS and longer TUG time were observed in the CKD patients with HFrEF although of no statistical significance. The Rockwood frailty

TABLE 1 | Baseline characteristics of older patients with different staging of CKD.

Characteristics	CKD stage 3A ($n = 147$)	CKD stage 3B ($n = 101$)	CKD stage 4 ($n = 52$)	CKD stage 5 ($n = 31$)	*p*-value
Age, years	83.1 (77.1–86.3)	81.8 (76.0–86.7)	83.2 (79.0–87.1)	78.8 (73.3–83.6)	0.043
Male	101 (68.7)	71 (70.3)	39 (75.0)	21 (67.7)	0.846
BMI, kg/m^2	24.6 (22.6–27.3)	24.5 (22.1–28.2)	24.0 (21.8–27.0)	23.8 (21.2–26.1)	0.275
Heart condition					0.001
Non–heart failure	119 (81.0)	84 (83.2)	36 (69.2)	15 (48.4)	
HFpEF	15 (10.2)	12 (11.9)	10 (19.2)	8 (25.8)	
HFrEF	13 (8.8)	5 (4.9)	6 (11.5)	8 (25.8)	
Atrial fibrillation	6 (4.1)	2 (2.0)	3 (5.8)	4 (12.9)	0.080
CCI	2.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	2.0 (1.0–3.5)	0.747
LVEF	59.0 (54.0–60.0)	58.0 (55.5–62.0)	56.5 (52.0–61.8)	59.0 (49.8–60.3)	0.742
Cardiac arrhythmia	10 (6.8)	6 (5.9)	4 (7.7)	6 (19.4)	0.094
Laboratory data					
NT-proBNP, pg/mL	670.6 (366.0–4,119.0)	1,780.0 (337.2–3,925.5)	3,495.0 (1,162.0–16,312.5)	9,150.0 (1,610.0–33,050.0)	0.001
LDL, mg/dL	98.0 (82.0–121.0)	103.5 (81.3–119.0)	87.0 (73.0–108.0)	79.5 (58.0–121.8)	0.037
Albumin, g/dL	4.0 (3.7–4.3)	3.9 (3.3–4.2)	3.8 (3.5–4.1)	3.6 (3.0–3.9)	0.001
Hba1c, %	6.1 (5.7–7.0)	6.3 (5.8–7.0)	6.2 (5.6–7.4)	5.6 (5.2–6.5)	0.010
Medications					
Diuretics	108 (73.5)	72 (71.3)	47 (90.4)	24 (77.4)	0.054
MRA	31 (21.1)	16 (15.8)	18 (34.6)	15 (48.4)	0.001
β-blocker	88 (59.9)	60 (59.4)	41 (78.9)	20 (64.5)	0.078
ACEI or ARB	110 (74.8)	77 (76.2)	43 (82.7)	19 (61.3)	0.183
Anti-platelet agents	95 (64.6)	66 (65.4)	44 (84.6)	21 (67.7)	0.052
Anti-coagulants	24 (16.3)	13 (12.9)	19 (36.5)	6 (19.4)	0.003
Digoxin	17 (11.6)	11 (10.9)	10 (19.2)	7 (22.6)	0.197

Continuous data were expressed as median (IQR) and analyzed by the Kruskal–Wallis test. Categorical data were expressed as number and percentage and analyzed by the Chi-Square test. CKD, chronic kidney disease; BMI, body mass index; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; CCI, Charlson Comorbidity Index; IQR, interquartile range; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LDL, low-density lipoprotein; Hba1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; eGFR, calculated by using modified Modification diet of renal disease (MDRD) formula, was utilized to evaluate renal function.

TABLE 2 | Baseline physical functionality in older patients with CKD.

Characteristics	CKD stage 3A ($n = 147$)	CKD stage 3B ($n = 101$)	CKD stage 4 ($n = 52$)	CKD stage 5 ($n = 31$)	*p*-value
MNA-SF (0–14)	13.0 (11.0–14.0)	13.0 (12.0–14.0)	12.5 (10.3–14.0)	12.0 (9.0–14.0)	0.025
Timed up-and-go test, sec	17.0 (13.0–24.0)	18.0 (13.0–24.0)	20.0 (15.3–26.0)	16.0 (13.0–24.0)	0.339
TUG, s ≥24	39 (26.5)	27 (26.7)	17 (32.7)	8 (25.8)	0.838
Handgrip strength, kg	21.5 (14.5–25.2)	18.0 (14.1–24.5)	21.8 (18.6–25.5)	17.7 (14.5–24.9)	0.622
HGS, kg					0.461
F ≤15.435/M ≤20.4	59 (40.1)	55 (54.5)	22 (42.3)	17 (54.8)	
Rockwood frailty index	26.7 (17.7–35.3)	29.4 (21.1–34.3)	29.7 (23.2–41.2)	36.8 (23.5–47.1)	0.003
Non-frail	9 (6.1)	4 (4.0)	1 (1.9)	3 (9.7)	0.233
Pre-frail	36 (24.5)	20 (19.8)	10 (19.2)	2 (6.5)	
Frail	102 (69.4)	77 (76.2)	41 (78.8)	26 (83.9)	

Continuous data were expressed as median (IQR) and analyzed by the Kruskal–Wallis test. Categorical data were expressed as number and percentage and analyzed by the Chi-Square test. CKD, chronic kidney disease; MNA-SF, mini-nutritional assessment-short form; TUG, Timed Up-and-Go test; HGS, handgrip strength.

index scores were significantly increased in the CKD patients with HFrEF.

Predictors of Survival in Patients With CKD

In terms of baseline characteristics of CKD survivors and non-survivors, non-survivors had a relatively longer TUG, significantly poorer HGS, and significantly higher Rockwood frailty scores [median (quartiles) = 34.3 (25.0–43.9) vs. 27.8 (18.8–35.3); **Table 4**]. In addition, non-survivors in CKD patients also had lower levels of serum LDL, albumin, and eGFR. More of them also received medications of diuretics, MRA, β-blocker, and digoxin (**Table 4**). When those patients were grouped into

TABLE 3 | Comprehensive geriatric assessment in older CKD patients with and without heart failure.

Characteristics	Non-heart failure ($n = 254$)	HFpEF ($n = 45$)	HFrEF ($n = 32$)	p-value
Age, years	82.8 (76.4–86.5)	81.2 (77.2–85.6)	82.4 (76.5–86.9)	0.980
Male	174 (68.5)	34 (75.6)	24 (75.0)	0.518
BMI	24.3 (22.0–27.2)	24.3 (22.8–26.6)	24.5 (22.1–28.8)	0.533
CCI	1.0 (1.0–2.0)	2.0 (1.0–2.5)	2.0 (1.0–2.3)	0.641
LVEF	60.0 (56.0–62.0)	59.0 (56.3–60.8)	42.0 (31.0–49.0)	<0.001
Cardiac arrhythmia	12 (4.7)	10 (22.2)	4 (12.5)	<0.001
Atrial fibrillation	3 (1.2)	9 (20.0)	3 (9.4)	<0.001
Geriatric assessment				
MNA-SF (0–14)	13.0 (11.0–14.0)	13.0 (12.0–14.0)	12.5 (10.0–13.0)	0.053
Timed up-and-go test, sec	18.0 (13.8–23.3)	17.0 (12.0–27.5)	18.5 (15.3–29.5)	0.126
Timed up-and-go test ≥24, s	63 (24.8)	15 (33.3)	13 (40.6)	0.108
Handgrip strength, kg	20.5 (14.2–25.0)	23.0 (15.3–27.3)	17.1 (14.3–19.2)	0.332
Handgrip strength, kg				
F ≤15.435/M ≤20.4	110 (43.3)	20 (44.4)	28 (87.5)	0.054
Rockwood frailty index	25.0 (17.4–33.3)	41.2 (33.3–47.2)	42.1 (33.3–50.0)	<0.001
Non-frail	17 (6.7)	0 (0.0)	0 (0.0)	<0.001
Pre-frail	68 (26.8)	0 (0.0)	0 (0.0)	
Frail	169 (66.5)	45 (100.0)	32 (100.0)	

Continuous data were expressed as median (IQR) and analyzed by the Mann–Whitney U-test. Categorical data were expressed as number and percentage and analyzed by the Chi-Square test. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; CCI, Charlson Comorbidity Index; LVEF, left ventricular ejection fraction; MNA-SF, mini-nutritional assessment-short form.

the combined HF and frailty status, 77 were HF and frail, none was HF and non-frail, 169 were non-HF and frail, and 85 were non-HF and non-frail (**Table 4**). During the follow-up period [median (quartiles) = 3.1 (1.1 to 4.7) years], a univariate Cox regression model (**Table 5**) showed that in CKD stages 4 and 5 compared with stage 3A, the continuous and discrete values of HGS were significantly associated with all-cause mortality. In the multivariate Cox proportional hazards model, poor HGS [model 1, **Table 5**, adjusted hazard ratio (aHR) = 0.91, 95% CI 0.84–0.99] and HFrEF (aHR = 4.78, 95% CI 1.26–18.11) were significantly associated with all-cause mortality after adjusting for age/gender, a heart condition, and different stages of CKD. When HGS was divided into categorized values (model 2, **Table 5**), those with low HGS (female ≤ 15.435 kg / male ≤ 20.4 kg) had a significant risk for all-cause death (aHR = 3.47, 95% CI 1.15–10.42). Patients of CKD stage 5, when compared with stage 3A (aHR = 3.84, 95% CI 1.51–9.75) and high Rockwood frailty score (aHR = 1.04, 95% CI 1.01–1.07), were associated with high patient mortality (model 3, **Table 5**). When patients were stratified into subgroups with and without HF and Rockwood frailty and abnormal physical functionality (HGS, TUG, 6MW), it was shown that HF patients associated with decreased HGS had the poorest survival, followed by non-HF patients with decreased HGS, HF with fair HGS, and non-HF patients with fair HGS, respectively ($p = 0.018$; **Figure 1**). However, there were no additive effects between HF and frailty, TUG, or 6MW on survival (**Supplementary Figures 1A–C**).

Survival Curves in the Subgroup Analyses Among HFpEF, HFrEF, and Different Levels of HGS, TUG, and 6MW in Patients With CKD

The KM survival curves showed no difference between HFpEF and HFrEF ($p = 0.718$) in the follow-up period (**Figure 2A**). In addition, there were also no composite effects of HFpEF and HFrEF with fair or poor HGS ($p = 0.365$; **Figure 2B**), short or long TUG (**Supplementary Figure 2A**), and 6MW (**Supplementary Figure 2B**) in old patients with CKD.

DISCUSSION

The principal findings on this retrospective cohort of old patients with CKD are their probably high prevalence of HF, impaired physical performance, and frailty, and mortality is significantly associated with low HGS, high Rockwood frailty score, and HF with reduced LVEF. The mortality is especially high among individuals with both HF and poor HGS.

In our study, we found that HGS was directly associated with survival in CKD patients, which was compatible with a previous study demonstrating that HGS is an independent predictor of composite renal outcomes in non-dialysis-dependent CKD (CKD-ND) patients (28). HGS, an indicator of frailty, has been used to approximate overall muscle function, particularly in patients with impaired tolerance of physical exertion and in hospitalized, deconditioned patients (29). Several potential

TABLE 4 | Comparison between survivors and non-survivors in older patients with CKD.

	Alive ($n = 287$)	Death ($n = 44$)	*p*-value
Age, years	82.6 (76.3–86.2)	83.4 (78.5–87.1)	0.250
Male	201 (70.0)	31 (70.5)	1.000
CKD			0.005
Stage 3A	135 (47.0)	12 (27.3)	
Stage 3B	89 (31.0)	12 (27.3)	
Stage 4	41 (14.3)	11 (25.0)	
Stage 5	22 (7.7)	9 (20.5)	
BMI, kg/m^2	24.3 (22.2–27.3)	24.5 (21.2–26.8)	0.504
CCI	1.0 (1.0–2.0)	1.5 (1.0–3.0)	0.242
Atrial fibrillation	10 (3.5)	5 (11.4)	0.052
Heart condition			0.525
Non-HF	223 (77.7)	31 (70.5)	
HFpEF	38 (13.2)	7 (15.9)	
HFrEF	26 (9.1)	6 (13.6)	
LVEF	58.0 (54.0–61.0)	58.0 (54.0–60.0)	0.455
Geriatric assessment			
MNA-SF (0–14)	13.0 (11.0–14.0)	13.0 (11.0–14.0)	0.807
Timed up-and-go test, sec	17.0 (13.0–24.0)	20.0 (15.3–28.8)	0.080
TUG, s ≥24	76 (26.5)	15 (34.1)	0.383
Handgrip strength, kg	21.2 (14.4–25.6)	17.7 (14.2–20.7)	0.102
HGS, kg			0.034
F ≤15.435/M ≤20.4	53 (42.4)	13 (72.2)	
Rockwood frailty index	27.8 (18.8–35.3)	34.3 (25.0–43.9)	0.002
Non-frail	17 (5.9)	0 (0.0)	0.092
Pre-frail	62 (21.6)	6 (13.6)	
Frail	208 (72.5)	38 (86.4)	
Group*			0.132
Non-HF & non-frail	79 (27.5)	6 (13.6)	
Non-HF & frail	144 (50.2)	25 (56.8)	
HF & frail	64 (22.3)	13 (29.5)	
Laboratory data			
NT-proBNP, pg/mL	1,897.5 (643.0–8,712.8)	2,735.0 (786.8–11,662.5)	0.405
LDL, mg/dL	97.0 (80.0–120.0)	85.0 (68.0–106.0)	0.017
Albumin, g/dL	4.0 (3.5–4.2)	3.5 (3.1–3.8)	<0.001
Hba1c, %	6.2 (5.7–7.0)	6.2 (5.5–7.0)	0.429
eGFR, ml/min per 1.73 m^2	44.2 (32.5–52.4)	32.9 (17.7–45.4)	<0.001
Proteinuria, mg/g	0.17 (0.10–0.42)	0.15 (0.07–0.39)	0.271
Medications			
Diuretics	208 (72.5)	43 (97.7)	0.001
MRA	61 (21.3)	19 (43.2)	0.003
β-blocker	173 (60.3)	36 (81.8)	0.010
ACEI or ARB	213 (74.2)	36 (81.8)	0.368
Anti-platelet agents	196 (68.3)	30 (68.2)	1.000
Anti-coagulants	49 (17.1)	13 (29.5)	0.077
Digoxin	32 (11.1)	13 (29.5)	0.002

** Frailty and non-frail older patients were classified according to the Rockwood frailty index. Continuous data were expressed as median (IQR) and analyzed by the Mann–Whitney U-test. Categorical data were expressed as number and percentage and analyzed by the Chi-Square test. CKD, chronic kidney disease; HF, heart failure; BMI, body mass index; CCI, Charlson Comorbidity Index; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MNA-SF, mini-nutritional assessment-short form; TUG, Timed Up-and-Go test; HGS, handgrip strength; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LDL, low density lipoprotein; Hba1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; eGFR, calculated by using modified Modification diet of renal disease (MDRD) formula, was utilized to evaluate renal function.*

TABLE 5 | Predictors of all-cause mortality in older CKD adults.

	Univariate model	Model 1	Model 2	Model 3
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age	1.01 (0.96–1.06)	1.06 (0.96–1.17)	1.06 (0.96–1.17)	1.02 (0.97–1.08)
Male vs. Female	0.88 (0.46–1.69)	1.15 (0.28–4.77)	0.87 (0.21–3.50)	0.71 (0.35–1.42)
Heart failure	1.42 (0.74–2.72)			
Non-HF	Ref. –	Ref. –	Ref. –	Ref. –
HFpEF	1.28 (0.56–2.91)	1.48 (0.31–7.00)	1.27 (0.26–6.09)	0.54 (0.21–1.41)
HFrEF	1.63 (0.68–3.92)	4.78 (1.26–18.11)*	3.66 (0.92–14.51)	0.56 (0.19–1.67)
CKD				
Stage 3A	Ref. –	Ref. –	ref. –	Ref. –
Stage 3B	1.53 (0.68–3.40)	1.17 (0.39–3.47)	0.95 (0.32–2.85)	1.35 (0.60–3.03)
Stage 4	2.63 (1.16–5.96)*	1.46 (0.36–5.91)	1.06 (0.27–4.27)	2.03 (0.87–4.73)
Stage 5	4.22 (1.77–10.03)**	0.94 (0.11–8.20)	0.87 (0.10–7.69)	3.84 (1.51–9.75)**
CCI	1.17 (0.95–1.43)			
Geriatric assessment				
MNA-SF	0.92 (0.81–1.05)			
TUG, s	1.01 (0.99–1.04)			
TUG ≥24, s	1.60 (0.86–2.99)			
HGS, kg	0.92 (0.86–0.99)*	0.91 (0.84–0.99)*		
HGS, kg				
F >15.435/M >20.4	ref. –		ref. –	
F ≤15.435/M ≤20.4	4.01 (1.42–11.34)**		3.47 (1.15–10.42)*	
Rockwood frailty index	1.04 (1.02–1.06)**			1.04 (1.01–1.07)**

*$p < 0.05$; **$p < 0.001$; *Model 1: The Cox proportional hazards model was used to evaluate the association of all-cause mortality with multivariate analysis among different stages of chronic kidney disease (CKD), the severity of heart failure (HF), and continuous levels of handgrip strength (HGS) in older adults. Model 2: The Cox proportional hazards model was used to evaluate the association of all-cause mortality with multivariate analysis among different stages of CKD, the severity of HF, and categorized HGS in older adults. Model 3: The Cox proportional hazards model was used to evaluate the association of all-cause mortality with multivariate analysis among different stages of CKD, the severity of HF, and Rockwood frailty index in older adults. All multivariate analysis was adjusted for age and gender. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; CCI, Charlson Comorbidity Index; MNA-SF, mini-nutritional assessment-short form; TUG, Timed Up-and-Go test; HGS, handgrip strength.*

mechanisms were speculated to explain the association between low HGS and poor outcomes in CKD patients. Lower HGS may represent underlying chronic systemic inflammation that may worsen patient outcomes by aggravating CVD and arterial stiffness and increasing susceptibility to infection (30). Besides this, the inflammation may be in association with acidosis, vitamin D deficiency, and uremic toxins, which decreased insulin sensitivity, leading to subsequent muscle wasting (30). Further studies are needed to elucidate the exact mechanisms linking HGS and outcome in CKD.

The findings of lower serum albumin and LDL values were both significantly associated with patient outcomes in patients with CKD_{1-5} or CKD_{3b-5} in univariate analyses. A previous study reports that a serum albumin level <3.7 g/dL was independently associated with poor composite renal outcomes (predialysis mortality and end-stage renal disease) in patients with CKD-ND (31). As serum albumin is highly influenced by inflammatory status, it is possible that the predictability of low serum albumin levels reflected more prevalent comorbidities or acute illnesses. Observational studies among apparently healthy individuals or patients with pre-existing CVD have repeatedly demonstrated a roughly linear relationship between serum total and LDL-cholesterol (LDL-C) and risk of death from CVD (32). Among patients with CKD, however, this relationship is much less obvious. Low total and LDL-C levels were also associated with higher mortality in patients with moderate to advanced stages of CKD, who were not yet on dialysis (33). The inverse association between low total and LDL-C levels and mortality may be explained in part by the presence of the so-called malnutrition–inflammation syndrome (32). It is suggested that decision to initiate statin treatment in patients with CKD should focus on the underlying cardiovascular risk and malnutrition-inflammation status, not just the lipid profile.

In our study, it was shown that there was no difference in HF and NT-proBNP between the group's death rates, but there was a significant difference concerning the use of diuretics, mineralocorticoid receptor antagonist (MRA), and digoxin. In addition, death risk was increased in patients with advanced CKD associated with HFrEF, which was in line with previous studies, indicating that concurrent renal disease and HF are directly related to a worse prognosis. Because of the finding that there were higher mortality risks among MRA, diuretics, and digoxin in our study, death was similar to some previous study reports (34–36) and probably attributable to several reasons. MRA (e.g., Spironolactone) in conjunction with ACEI and ARB may increase the risk of hyperkalemia in association with subsequent hospital readmission for hyperkalemia and in-hospital death (37). Furthermore, MRA may aggravate the

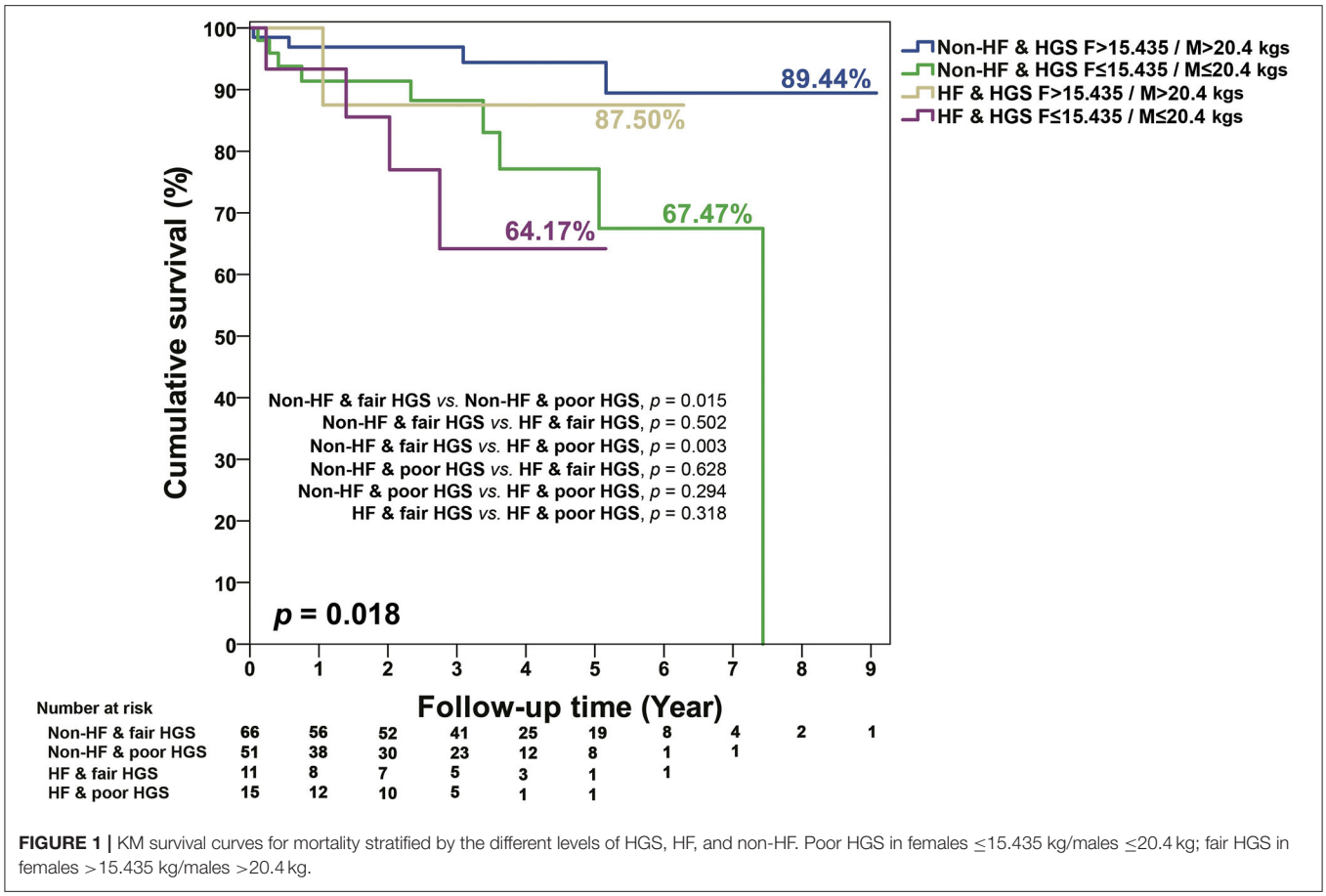


FIGURE 1 | KM survival curves for mortality stratified by the different levels of HGS, HF, and non-HF. Poor HGS in females ≤15.435 kg/males ≤20.4 kg; fair HGS in females >15.435 kg/males >20.4 kg.

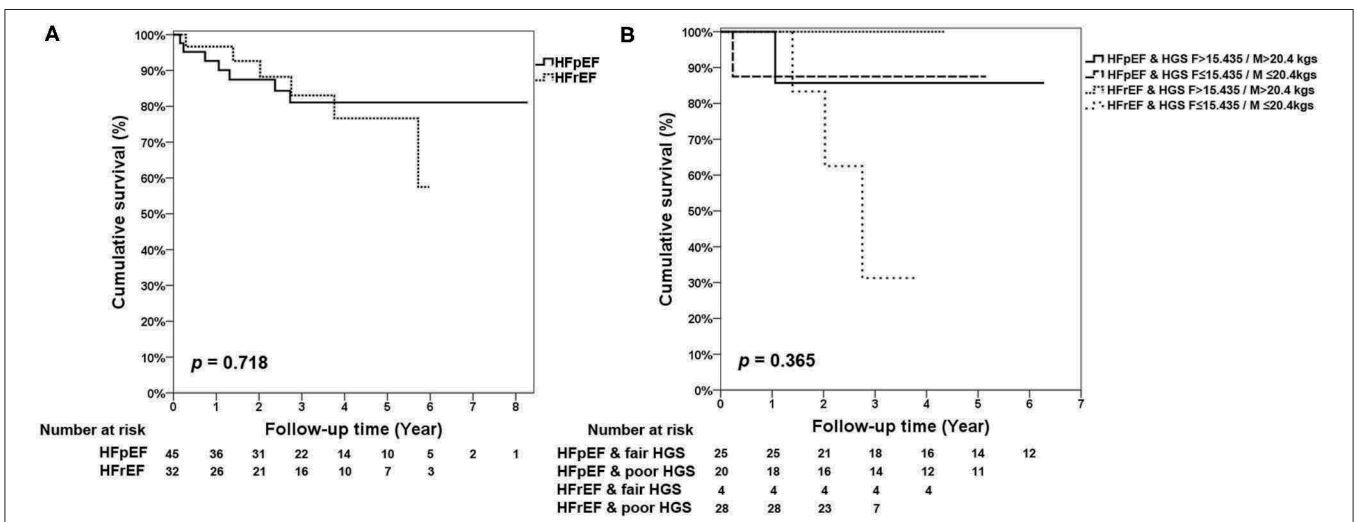


FIGURE 2 | KM survival curves for **(A)** HFpEF and HFrEF. **(B)** Mortality stratified by the different levels of HGS, HFpEF, and HFrEF.

extent of acidosis, which further depresses cardiac contractility and worsens HF (38). Although loop diuretics can alleviate body fluid overload, they also reduce GFR with neurohormonal activation and electrolyte disturbances. Besides this, it may increase myocardial fibrosis, which may be associated with disease progression and poor prognosis of HF (36, 39). Digoxin is predominantly excreted by the kidneys, and in impaired renal function, its pharmacokinetics can be influenced, resulting in toxicity of nausea and vomiting, and exacerbation of CKD (35).

Our results show that death risk was increased in CKD older patients associated with HF, which corresponds to previous studies indicating that concurrent renal disease and HF are directly related to a worse prognosis (7). Cardiac and renal diseases share common vascular risk factors, including the hemodynamic interactions of the heart and kidney in HF, the impact of atherosclerotic disease across both organ systems, neurohormonal activation, cytokines, the biochemical perturbations across the anemia–inflammation–bone mineral axis in CKD, and structural changes in the heart unique to kidney disease progression. The term cardiorenal syndrome (CRS) has been used to define different clinical conditions in which heart and kidney dysfunction overlap (40, 41), among which the classification of type 2 CRS is characterized by chronic abnormalities in cardiac function leading to kidney injury or dysfunction, and type 4 is characterized by cardiovascular involvement in patients affected by CKD at any stage. In CKD, it has been proposed that risks for HF include factors that affect preload and afterload, cardiomyopathic factors including left ventricular (LV) hypertrophy and fibrosis, and load-independent factors (neurohormonal activation, impaired iron utilization, anemia, demand ischemia, profibrotic factors, and inflammation) (42). However, our study was limited in the causes, and time sequences of CKD and CHF were not determined, and we were unable to examine which of the two disease processes was primary vs. secondary. Therefore, additional prospective studies to determine the temporal profile/change to both kidney and cardiac function over time with risk identification are necessary.

The diagnosis of HFrEF in the population with non-dialysis CKD parallels that of the population without CKD. The diagnosis of HFpEF in patients with non-dialysis CKD is difficult and should be supported by multiple objective measures, including HF symptoms and signs, typical clinical demographics, diagnostic laboratory tests, electrocardiogram, echocardiography, and function testing with exercise (16). The literature concerning mortality in HFpEF and CKD is inconsistent. Our study found that CKD was associated with a little higher mortality in HFrEF than in HFpEF, which was in line with previous studies, showing a lower mortality rate and a lower association between CKD and death in patients with HFpEF (43, 44). However, some studies report that, in CKD, HFpEF was a more powerful predictor of death than in HFrEF (45). As for reasons for the different prognosis of CKD with HFpEF and HFrEF, it was speculated that reduced EF may be associated with more advanced CKD with sympathetic and neurohormonal activation, which contributes to further renal deterioration (46), whereas in HFpEF, it may be due to endothelial dysfunction and inflammation leading to both cardiac and renal fibrosis (47, 48) and/or only reflections of the greater age and comorbidity burden.

In old CKD patients, the additional impacts of frailty and HF on prognosis were poorly known. Using the multivariate Cox proportional hazards analysis, we found that HFrEF combined with HGS resulting in severe or profound core activity limitation was associated with all-cause death in old CKD patients although TUG and 6MW insignificantly predicted mortality. As functional frailty was common with heterogeneity in old CKD populations, and it had prognostic implications, a joint evaluation on both physical function and HF should be necessary to predict patient outcomes more accurately.

The limitations of our study are as follows. First, this is a retrospective study. Therefore, longitudinal and prospective analyses are needed to further determine the effects of the physical decline associated with HF in different severity on mortality in these patients. Second, although the diagnosis of HFrEF was less debatable in this study, the reliability of the HFpEF diagnosis still needs further confirmation (15, 16). Third, the average cutoff values of TUG, HGS, and 6MW were set arbitrarily due to diverse physical function in different groups of patients with a major illness although reasonable for statistical analysis. Further studies on multimorbidity, drug history, lifestyle, or habits of a minimum volume of exercise can help to clarify these issues. Finally, the study was limited in that we did not have the direct causes of death, and knowing the causes of death may help better understand the reciprocal relationship between CKD, HF, and frailty in old patients.

In conclusion, frailty and CHF were two common conditions in old patients with CKD, and the two were associated with CKD stages. Physical limitation, frailty, and HF all predicted prognosis. Further, the combination of HF and poor HGS identified patients with high mortality risk. Efforts should be made to identify relevant factors of frailty and HF in these patients for better management strategies to improve morbidity, mortality, and patient-reported outcomes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Taichung Veterans General Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

S-CW, Y-CC, C-SL, and S-YL conceived the idea and designed the study. S-CW, Y-CC, C-YH, C-SL, and S-YL carried out the analyses. S-CW and S-YL written and revised the manuscript. D-CT and S-YL supervised the implementation of the study. All authors reviewed and approved the manuscript prior to submission.

FUNDING

We are deeply indebted to Taichung Veterans General Hospital, Taichung for providing the grants for this study (TCVGH-YM1080103, TCVGH-YM1090105, TCVGH-1108201B, TCVGH-1108202D, and TCVGH-T1107808). This study was also supported by Taiwan Ministry of Science and Technology (MOST 106-2314-B-075A-003). This work was

financially supported by the Center for Intelligent Drug Systems and Smart Bio-devices (IDS2B) from The Featured Areas Research Center Program within the framework of the Higher Education Sprout Project by the Ministry of Education (MOE) in Taiwan.

ACKNOWLEDGMENTS

We are grateful to the Biostatistics Task Force and the Clinical Information Research & Development Center of Taichung Veterans General Hospital, Taichung, Taiwan, ROC, for assistance in statistics. The authors sincerely appreciate the assistance of the Center for Translational Medicine of Taichung Veterans General Hospital, Taichung, Taiwan.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.680098/full#supplementary-material

REFERENCES

1. Zhang QL, Rothenbacher D. Prevalence of chronic kidney disease in population-based studies: systematic review. *BMC Public Health.* (2008) 8:117. doi: 10.1186/1471-2458-8-117
2. Saran R, Li Y, Robinson B, Abbott KC, Agodoa LY, Ayanian J, et al. US renal data system 2015 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis.* (2016) 67:S1–305. doi: 10.1053/j.ajkd.2015.12.015
3. Afkarian M, Katz R, Bansal N, Correa A, Kestenbaum B, Himmelfarb J, et al. Diabetes, kidney disease, and cardiovascular outcomes in the jackson heart study. *Clin J Am Soc Nephrol.* (2016) 11:1384–91. doi: 10.2215/CJN.13111215
4. Kottgen A, Russell SD, Loehr LR, Crainiceanu CM, Rosamond WD, Chang PP, et al. Reduced kidney function as a risk factor for incident heart failure: the atherosclerosis risk in communities (ARIC) study. *J Am Soc Nephrol.* (2007) 18:1307–15. doi: 10.1681/ASN.2006101159
5. Tuegel C, Bansal N. Heart failure in patients with kidney disease. *Heart.* (2017) 103:1848–53. doi: 10.1136/heartjnl-2016-310794
6. Damman K, Tang WH, Felker GM, Lassus J, Zannad F, Krum H, et al. Current evidence on treatment of patients with chronic systolic heart failure and renal insufficiency: practical considerations from published data. *J Am Coll Cardiol.* (2014) 63:853–71. doi: 10.1016/j.jacc.2013.11.031
7. Rangaswami J, Bhalla V, Blair JEA, Chang TI, Costa S, Lentine KL, et al. Cardiorenal syndrome: classification, pathophysiology, diagnosis, and treatment strategies: a scientific statement from the American heart association. *Circulation.* (2019) 139:e840–78. doi: 10.1161/CIR.0000000000000664
8. Weng SC, Lin CS, Tarng DC, Lin SY. Physical frailty and long-term mortality in older people with chronic heart failure with preserved and reduced ejection fraction: a retrospective longitudinal study. *BMC Geriatr.* (2021) 21:92. doi: 10.1186/s12877-020-01971-4
9. Dalrymple LS, Katz R, Rifkin DE, Siscovick D, Newman AB, Fried LF, et al. Kidney function and prevalent and incident frailty. *Clin J Am Soc Nephrol.* (2013) 8:2091–9. doi: 10.2215/CJN.02870313
10. Rodriguez-Pascual C, Paredes-Galan E, Vilches-Moraga A, Ferrero-Martinez AI, Torrente-Carballido M, Rodriguez-Artalejo F. Comprehensive geriatric assessment and 2-year mortality in elderly patients hospitalized for heart failure. *Circ Cardiovasc Qual Outcomes.* (2014) 7:251–8. doi: 10.1161/CIRCOUTCOMES.113.000551
11. Pulignano G, Del Sindaco D, Di Lenarda A, Alunni G, Senni M, Tarantini L, et al. Incremental value of gait speed in predicting prognosis of older adults with heart failure: insights from the IMAGE-HF study. *JACC Heart Fail.* (2016) 4:289–98. doi: 10.1016/j.jchf.2015.12.017
12. Hwang R, Morris NR, Mandrusiak A, Mudge A, Suna J, Adsett J, et al. Timed up and go test: a reliable and valid test in patients with chronic heart failure. *J Card Fail.* (2016) 22:646–50. doi: 10.1016/j.cardfail.2015.09.018
13. Kuo YT, Chiu KM, Tsang YM, Chiu CM, Chien MY. Influence of chronic kidney disease on physical function and quality of life in patients after coronary artery bypass grafting. *Cardiorenal Med.* (2015) 5:237–45. doi: 10.1159/000433447
14. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American society of echocardiography and the European association of cardiovascular imaging. *J Am Soc Echocardiogr.* (2016) 29:277–314. doi: 10.1016/j.echo.2016.01.011
15. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation.* (2018) 138:861–70. doi: 10.1161/CIRCULATIONAHA.118.034646
16. Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the heart failure association (HFA) of the european society of cardiology (ESC). *Eur Heart J.* (2019) 40:3297–317. doi: 10.1093/eurheartj/ehz641
17. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American college of cardiology foundation/American heart association task force on practice guidelines. *J Am Coll Cardiol.* (2013) 62:e147–239. doi: 10.1161/CIR.0b013e31829e8776
18. Weaver RG, James MT, Ravani P, Weaver CGW, Lamb EJ, Tonelli M, et al. Estimating urine albumin-to-creatinine ratio from protein-to-creatinine ratio: development of equations using same-day measurements. *J Am Soc Nephrol.* (2020) 31:591–601. doi: 10.1681/ASN.2019060605
19. Kamińska J, Dymicka-Piekarska V, Tomaszewska J, Matowicka-Karna J, Koper-Lenkiewicz OM. Diagnostic utility of protein to creatinine ratio (P/C ratio) in spot urine sample within routine clinical practice. *Crit Rev Clin Lab Sci.* (2020) 57:345–64. doi: 10.1080/10408363.2020.1723487
20. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* (1987) 40:373–83. doi: 10.1016/0021-9681(87)90171-8
21. Chen YM, Chuang YW, Liao SC, Lin CS, Yang SH, Tang YJ, et al. Predictors of functional recovery (FR) for elderly hospitalized patients in a geriatric evaluation and management unit (GEMU) in Taiwan. *Arch Gerontol Geriatr.* (2010) 50 (Suppl. 1):S1–5. doi: 10.1016/S0167-4943(10)00041-5
22. Guigoz Y. The mini nutritional assessment (MNA) review of the literature–What does it tell us? *J Nutr Health Aging.* (2006) 10:466–85; discussion 485–7.
23. Savva GM, Donoghue OA, Horgan F, O'Regan C, Cronin H, Kenny RA. Using timed up-and-go to identify frail members of the older population. *J Gerontol A Biol Sci Med Sci.* (2013) 68:441–6. doi: 10.1093/gerona/gls190
24. Dent E, Lien C, Lim WS, Wong WC, Wong CH, Ng TP, et al. The Asia-Pacific clinical practice guidelines for the management of frailty. *J Am Med Dir Assoc.* (2017) 18:564–75. doi: 10.1016/j.jamda.2017.04.018
25. Peña FG, Theou O, Wallace L, Brothers TD, Gill TM, Gahbauer EA, et al. Comparison of alternate scoring of variables on the performance of the frailty index. *BMC Geriatr.* (2014) 14:25. doi: 10.1186/1471-2318-14-25
26. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci.* (2001) 56:M146–56. doi: 10.1093/gerona/56.3.M146
27. Orkaby AR, Lunetta KL, Sun FJ, Driver JA, Benjamin EJ, Hamburg NM, et al. Cross-sectional association of frailty and arterial stiffness in community-dwelling older adults: the Framingham heart study. *J Gerontol A Biol Sci Med Sci.* (2019) 74:373–9. doi: 10.1093/gerona/gly134
28. Chang YT, Wu HL, Guo HR, Cheng YY, Tseng CC, Wang MC, et al. Handgrip strength is an independent predictor of renal outcomes in patients with chronic kidney diseases. *Nephrol Dial Transplant.* (2011) 26:3588–95. doi: 10.1093/ndt/gfr013

29. Rantanen T, Volpato S, Ferrucci L, Heikkinen E, Fried LP, Guralnik JM. Handgrip strength and cause-specific and total mortality in older disabled women: exploring the mechanism. *J Am Geriatr Soc.* (2003) 51:636–41. doi: 10.1034/j.1600-0579.2003.00207.x
30. Mak RH, Ikizler AT, Kovesdy CP, Raj DS, Stenvinkel P, Kalantar-Zadeh K. Wasting in chronic kidney disease. *J Cachexia Sarcopenia Muscle.* (2011) 2:9–25. doi: 10.1007/s13539-011-0019-5
31. Kovesdy CP, George SM, Anderson JE, Kalantar-Zadeh K. Outcome predictability of biomarkers of protein-energy wasting and inflammation in moderate and advanced chronic kidney disease. *Am J Clin Nutr.* (2009) 90:407–14. doi: 10.3945/ajcn.2008.27390
32. Massy ZA, de Zeeuw D. LDL cholesterol in CKD–to treat or not to treat? *Kidney Int.* (2013) 84:451–6. doi: 10.1038/ki.2013.181
33. Chiu H, Wu PY, Huang JC, Tu HP, Lin MY, Chen SC, et al. There is a U shaped association between non high density lipoprotein cholesterol with overall and cardiovascular mortality in chronic kidney disease stage 3-5. *Sci Rep.* (2020) 10:12749. doi: 10.1038/s41598-020-69794-2
34. Lund LH, Svennblad B, Melhus H, Hallberg P, Dahlström U, Edner M. Association of spironolactone use with all-cause mortality in heart failure: a propensity scored cohort study. *Circ Heart Fail.* (2013) 6:174–83. doi: 10.1161/CIRCHEARTFAILURE.112.000115
35. Yang LJ, Hsu SM, Wu PH, Lin MY, Huang TH, Lin YT, et al. Association of digoxin with mortality in patients with advanced chronic kidney disease: a population-based cohort study. *PLoS ONE.* (2021) 16:e0245620. doi: 10.1371/journal.pone.0245620
36. Hamaguchi S, Kinugawa S, Tsuchihashi-Makaya M, Goto D, Yamada S, Yokoshiki H, et al. Loop diuretic use at discharge is associated with adverse outcomes in hospitalized patients with heart failure: a report from the Japanese cardiac registry of heart failure in cardiology (JCARE-CARD). *Circ J.* (2012) 76:1920–7. doi: 10.1253/circj.CJ-11-1196
37. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, et al. Rates of hyperkalemia after publication of the randomized Aldactone evaluation study. *N Engl J Med.* (2004) 351:543–51. doi: 10.1056/NEJMoa040135
38. Henger A, Tutt P, Riesen WF, Hulter HN, Krapf R. Acid-base and endocrine effects of aldosterone and angiotensin II inhibition in metabolic acidosis in human patients. *J Lab Clin Med.* (2000) 136:379–89. doi: 10.1067/mlc.2000.110371
39. López B, Querejeta R, González A, Sánchez E, Larman M, Díez J. Effects of loop diuretics on myocardial fibrosis and collagen type I turnover in chronic heart failure. *J Am Coll Cardiol.* (2004) 43:2028–35. doi: 10.1016/j.jacc.2003.12.052
40. Di Lullo L, Bellasi A, Barbera V, Russo D, Russo L, Di Iorio B, et al. Pathophysiology of the cardio-renal syndromes types 1-5: an uptodate. *Indian Heart J.* (2017) 69:255–65. doi: 10.1016/j.ihj.2017.01.005
41. Bagshaw SM, Cruz DN, Aspromonte N, Daliento L, Ronco F, Sheinfeld G, et al. Epidemiology of cardio-renal syndromes: workgroup statements from the 7th ADQI consensus conference. *Nephrol Dial Transplant.* (2010) 25:1406–16. doi: 10.1093/ndt/gfq066
42. House AA, Wanner C, Sarnak MJ, Piña IL, McIntyre CW, Komenda P, et al. Heart failure in chronic kidney disease: conclusions from a kidney disease: improving global outcomes (KDIGO) controversies conference. *Kidney Int.* (2019) 95:1304–17. doi: 10.1016/j.kint.2019.02.022
43. McAlister FA, Ezekowitz J, Tarantini L, Squire I, Komajda M, Bayes-Genis A, et al. Renal dysfunction in patients with heart failure with preserved versus reduced ejection fraction: impact of the new chronic kidney disease-epidemiology collaboration group formula. *Circ Heart Fail.* (2012) 5:309–14. doi: 10.1161/CIRCHEARTFAILURE.111.966242
44. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. *Eur Heart J.* (2012) 33:1750–7. doi: 10.1093/eurheartj/ehr254
45. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J.* (2014) 35:455–69. doi: 10.1093/eurheartj/eht386
46. Metra M, Cotter G, Gheorghiade M, Dei Cas L, Voors AA. The role of the kidney in heart failure. *Eur Heart J.* (2012) 33:2135–42. doi: 10.1093/eurheartj/ehs205
47. Gori M, Senni M, Gupta DK, Charytan DM, Kraigher-Krainer E, Pieske B, et al. Association between renal function and cardiovascular structure and function in heart failure with preserved ejection fraction. *Eur Heart J.* (2014) 35:3442–51. doi: 10.1093/eurheartj/ehu254
48. Ter Maaten JM, Damman K, Verhaar MC, Paulus WJ, Duncker DJ, Cheng C, et al. Connecting heart failure with preserved ejection fraction and renal dysfunction: the role of endothelial dysfunction and inflammation. *Eur J Heart Fail.* (2016) 18:588–98. doi: 10.1002/ejhf.497

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 26 July 2021
doi: 10.3389/fcvm.2021.712696

Translation, Cultural Adaptation, and Reproducibility of the Physical Activity Readiness Questionnaire for Everyone (PAR-Q+): The Brazilian Portuguese Version

Juliano Schwartz[1], Paul Oh[2], Monica Y. Takito[3], Bryan Saunders[4,5], Eimear Dolan[4], Emerson Franchini[6], Ryan E. Rhodes[7], Shannon S. D. Bredin[1], Josye P. Coelho[8], Pedro dos Santos[9], Melina Mazzuco[10] and Darren E. R. Warburton[1]*

[1] Physical Activity Promotion and Chronic Disease Prevention Unit, University of British Columbia, Vancouver, BC, Canada, [2] Cardiovascular Prevention and Rehabilitation Program, Toronto Rehabilitation Institute, University Health Network, Toronto, ON, Canada, [3] Department of Pedagogy of the Human Body Movement, School of Physical Education and Sport, University of São Paulo, São Paulo, Brazil, [4] Applied Physiology and Nutrition Research Group, School of Physical Education and Sport, Rheumatology Division, Faculdade de Medicina FMUSP, University of São Paulo, São Paulo, Brazil, [5] Institute of Orthopaedics and Traumatology, Faculty of Medicine FMUSP, University of São Paulo, São Paulo, Brazil, [6] Sport Department, School of Physical Education and Sport, University of São Paulo, São Paulo, Brazil, [7] School of Exercise Science, Physical and Health Education, University of Victoria, Victoria, BC, Canada, [8] Association for Assistance of Disabled Children, São Paulo, Brazil, [9] Department of French, Hispanic and Italian Studies, University of British Columbia, Vancouver, BC, Canada, [10] Aurora Physio & Care, Physiotherapy Center, Campinas, Brazil

OPEN ACCESS

Edited by:
Sebastian Kelle, Deutsches Herzzentrum Berlin, Germany

Reviewed by:
Lígia Mendes, Hospital da Luz Setúbal, Portugal
Luís Cavalheiro, Escola Superior de Tecnologia da Saúde de Coimbra, Portugal

***Correspondence:**
Juliano Schwartz
julianofisio@gmail.com

Specialty section:
This article was submitted to General Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

Received: *21 May 2021*
Accepted: *05 July 2021*
Published: *26 July 2021*

Citation:
Schwartz J, Oh P, Takito MY, Saunders B, Dolan E, Franchini E, Rhodes RE, Bredin SSD, Coelho JP, dos Santos P, Mazzuco M and Warburton DER (2021) Translation, Cultural Adaptation, and Reproducibility of the Physical Activity Readiness Questionnaire for Everyone (PAR-Q+): The Brazilian Portuguese Version. Front. Cardiovasc. Med. 8:712696. doi: 10.3389/fcvm.2021.712696

Background: The Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) is the international standard for pre-participation risk stratification and screening. In order to provide a practical and valid screening tool to facilitate safe engagement in physical activity and fitness assessments for the Brazilian population, this study aimed to translate, culturally adapt, and verify the reproducibility of the evidence-based PAR-Q+ to the Brazilian Portuguese language.

Method: Initially, the document was translated by two independent translators, before Brazilian experts in health and physical activity evaluated the translations and produced a common initial version. Next, two English native speakers, fluent in Brazilian Portuguese and accustomed to the local culture, back-translated the questionnaire. These back translations were assessed by the organization in charge of the PAR-Q+, then a final Brazilian version was approved. A total of 493 Brazilians between 5 and 93 yr (39.9 ± 25.4 yr), 59% female, with varying levels of health and physical activity, completed the questionnaire twice, in person or online, 1–2 weeks apart. Cronbach's alpha was used to calculate the internal consistency of all items of the questionnaire, and the Kappa statistic was used to assess the individual reproducibility of each item of the document. Additionally, the intraclass correlation coefficient and its 95% confidence interval (CI) were used to verify the general reproducibility (reliability) of the translated version.

Results: The Brazilian version had an excellent internal consistency (0.993), with an almost perfect agreement in 93.8% of the questions, and a substantial agreement in the other 6.2%. The translated version also had a good to excellent total reproducibility (0.901, 95% CI: 0.887–0.914).

Conclusion: The results show this translation is a valid and reliable screening tool, which may facilitate a larger number of Brazilians to start or increase physical activity participation in a safe manner.

Keywords: health, exercise, cardiovascular disease, physical activity, risk stratification, translation

INTRODUCTION

Physical inactivity is related to several health problems and is estimated to lead to the premature death of ∼9% of the global population (1). Routine physical activity participation protects against more than 25 chronic medical conditions, such as cardiovascular disease, diabetes, some types of cancer, depression, and osteoporosis, and significantly reduces the risk of early mortality (2, 3). Owing to these benefits, governments and health organizations around the world are investing in initiatives for the promotion of regular physical activity, including changes in the physical environment and public policies (4). However, there are other factors associated with physical inactivity, such as biological and psychological aspects (3, 5). In this respect, the fear of injury, getting sick, and even dying are reported, among others, as some of the most common barriers to physical activity (6–8). These concerns are shared by health professionals who prescribe supervised as well as unsupervised physical activity and exercise to prevent and manage chronic diseases (8–10).

To address this issue the Physical Activity Readiness Questionnaire (PAR-Q) was created in Canada in the 1970s, as a pre-participation screening tool, based on experts' opinion (11, 12). With seven health-related questions to be answered as Yes or No, the document was used extensively globally (13). However, various limitations to the survey were acknowledged (14–16). For instance, a major limitation of the PAR-Q was that its use was restricted to people between 15 and 69 years of age (17). Age restrictions on a front-line pre-participation screening tool is a contemporary issue for physical activity participation given population aging worldwide (18). Another significant limitation was the conservative nature of the PAR-Q, which led to many false positives (19). When an individual answered Yes to one or more questions, they were advised to consult a physician for clearance to participate in physical activity (20, 21). However, obtaining physical activity clearance from a physician may not be feasible in several jurisdictions (22). On a global scale, access to medical professionals can involve very long waiting lists for public services, and access to private options is limited and unaffordable for many (23, 24).

Given such limitations, a series of systematic reviews together with an evidence-based consensus process were performed to establish best practices in risk stratification for physical activity participation (25–34). From this process, a new, evidence-based pre-participation screening tool was created: The Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) (20). In the current PAR-Q+, when the respondent answers No to all seven evidence-informed initial questions, they are self-cleared for unrestricted physical activity participation (35). If the individual answers Yes to one or more of these general health questions, they are required to complete follow-up questions on specific chronic medical conditions. If the individual responds No to all follow-up items, they are cleared to become more physically active. If a respondent answers Yes to one or more of these supplementary questions, they are referred to the electronic Physical Activity Readiness Medical Examination (ePARmed-X+; www.eparmedx.com), or to consult with a health professional qualified to prescribe exercise (19). Through this screening process, the vast majority of participants are able to self-clear for physical activity or exercise (36). Also, while the document has a total of 48 items, completing the tool is straightforward and takes ∼5 min (19). Additionally, this new questionnaire was recently published in a digital format, thus providing the advantage of online completion (37).

Although chronic medical conditions are the primary cause of mortality in high-income countries, such as in Canada, these diseases affect low- and middle-income countries in a much higher proportion, with more than 75% of worldwide deaths from such diseases occurring in these nations (38, 39). This is the case of Brazil, a middle-income country, where chronic diseases are also a leading health problem (40). Before the COVID-19 pandemic, the main causes of deaths in the country were cancer and cardiovascular disease, which are directly linked to obesity (41, 42). The prevalence of obesity has been dramatically increasing in the country, with 12% of the youth population, as well as 20% of adults and 21% of older adults being considered obese in Brazil (43, 44). In large part, this scenario is due to sedentary lifestyles (45). Physical inactivity, a preeminent behavioral risk factor for chronic diseases and early mortality, is one of the most prevalent unhealthy behaviors in Brazilians (46, 47). According to studies about perceived barriers to physical activity in Brazil, having a disease and being afraid of getting injured are also among the main reasons preventing minors, adults, and the elderly from becoming more physically active (48–50). The country has one of the world's fastest aging populations, and over 70% of Brazilian seniors are considered insufficiently active (51, 52). This prevalence is 61% for adults (44) and over 80% for children and adolescents in the country (53).

Since the fear of worsening their health condition is among the main barriers to physical activity in Brazilians, an instrument like the PAR-Q+, validated to Brazilian Portuguese, could be crucial to allow numerous individuals to safely start or increase physical activity participation. Accordingly, the purpose of this study was to translate, culturally adapt, and verify the reproducibility of the questionnaire to the Brazilian context.

METHODS

This study was designed in two phases. Initially, the questionnaire was translated and culturally adapted to the targeted language. Subsequently, a test re-test procedure was adopted with different age groups to verify reproducibility.

TRANSLATION AND ADAPTATION

Permission to develop the Brazilian Portuguese version of the document was granted from the organization in charge of the questionnaire (i.e., the PAR-Q+ Collaboration). The screening tool was first translated into Brazilian Portuguese by two independent translators who speak Brazilian Portuguese as their native language. A group of Brazilian experts in health and physical activity then came together to produce a combined initial version. Overall, the experts involved in validating the PAR-Q+ in Brazilian Portuguese agreed with the translators' versions. Only a couple of minor phrasing adjustments were necessary to culturally adapt the PAR-Q+ to the Brazilian context. The next step was for two native English speakers, fluent in Brazilian Portuguese and accustomed to the Brazilian culture, with no previous exposure to the original PAR-Q+, to back-translate the questionnaire into English. When assessing these back-translations, the PAR-Q+ Collaboration noted a few terms slightly different from the original document. These were considered to have occurred due to the choice of terms in Brazilian Portuguese to allow a better understanding of the questionnaire by the Brazilian population, and these adaptations did not modify the original meaning. After having its accuracy ensured, a final version was approved (see **Appendix 1**).

FIELD TESTING

To assess the reproducibility of the translated version, Brazilians living in Brazil and abroad responded to the questionnaire on two separate occasions, 1–2 weeks apart. A total of 567 individuals attending health and fitness facilities as well as members from the general public, male and female from all age groups, were invited to take part in this project. There were no exclusion criteria. However, 74 individuals did not complete the questionnaire for the second time, mainly due to schedule incompatibility. Therefore, the sample was composed of 493 participants (59% female), between 5 and 93 years old (39.9 ± 25.4 yr). A total of 114 were children and adolescents, 252 were adults, and 127 were older adults. The questionnaire was administered in person to 84 individuals in a lifestyle management program focusing on chronic disease prevention, 11 clients at a physiotherapy clinic, 24 participants of a fitness project, 14 members of a CrossFit gym, and 43 patients from a rehabilitation center. The remaining 317 questionnaires were completed online. Respondents represented a variety of health status cohorts such as clinical populations, healthy individuals, athletes, and non-competitive exercisers. As per the guidelines of the PAR-Q+, those under the legal age had the questionnaire completed by their parents/guardians. In all settings and forms of application the participants were welcomed to provide comments, if any, about their understanding of the document. Participants also reported the time taken to answer the questionnaire for the first time.

Statistical Analysis

Data were analyzed with SPSS for Windows (version 27.0). Using a 95% confidence interval, Kappa was calculated to evaluate the reproducibility of each question between the two applications (54). Additionally, the intraclass correlation coefficient (ICC) and its 95% confidence interval (CI) were calculated to verify the total reproducibility (reliability) (55). The sum of all positive questions was compared between the first and the second times the questionnaire was administered. The criteria for agreement was as follows: 0.0–0.20 (poor), 0.21–0.40 (fair), 0.41–0.6 (moderate), 0.61–0.8 (substantial), and 0.81–1.0 (almost perfect) (56). Internal consistency was calculated with Cronbach's alpha, using all initial and follow-up questions of the translated version. Significance level was set at 5% for all tests.

RESULTS

The Brazilian Portuguese version of the PAR-Q+ had excellent internal consistency with a Cronbach's alpha of 0.993. In terms of reproducibility, out of the 48 items of the questionnaire, 45 (93.8%) had an almost perfect agreement between the first and second applications, and three (6.2%) had a substantial agreement (follow-up questions 2a, 5e, and 8b). The translated version of the questionnaire had a good to excellent general reproducibility (ICC = 0.901, 95% CI: 0.887–0.914). Specifically, as shown in **Table 1**, every one of the seven general health questions of the questionnaire had an almost perfect agreement.

The maximum of questions answered positively was 20. A total of 405 (82.2%) participants provided the same answer to every question they answered both times they completed the questionnaire. Out of those, 229 answered negatively to all questions. For those individuals who did not have the same answer for all questions in both applications, 62 had one different answer, 16 responded two questions with different answers, and 10 had three answers that did not match. **Figure 1** shows the comparison of the sum of questions answered positively between the first and the second administrations of the questionnaire.

The time reported to answer the PAR-Q+ in Brazilian Portuguese was 4.4 ± 2.3 min. After answering the questionnaire, a few participants provided their opinion about their

TABLE 1 | Kappa value for each general health question between two applications of the Brazilian version of the PAR-Q+.

General health question	Agreement between applications
1	0.949
2	0.915
3	0.927
4	0.950
5	0.976
6	0.882
7	0.904

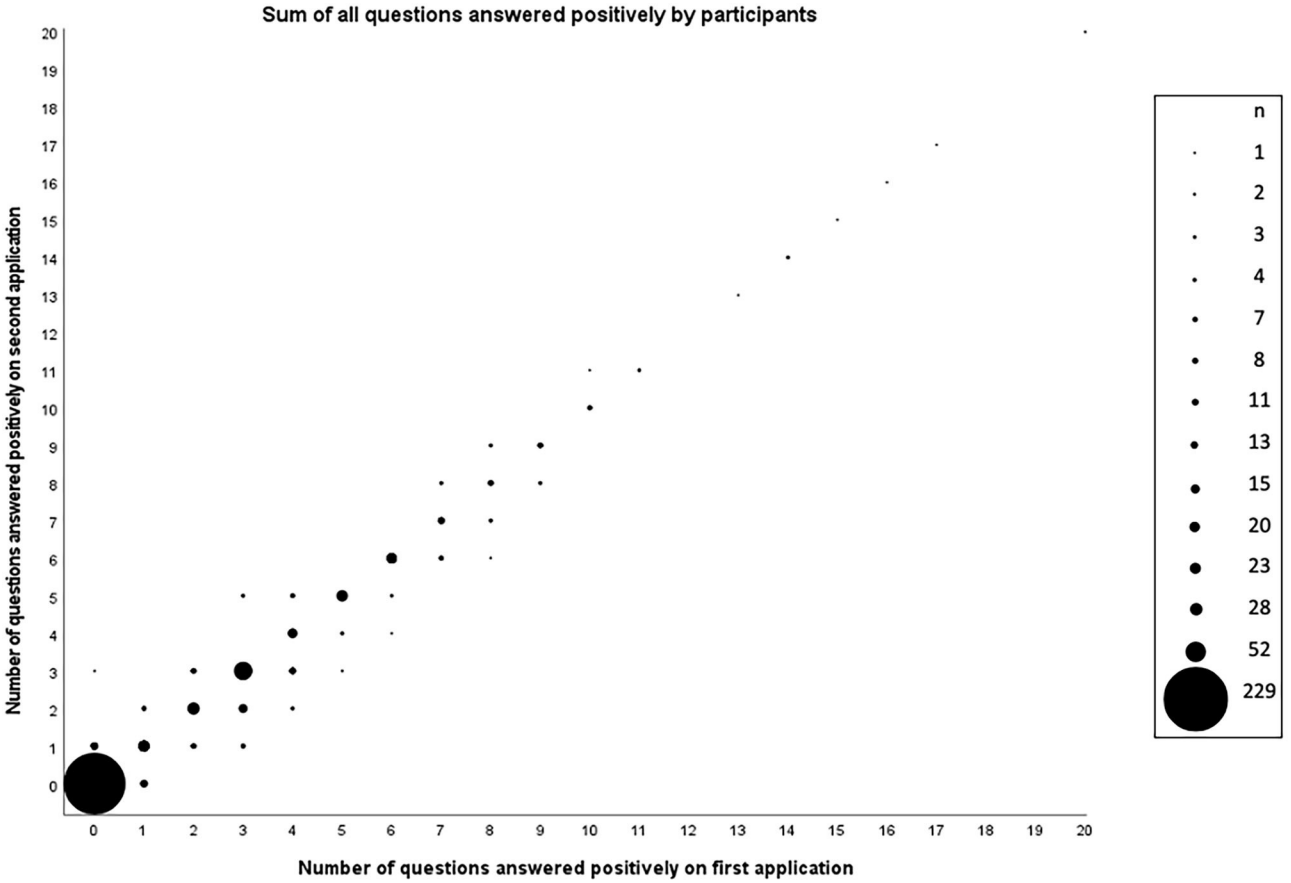


FIGURE 1 | Number of questions answered positively by participants ($n = 493$) in the first and second applications of the Brazilian Portuguese version of the PAR-Q+.

comprehension of the questionnaire. Two individuals taking medication reported uncertainty about how to answer the following question: Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments). Since their health conditions were under control, these individuals received clarification from the researcher, explaining they should answer negatively. No other concern was raised by any participant.

Specifically, the subsample of children and adolescents had 46 questions (95.8%) presenting an almost perfect agreement and two questions (4.2%) presenting a substantial agreement: follow-up items 1 and 5e. The group of adults also had 46 items (95.8%) with an almost perfect agreement, and two items (4.2%) with a substantial agreement, namely follow-up questions 7c and 8b. In the subsample of older adults, 45 questions (93.8%) had an almost perfect agreement and three questions (6.2%) had a substantial agreement: follow-up items 4a, 5a, and 6. All age groups had excellent internal consistency. The group of children and adolescents had a good general reproducibility, and the other two subsamples, adults and older adults, had a good to excellent total reproducibility. The time reported to answer the questionnaire, the internal consistency, as well as the general reproducibility for each one of the age groups are presented in **Table 2**.

DISCUSSION

The Brazilian version of the PAR-Q+ showed strong reproducibility, with all items demonstrating an agreement between substantial and almost perfect in the whole sample, as well as in each age group. This strong reproducibility is similar to the one presented by the sample of Spanish speakers, which also had all questions in these categories of agreement (57).

The PAR-Q+ was initially developed in two languages, English and French, since it was created in Canada, which is a bilingual country (58, 59). To date, the questionnaire has been officially translated into Spanish, and multiple other translation processes are in progress (57). The study about the Spanish version analyzed the participants as a single group, which had 47 items presenting an almost perfect agreement and only one presenting a substantial agreement. In the whole sample of the Brazilian study this proportion was slightly different, with 45 items presenting an almost perfect agreement and three presenting substantial agreement. There are a number

TABLE 2 | Time to complete the questionnaire, internal consistency, and total reproducibility according to each age group of individuals to validate the Brazilian Portuguese version of the PAR-Q+.

	Children and adolescents (5–17 yr)	Adults (18–64 yr)	Older adults (65–93 yr)
Time to complete (mean ± standard deviation)	4.0 ± 2.2 min	4.1 ± 2.6 min	5.0 ± 1.8 min
Internal consistency (Cronbach's alpha)	0.980	0.993	0.997
Total reproducibility (ICC; 95% CI)	0.819 (0.766–0.866)	0.905 (0.888–0.921)	0.885 (0.843–0.920)

of potential explanations for this variation. The Brazilian Portuguese document was validated with almost triple the sample size than the Spanish version (177 participants), and with some individuals much younger and others much older than the participants in that study (13–85 years old). Also, most individuals in the Brazilian version answered the questionnaire online. Both of these factors could be considered strengths of the current validation, given that the larger age range increases the representativeness of the population, while the online application allows for a more widespread application. It is also possible, however, that these aspects led to a couple of answers being less consistent, which could explain the slightly higher number of questions below an almost perfect agreement. However, when providing feedback about their understanding of the questionnaire, other than two individuals requiring further clarification about one question, no additional concerns were raised.

For the whole sample and for each age group, all of the seven initial questions of the Brazilian version had an almost perfect agreement. However, it is possible that some participants did not pay full attention to all follow-up questions when answering the questionnaire for the second time. This may be a factor for those who answered the PAR-Q+ online by themselves, without the presence of a health/fitness professional. According to Kung et al. (60), a low rate of inattentive answers is expected in any research based on survey responses, and this rate can be higher if there is little or no incentive for respondents to complete a survey. Although our participants voluntarily accepted to participate in the study and received a sound and thorough explanation about the research's importance and how to proceed, they were not financially compensated. Additionally, according to Schneider et al. (61), who examined self-administered and internet-based questions on quality of life, some individuals may provide careless responses when there is a lack of personal, face-to-face interaction. This is supported by Meade and Craig (62), who pointed out that the distance from the respondent to the professional in charge of the questionnaire can lead to less accountability when completing the survey. An additional possible cause of some level of inattention is the need to repeatedly answer the same questionnaire in a short period of time (63, 64). This could have been a factor in the present study, since the validation process required participants to answer the same questionnaire twice, seven to 14 days apart. However, in real-life situations, this repetitive process will not be necessary to start or increase participation in physical activity, as per the questionnaire guidelines individuals will only have to respond once within any 12-month period, unless there is a change in their health conditions. Furthermore, in their validation study of the International Physical Activity Questionnaire in 12 countries, Craig et al. (65) noted that longer questionnaires can be seen as boring and repetitive. Although the PAR-Q+ has many more questions than the previous PAR-Q, this innovative format, with the initial and the follow-up evidenced-based questions, is what makes this new screening tool unique, in providing physical activity clearance to 99% of its respondents without needing to be referred to a physician (66). Nevertheless, we showed that the Brazilian Portuguese version of the PAR-Q+, like the original document, takes approximately only 5 min to complete (19).

This questionnaire does not require that every individual who answers positively to one or more of the health general questions obtains clearance from a physician, making it a convenient screening tool in high- as well as in low- and middle-income nations. In industrialized countries, where the offer of medical services is usually sufficient for most the population, providing clearance for physical activity is often considered a time consuming and cumbersome process by physicians (67). Removing unnecessary consultations with this health professional before participating in physical activity or in a fitness appraisal is especially important in lower-income countries like Brazil, since due to social inequities in health, a large number of individuals have limited access to medical professionals (68). In fact, there is a need for low-cost and accurate self-assessment tools related to physical activity that can be utilized around the world in different cultures and ethnic groups (69). Specifically, effective screening provides a significant contribution to maximize physical activity engagement at the population level (16). Accordingly, having the PAR-Q+ properly translated and culturally validated to the Brazilian Portuguese language can contribute to greater numbers of individuals to safely start or increase physical activity participation.

LIMITATIONS

While the present study has a considerable sample size, with individuals living in different locations, this cohort is not necessarily representative of the entire Brazilian population. To address this issue, participants were recruited in the most populous city in the country (São Paulo), which contains individuals from all Brazilian states. Participants were also recruited in two other major cities: Campinas and Vancouver (Canada). Another limitation was the fact that the cognitive debrief happened during the data collection instead of at a specific pre-test moment. The intention was to allow every

participant to provide feedback about their understanding of the questionnaire.

CONCLUSION

Based on the findings of this study it can be concluded that, overall, Brazilians of different ages, male and female, healthy or living with chronic medical conditions, had no difficulty in understanding the translated and adapted version of the questionnaire. The results also indicate that participants were able to similarly complete the Brazilian Portuguese version of the PAR-Q+ on two independent occasions, showing the strong reproducibility of the questionnaire. Altogether, these outcomes demonstrate that the PAR-Q+ in Brazilian Portuguese is a valid and reliable screening tool. It is expected that nationwide implementation of the questionnaire could allow a substantial number of Brazilians to safely engage in more physical activity participation, as well as in fitness assessments, providing ways to enhance wellness and to contribute toward the prevention and management of chronic diseases in this population.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research and Ethics Board of the University of British Columbia. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

JS and PO designed the study. JS, MT, BS, ED, JC, and MM were responsible for data collection. JS and MT were responsible for statistical analyses. JS drafted the manuscript. PO, MT, BS, ED, EF, RR, SB, JC, PdS, MM, and DW critically revised the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES 2185-15-6 to JS); Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP 2016/50438-0 to BS, 2019/05616-6 and 2019/26899-6 to ED); Faculdade de Medicina da Universidade de São Paulo (FMUSP 2020.1.362.5.2 to BS); and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq 301003/2019-0 to EF).

ACKNOWLEDGMENTS

The authors would like to thank the Cardiovascular Prevention and Rehabilitation Program, Toronto Rehabilitation Institute, University Health Network for the financial support, Vinicius de Oliveira Damasceno and Tony Meireles dos Santos for their contributions, and all the participants for volunteering their time.

REFERENCES

1. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet.* (2012) 380:219–29. doi: 10.1016/S0140-6736(12)61031-9
2. Pedersen BK, Saltin B. Exercise as medicine–evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scand J Med Sci Sports.* (2015) 25:1–72. doi: 10.1111/sms.12581
3. Rhodes RE, Janssen I, Bredin SSD, Warburton DER, Bauman A. Physical activity: health impact, prevalence, correlates and interventions. *Psychol Health.* (2017) 32:1–34. doi: 10.1080/08870446.2017.1325486
4. Schwartz J, Rhodes R, Bredin SS, Oh P, Warburton DE. Effectiveness of approaches to increase physical activity behavior to prevent chronic disease in adults: a brief commentary. *J Clin Med.* (2019) 8:295. doi: 10.3390/jcm8030295
5. Bauman AE, Reis RS, Sallis JF, Wells JC, Loos RJF, Martin BW, et al. Correlates of physical activity: why are some people physically active and others not? *Lancet.* (2012) 380:258–71. doi: 10.1016/S0140-6736(12)60735-1
6. Schutzer KA, Graves BS. Barriers and motivations to exercise in older adults. *Prev Med.* (2004) 39:1056–61. doi: 10.1016/j.ypmed.2004.04.003
7. Burton E, Farrier K, Lewin G, Pettigrew S, Hill A-M, Airey P, et al. Motivators and barriers for older people participating in resistance training: a systematic review. *J Aging Phys Act.* (2017) 25:311–24. doi: 10.1123/japa.2015-0289
8. Herazo-Beltrán Y, Pinillos Y, Vidarte J, Crissien E, Suarez D, García R. Predictors of perceived barriers to physical activity in the general adult population: a cross-sectional study. *Braz J Phys Ther.* (2017) 21:44–50. doi: 10.1016/j.bjpt.2016.04.003
9. Granger CL, Connolly B, Denehy L, Hart N, Antippa P, Lin K-Y, et al. Understanding factors influencing physical activity and exercise in lung cancer: a systematic review. *Support Care Cancer.* (2017) 25:983–99. doi: 10.1007/s00520-016-3484-8
10. Mazzuca P, Montesi L, Mazzoni G, Grazzi G, Micheli MM, Piergiovanni S, et al. Supervised vs. self-selected physical activity for individuals with diabetes and obesity: the Lifestyle Gym program. *Intern Emerg Med.* (2017) 12:45–52. doi: 10.1007/s11739-016-1506-7
11. Chisholm DM, Collis ML, Kulak LL, Davenport W, Gruber N. Physical activity readiness. *B C Med J.* (1975) 17:375–8.
12. Warburton DE, Gledhill N, Jamnik VK, Bredin SS, McKenzie DC, Stone J, et al. Evidence-based risk assessment and recommendations for physical activity clearance: Consensus Document 2011. *Appl Physiol Nutr Metab.* (2011) 36:S266–98. doi: 10.1139/h11-062
13. Warburton DE, Jamnik VK, Bredin SS, McKenzie DC, Stone J, Shephard RJ, et al. Evidence-based risk assessment and recommendations for physical activity clearance: an introduction. *Appl Physiol Nutr Metab.* (2011) 36(Suppl. 1):S1–2. doi: 10.1139/h11-060
14. Thomas S, Reading J, Shephard RJ. Revision of the physical activity readiness questionnaire (PAR-Q). *Can J Sport Sci.* (1992) 17:338–45.
15. Jamnik VK, Gledhill N, Shephard RJ. Revised clearance for participation in physical activity: greater screening responsibility for qualified university-educated fitness professionals. *Appl Physiol Nutr Metab.* (2007) 32:1191–7. doi: 10.1139/H07-128
16. Shephard RJ. Qualified fitness and exercise as professionals and exercise prescription: evolution of the PAR-Q and Canadian aerobic fitness test. *J Phys Act Health.* (2015) 12:454–61. doi: 10.1123/jpah.2013-0473
17. Shephard RJ. Does insistence on medical clearance inhibit adoption of physical activity in the elderly? *J Aging Phys Act.* (2000) 8:301–11. doi: 10.1123/japa.8.4.301

18. WHO. *Global Health Aging*. Bethesda, MD: National Institute on Aging, National Institutes of Health, U.S. Department of Health and Human Services (2011).
19. Bredin SS, Gledhill N, Jamnik VK, Warburton DE. PAR-Q+ and ePARmed-X+: new risk stratification and physical activity clearance strategy for physicians and patients alike. *Can Fam Phys.* (2013) 59:273–7.
20. Warburton DER, Jamnik VK, Bredin SSD, Gledhill N. Enhancing the effectiveness of the PAR-Q and PARmed-X screening for physical activity participation. *J Phys Act Health.* (2010) 7(Suppl. 3):S338—40.
21. Cardinal BJ, Cardinal MK. Screening efficiency of the revised physical activity readiness questionnaire in older adults. *J Aging Phys Act.* (1995) 3:299–308. doi: 10.1123/japa.3.3.299
22. Armstrong M, Paternostro-Bayles M, Conroy MB, Franklin BA, Richardson C, Kriska A. Preparticipation screening prior to physical activity in community lifestyle interventions. *Transl J Am Coll Sports Med.* (2018) 3:176. doi: 10.1249/TJX.0000000000000073
23. Asch SM, Kerr EA, Keesey J, Adams JL, Setodji CM, Malik S, et al. Who is at greatest risk for receiving poor-quality health care? *N Engl J Med.* (2006) 354:1147–56. doi: 10.1056/NEJMsa044464
24. Tulimiero M, Garcia M, Rodriguez M, Cheney AM. Overcoming barriers to health care access in rural latino communities: an innovative model in the eastern coachella valley. *J Rural Health*. (2021) 37:635–44. doi: 10.1111/jrh.12483
25. Charlesworth S, Foulds HJA, Burr JF, Bredin SSD. Evidence-based risk assessment and recommendations for physical activity clearance: pregnancy. *Appl Physiol Nutr Metab.* (2011) 36:S33–48. doi: 10.1139/h11-061
26. Chilibeck PD, Vatanparast H, Cornish SM, Abeysekara S, Charlesworth S. Evidence-based risk assessment and recommendations for physical activity: arthritis, osteoporosis, and low back pain. *Appl Physiol Nutr Metab.* (2011) 36:S49–79. doi: 10.1139/h11-037
27. Eves ND, Davidson WJ. Evidence-based risk assessment and recommendations for physical activity clearance: respiratory disease. *Appl Physiol Nutr Metab.* (2011) 36:S80–100. doi: 10.1139/h11-057
28. Goodman JM, Thomas SG, Burr J. Evidence-based risk assessment and recommendations for exercise testing and physical activity clearance in apparently healthy individuals. *Appl Physiol Nutr Metab.* (2011) 36:S14–32. doi: 10.1139/h11-048
29. Jones LW. Evidence-based risk assessment and recommendations for physical activity clearance: cancer. *Appl Physiol Nutr Metab.* (2011) 36:S101–12. doi: 10.1139/h11-043
30. Rhodes RE, Temple VA, Tuokko HA. Evidence-based risk assessment and recommendations for physical activity clearance: cognitive and psychological conditions. *Appl Physiol Nutr Metab.* (2011) 36:S113–53. doi: 10.1139/h11-041
31. Riddell MC, Burr J. Evidence-based risk assessment and recommendations for physical activity clearance: diabetes mellitus and related comorbidities. *Appl Physiol Nutr Metab.* (2011) 36:S154–89. doi: 10.1139/h11-063
32. Thomas SG, Goodman JM, Burr JF. Evidence-based risk assessment and recommendations for physical activity clearance: established cardiovascular disease. *Appl Physiol Nutr Metab.* (2011) 36:S190–213. doi: 10.1139/h11-050
33. Zehr EP. Evidence-based risk assessment and recommendations for physical activity clearance: stroke and spinal cord injury. *Appl Physiol Nutr Metab.* (2011) 36:S214–31. doi: 10.1139/h11-055
34. Warburton DER, Bredin SSD, Charlesworth SA, Foulds HJA, McKenzie DC, Shephard RJ. Evidence-based risk recommendations for best practices in the training of qualified exercise professionals working with clinical populations. *Appl Physiol Nutr Metab.* (2011) 36:S232–65. doi: 10.1139/h11-054
35. Warburton DER, Bredin SSD, Jamnik VK, Gledhill N. Validation of the PAR-Q+ and ePARmed-X+. *Health Fitness J Can.* (2011) 4:38–46. doi: 10.14288/hfjc.v4i2.151
36. Warburton DER, Gledhill N, Jamnik VK, Bredin SSD, McKenzie DC, Stone J, et al. International launch of the PAR-Q+ and ePARmed-X. The physical activity readiness questionnaire (PAR-Q+) and electronic physical activity readiness medical examination (ePARmed-X+): summary of consensus panel recommendations. *Health Fitness J Can.* (2011) 4:26–37. doi: 10.14288/hfjc.v4i2.103
37. Warburton DE, Jamnik V, Bredin SS, Shephard RJ, Gledhill N. The 2019 physical activity readiness questionnaire for everyone (PAR-Q+) and electronic physical activity readiness medical examination (ePARmed-X+). *Health Fitness J Can.* (2018) 11:80–3. doi: 10.14288/hfjc.v11i4.270
38. Varin M, Baker M, Palladino E, Lary T. Canadian chronic disease indicators, 2019 - updating the data and taking into account mental health. *Health Promot Chronic Dis Prev Can.* (2019) 39:281. doi: 10.24095/hpcdp.39.10.02
39. Ranasinghe PD, Pokhrel S, Anokye NK. Economics of physical activity in low-income and middle-income countries: a systematic review. *BMJ open.* (2021) 11:e037784. doi: 10.1136/bmjopen-2020-037784
40. Enes CC, Nucci LB. A telephone surveillance system for noncommunicable diseases in Brazil. *Public Health Rep.* (2019) 134:324–7. doi: 10.1177/0033354919848741
41. Triaca LM, Jacinto PdA, França MTA, Tejada CAO. Does greater unemployment make people thinner in Brazil? *Health Econ.* (2020) 29:1279–88. doi: 10.1002/hec.4139
42. Brasil. Ministério da Saúde. Departamento de Informática do SUS – DATASUS. *Informações de Saúde, Epidemiológicas e Morbidade: banco de dados.* (2019). Available from: http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sim/cnv/obt10uf.def (accessed October 19, 2020).
43. Ferreira CM, Reis NDD, Castro AO, Höfelmann DA, Kodaira K, Silva MT, et al. Prevalence of childhood obesity in Brazil: systematic review and meta-analysis. *J Pediatr.* (2021). doi: 10.1016/j.jped.2020.12.003. [Epub ahead of print].
44. Brasil. *Vigitel Brasil 2019: vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico: estimativas sobre frequência e distribuição sociodemográfica de fatores de risco e proteção para doenças crônicas nas capitais dos 26 estados brasileiros e no Distrito Federal em 2019*. Brasilia: Ministerio da saude (2020).
45. Dunker KLL, Alvarenga MDS, Teixeira PC, Grigolon RB. Effects of participation level and physical activity on eating behavior and disordered eating symptoms in the Brazilian version of the New Moves intervention: data from a cluster randomized controlled trial. *São Paulo Med J.* (2021) 139:269–78. doi: 10.1590/1516-3180.2020.0420.r2.04022021
46. Ekelund U, Steene-Johannessen J, Brown WJ, Fagerland MW, Owen N, Powell KE, et al. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. *Lancet.* (2016) 388:1302–10. doi: 10.1016/S0140-6736(16)30370-1
47. Silva DA, Rinaldi AEM, Azeredo CM. Clusters of risk behaviors for noncommunicable diseases in the Brazilian adult population. *Int J Public Health.* (2019) 64:821–30. doi: 10.1007/s00038-019-01242-z
48. Cruz MS, Garcia LMT, Andrade DR, Florindo AA. Barriers to leisure-time physical activity in adults living in a low socioeconomic area of the Brazilian Southeast. *Rev Bras Ativ Fis e Saúde.* (2018) 23:1–9. doi: 10.12820/rbafs.23e0041
49. Rech CR, Camargo EMd, Araujo PABd, Loch MR, Reis RS. Perceived barriers to leisure-time physical activity in the brazilian population. *Rev Bras Med Esporte.* (2018) 24:303–9. doi: 10.1590/1517-869220182404175052
50. Sousa AW, Cabral ALB, Martins MA, Carvalho CR. Barriers to daily life physical activities for Brazilian children with asthma: a cross-sectional study. *J Asthma.* (2020) 57:575–83. doi: 10.1080/02770903.2019.1594249
51. Lima-Costa MF. Aging and public health: the Brazilian Longitudinal Study of Aging (ELSI-Brazil). *Rev Saude Publica.* (2018) 52:2s. doi: 10.11606/S1518-8787.2018052000supl1ap
52. Souza AMR, Fillenbaum GG, Blay SL. Prevalence and correlates of physical inactivity among older adults in Rio Grande do Sul, Brazil. *PLoS ONE.* (2015) 10:e0117060. doi: 10.1371/journal.pone.0117060
53. Mendes AA, Lopes WA, Locateli JC, Oliveira GHd, Bim RH, Simões CF, et al. The prevalence of Active Play in Brazilian children and adolescents: a systematic review. *Rev Bras Cineantr Desempenho Hum.* (2018) 20:395–405. doi: 10.5007/1980-0037.2018v20n4p395
54. Mackinnon A. A spreadsheet for the calculation of comprehensive statistics for the assessment of diagnostic tests and inter-rater agreement. *Comp Biol Med.* (2000) 30:127–34. doi: 10.1016/S0010-4825(00)00006-8
55. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J Chiropr Med.* (2016) 15:155–63. doi: 10.1016/j.jcm.2016.02.012
56. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics.* (1977) 33:159–74. doi: 10.2307/2529310

57. Schwartz J, Mas-Alòs S, Takito MY, Martinez J, Cueto MEÁ, Mibelli MSR, et al. Cross-cultural translation, adaptation, and reliability of the Spanish version of the Physical Activity Readiness Questionnaire for Everyone (PAR-Q+). *Health Fitness J Can.* (2019) 12:3–14. doi: 10.14288/hfjc.v12i4.291
58. Warburton DER, Jamnik V, Bredin SSD, Gledhill N. The 2011 physical activity readiness questionnaire for everyone (PAR-Q+): French North America Version (Questionnaire sur l'aptitude à l'activité physique pour tous (2011 Q-AAP+)). *Health Fitness J Can.* (2011) 4:21–3. doi: 10.14288/hfjc.v4i2.107
59. Warburton DER, Jamnik VK, Bredin SSD, Gledhill N. The physical activity readiness questionnaire for everyone (PAR-Q+): English North America Version. *Health Fitness J Can.* (2011) 4:18–20. doi: 10.14288/hfjc.v4i2.106
60. Kung FYH, Kwok N, Brown DJ. Are attention check questions a threat to scale validity? *Appl Psychol.* (2018) 67:264–83. doi: 10.1111/apps.12108
61. Schneider S, May M, Stone AA. Careless responding in internet-based quality of life assessments. *Qual Life Res.* (2018) 27:1077–88. doi: 10.1007/s11136-017-1767-2
62. Meade AW, Craig SB. Identifying careless responses in survey data. *Psychol Methods.* (2012) 17:437. doi: 10.1037/a0028085
63. Conijn JM, Franz G, Emons WHM, De Beurs E, Carlier IVE. The assessment and impact of careless responding in routine outcome monitoring within mental health care. *Multivariate Behav Res.* (2019) 54:593–611. doi: 10.1080/00273171.2018.1563520
64. Wardell JD, Rogers ML, Simms LJ, Jackson KM, Read JP. Point and click, carefully: investigating inconsistent response styles in middle school and college students involved in web-based longitudinal substance use research. *Assessment.* (2014) 21:427–42. doi: 10.1177/1073191113505681
65. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc.* (2003) 35:1381–95. doi: 10.1249/01.MSS.0000078924.61453.FB
66. Joy EA, Pescatello LS. Pre-exercise screening: role of the primary care physician. *Isr J Health Policy Res.* (2016) 5:29. doi: 10.1186/s13584-016-0089-0
67. Warburton DER, Jamnik VK, Bredin SSD, Burr J, Charlesworth S, Chilibeck P, et al. Executive summary: the 2011 physical activity readiness questionnaire for everyone (PAR-Q+) and the electronic physical activity readiness medical examination (ePARmed-X+). *Health Fitness J Can.* (2011) 4:24–5. doi: 10.14288/hfjc.v4i2.104
68. Boccolini CS, de Souza Junior PRB. Inequities in healthcare utilization: results of the Brazilian National Health Survey, 2013. *Int J Equity Health.* (2016) 15:150. doi: 10.1186/s12939-016-0444-3
69. Sebastiao E, Gobbi S, Chodzko-Zajko W, Schwingel A, Papini CB, Nakamura PM, et al. The International Physical Activity Questionnaire-long form overestimates self-reported physical activity of Brazilian adults. *Public Health.* (2012) 126:967–75. doi: 10.1016/j.puhe.2012.07.004

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

APPENDIX 1

PAR-Q+ em português

Questionário de Prontidão para Atividade Física para Todos

Os benefícios da atividade física regular para a saúde são evidentes. Mais pessoas deveriam praticar atividade física todos os dias da semana. Fazer atividade física é muito seguro para a MAIORIA das pessoas. Este questionário indicará se você precisa de orientação adicional de um médico OU profissional de saúde qualificado para atuar com exercício físico, antes de se tornar mais ativo fisicamente.

PERGUNTAS GERAIS SOBRE A SAÚDE

Leia as 7 perguntas abaixo cuidadosamente e responda com sinceridade, assinalando SIM ou NÃO.	SIM	NÃO
1) O médico alguma vez disse que você tem problema de coração☐ **OU** pressão alta☐?	☐	☐
2) Você sente dor no peito em repouso, ao fazer suas atividades cotidianas comuns **OU** ao praticar atividade física?	☐	☐
3) Você perde o equilíbrio devido a tontura **OU** ficou inconsciente nos últimos 12 meses? Responda **NÃO** se sua tontura estiver associada a respiração rápida e/ou profunda (inclusive durante exercícios intensos).	☐	☐
4) Você foi diagnosticado com alguma outra condição crônica de saúde (que não seja pressão alta ou doença cardíaca)? **LISTE AS CONDIÇÕES AQUI:** _____	☐	☐
5) Você está tomando medicamentos prescritos pelo médico para uma condição crônica de saúde? **LISTE AS CONDIÇÕES E OS MEDICAMENTOS AQUI:** _____	☐	☐
6) Você atualmente tem (ou teve nos últimos 12 meses) um problema ósseo, articular ou de tecido mole (músculo, ligamento ou tendão) que poderia se agravar se você se tornasse mais ativo fisicamente? Responda **NÃO** se você tiver tido um problema que **hoje não limita mais a sua capacidade** de fazer atividade física. **LISTE AS CONDIÇÕES AQUI:** _____	☐	☐
7) O médico alguma vez disse que você só deveria fazer atividade física sob supervisão médica?	☐	☐

Se você respondeu NÃO a todas as perguntas acima, você está liberado para fazer atividade física. Por favor assine a DECLARAÇÃO DO PARTICIPANTE. Você não precisa preencher as páginas 2 e 3.

- Comece a ser muito mais ativo fisicamente – comece devagar e aumente o ritmo aos poucos
- Siga as recomendações da Organização Mundial de Saúde para a sua idade contidas em International Physical Activity Guidelines (https://www.who.int/dietphysicalactivity/factsheet_recommendations/en/).
- Você está liberado para participar de avaliações de saúde e condicionamento físico.
- Se você tiver acima de 45 anos e **NÃO** estiver acostumado a fazer exercícios intensos ou de esforço máximo, consulte um profissional de saúde qualificado para atuar com exercício físico, antes de participar de exercícios dessa intensidade.
- Caso tenha alguma dúvida adicional, entre em contato com um profissional de saúde qualificado para atuar com exercício físico.

DECLARAÇÃO DO PARTICIPANTE

Se você for menor de idade ou precisar do consentimento de um responsável, seu pai, mãe, responsável legal ou cuidador também precisa assinar este formulário.

Eu, abaixo-assinado, li, compreendi satisfatoriamente e preenchi este questionário. Reconheço que esta liberação para a prática de atividade física é válida por no máximo 12 meses a partir da data do preenchimento, e será invalidada caso minha condição de saúde mude. Reconheço também que o estabelecimento onde irei praticar atividade física pode guardar uma cópia deste formulário para registro. Neste caso, ele manterá a confidencialidade do mesmo, respondendo às leis e regulamentações aplicáveis.

NOME _____ DATA _____

ASSINATURA _____ TESTEMUNHA _____

ASSINATURA DO PAI/MÃE/RESPONSÁVEL/CUIDADOR _____

Se você respondeu SIM a uma ou mais perguntas, PREENCHA AS PÁGINAS 2 E 3.

Deixe para ficar mais ativo mais tarde se:

- Você tiver uma infecção aguda, como resfriado ou febre – é melhor esperar até se sentir bem.
- Você estiver grávida – fale com um profissional de saúde, um médico, um profissional de saúde qualificado para atuar com exercício físico, e/ou preencha o formulário ePARmed-X+ (**www.eparmedx.com**) antes de se tornar mais ativa fisicamente.
- Sua saúde mudar – responda às perguntas das páginas 2 e 3 deste documento e/ou fale com um médico ou um profissional de saúde qualificado para atuar com exercício físico, antes de continuar com qualquer programa de atividade física.

Traduzido por Bianca Bold (tradutora profissional) e Juliano Schwartz (CAPES/UBC), com apoio financeiro da University Health Network

 1/4

PAR-Q+ em português

PERGUNTAS ADICIONAIS SOBRE PROBLEMA(S) DE SAÚDE

1. Você tem artrite, osteoporose ou problemas de coluna?

Se a resposta for positiva, responda às perguntas 1a–1c — Se **NÃO** ☐ pule para a pergunta 2

1a.	Você tem dificuldade em controlar sua condição com medicamentos ou outros tratamentos prescritos por médicos? (Responda **NÃO** se não estiver tomando medicamentos ou fazendo outros tratamentos no momento)	SIM ☐ NÃO ☐
1b.	Você tem problemas articulares que causam dor, uma fratura recente ou fratura causada por osteoporose ou câncer, vértebra deslocada (como espondilolistese) e/ou espondilólise/defeito da pars interarticularis (fratura no anel ósseo na parte posterior da coluna vertebral)?	SIM ☐ NÃO ☐
1c.	Você recebeu injeções de esteroides ou tomou comprimidos de esteroides regularmente por mais de 3 meses?	SIM ☐ NÃO ☐

2. Você tem algum tipo de câncer?

Se a resposta for positiva, responda às perguntas 2a–2b — Se **NÃO** ☐ pule para a pergunta 3

2a.	O seu diagnóstico de câncer inclui algum destes tipos: pulmão/broncogênico, mieloma múltiplo (câncer de células plasmáticas), cabeça e/ou pescoço?	SIM ☐ NÃO ☐
2b.	Você está recebendo tratamento para o câncer (como quimioterapia ou radioterapia)?	SIM ☐ NÃO ☐

3. Você tem algum problema cardíaco ou cardiovascular? Isto inclui doença arterial coronariana, insuficiência cardíaca, anormalidade do ritmo cardíaco

Se a resposta for positiva, responda às perguntas 3a–3d — Se **NÃO** ☐ pule para a pergunta 4

3a.	Você tem dificuldade em controlar sua condição com medicamentos ou outros tratamentos prescritos por médicos? (Responda **NÃO** se não estiver tomando medicamentos ou fazendo outros tratamentos no momento)	SIM ☐ NÃO ☐
3b.	Você tem batimentos cardíacos irregulares que requerem acompanhamento médico (como fibrilação atrial, contração ventricular prematura)?	SIM ☐ NÃO ☐
3c.	Você tem insuficiência cardíaca crônica?	SIM ☐ NÃO ☐
3d.	Você foi diagnosticado com doença arterial coronariana (cardiovascular) e não praticou atividades físicas regulares nos últimos 2 meses?	SIM ☐ NÃO ☐

4. Você tem pressão alta?

Se a resposta for positiva, responda às perguntas 4a–4b — Se **NÃO** ☐ pule para a pergunta 5

4a.	Você tem dificuldade em controlar sua condição com medicamentos ou outros tratamentos prescritos por médicos? (Responda **NÃO** se não estiver tomando medicamentos ou fazendo outros tratamentos no momento)	SIM ☐ NÃO ☐
4b.	Você tem pressão arterial em repouso igual ou superior a 160/90 mmHg com ou sem medicação? (Responda **SIM** se você não souber sua pressão arterial em repouso)	SIM ☐ NÃO ☐

5. Você tem algum problema metabólico? Isto inclui diabetes tipo 1, diabetes tipo 2, pré-diabetes

Se a resposta for positiva, responda às perguntas 5a–5e — Se **NÃO** ☐ pule para a pergunta 6

5a.	Você costuma ter dificuldade em controlar seus níveis de açúcar no sangue com a alimentação, com medicamentos, ou com outros tratamentos prescritos por médicos?	SIM ☐ NÃO ☐
5b.	Você costuma ter sinais e sintomas de pouco açúcar no sangue (hipoglicemia) após exercícios e/ou durante suas atividades cotidianas? Sinais de hipoglicemia podem incluir tremores, nervosismo, irritabilidade fora do comum, transpiração excessiva, tontura, confusão mental, dificuldade para falar, fraqueza ou sonolência.	SIM ☐ NÃO ☐
5c.	Você tem algum sinal ou sintoma de complicações do diabetes, como doença cardíaca ou vascular e/ou complicações que afetam seus olhos, os rins **OU** perda de sensibilidade nos pés e dedos dos pés?	SIM ☐ NÃO ☐
5d.	Você tem outros problemas metabólicos (como diabetes gestacional, doença renal crônica ou problemas no fígado)?	SIM ☐ NÃO ☐
5e.	Você planeja fazer, num futuro próximo, exercícios que para você são mais intensos/vigorosos que o normal?	SIM ☐ NÃO ☐

Traduzido por Bianca Bold (tradutora profissional) e Juliano Schwartz (CAPES/UBC), com apoio financeiro da University Health Network

 2/4

PAR-Q+ em português

6. **Você tem problemas de saúde mental ou dificuldades de aprendizagem?** Isto inclui Alzheimer, transtorno de ansiedade, depressão, demência, transtorno alimentar, transtorno psicótico, disfunção intelectual, síndrome de Down

Se a resposta for positiva, responda às perguntas 6a-6b — Se **NÃO** ☐ pule para a pergunta 7

6a.	Você tem dificuldade em controlar sua condição com medicamentos ou outros tratamentos prescritos por médicos? (Responda **NÃO** se não estiver tomando medicamentos ou fazendo outros tratamentos no momento)	**SIM** ☐ **NÃO** ☐
6b.	Você tem síndrome de Down **E** problemas na coluna que afetam nervos ou músculos?	**SIM** ☐ **NÃO** ☐

7. **Você tem alguma doença respiratória?** Isto inclui doença pulmonar obstrutiva crônica, asma, hipertensão arterial pulmonar

Se a resposta for positiva, responda às perguntas 7a–7d — Se **NÃO** ☐ pule para a pergunta 8

7a.	Você tem dificuldade em controlar sua condição com medicamentos ou outros tratamentos prescritos por médicos? (Responda **NÃO** se não estiver tomando medicamentos ou fazendo outros tratamentos no momento)	**SIM** ☐ **NÃO** ☐
7b.	O médico alguma vez disse que você tem baixos níveis de oxigênio no sangue em repouso ou durante exercícios e/ou que você precisa de terapia de oxigênio suplementar?	**SIM** ☐ **NÃO** ☐
7c.	Se asmático, você atualmente apresenta sintomas como sensação de aperto no peito, respiração sibilante, dificuldade em respirar, tosse constante (mais de 2 dias/semana) ou você usou sua medicação de resgate mais de 2 vezes na última semana?	**SIM** ☐ **NÃO** ☐
7d.	O médico alguma vez disse que você tem pressão alta nos vasos sanguíneos dos pulmões?	**SIM** ☐ **NÃO** ☐

8. **Você tem alguma lesão na medula espinhal?** Isto inclui tetraplegia e paraplegia

Se a resposta for positiva, responda às perguntas 8a–8c — Se **NÃO** ☐ pule para a pergunta 9

8a.	Você tem dificuldade em controlar sua condição com medicamentos ou outros tratamentos prescritos por médicos? (Responda **NÃO** se não estiver tomando medicamentos ou fazendo outros tratamentos no momento)	**SIM** ☐ **NÃO** ☐
8b.	Você costuma apresentar pressão arterial baixa em repouso a ponto de causar tonturas e/ou desmaios?	**SIM** ☐ **NÃO** ☐
8c.	O médico alguma vez mencionou que você apresenta surtos repentinos de pressão arterial alta (conhecidos como disreflexia autonômica)?	**SIM** ☐ **NÃO** ☐

9. **Você já teve derrame cerebral alguma vez?** Isto inclui ataque isquêmico transitório ou acidente vascular cerebral

Se a resposta for positiva, responda às perguntas 9a–9c — Se **NÃO** ☐ pule para a pergunta 10

9a.	Você tem dificuldade em controlar sua condição com medicamentos ou outros tratamentos prescritos por médicos? (Responda **NÃO** se não estiver tomando medicamentos ou fazendo outros tratamentos no momento)	**SIM** ☐ **NÃO** ☐
9b.	Você tem dificuldade para caminhar ou mobilidade comprometida?	**SIM** ☐ **NÃO** ☐
9c.	Você sofreu um derrame ou teve comprometimento nos nervos ou músculos nos últimos 6 meses?	**SIM** ☐ **NÃO** ☐

10. Você tem qualquer outro problema de saúde não listado acima, ou você tem dois ou mais problemas de saúde?

Se tiver outras condições, responda às perguntas 10a–10c — Se **NÃO** ☐ leia as recomendações da página 4

10a.	Você sofreu de escurecimento da visão, desmaio ou perda de consciência como resultado de lesão na cabeça nos últimos 12 meses **OU** você teve uma concussão cerebral diagnosticada nos últimos 12 meses?	**SIM** ☐ **NÃO** ☐
10b.	Você tem um problema de saúde que não está listado (como epilepsia, problemas neurológicos, problemas renais)?	**SIM** ☐ **NÃO** ☐
10c.	Você tem atualmente dois ou mais problemas de saúde?	**SIM** ☐ **NÃO** ☐

LISTE OS SEU(S) PROBLEMA(S) DE SAÚDE _____

E RESPECTIVO(S) MEDICAMENTO(S) AQUI: _____

Vá até a página 4 para obter recomendações sobre sua condição atual de saúde e assine a DECLARAÇÃO DO PARTICIPANTE.

Traduzido por Bianca Bold (tradutora profissional) e Juliano Schwartz (CAPES/UBC), com apoio financeiro da University Health Network

 3/4

PAR-Q+ em português

Se você respondeu NÃO a todas as perguntas ADICIONAIS (páginas 2-3) sobre problemas de saúde, você está apto a se tornar mais ativo fisicamente - Assine a DECLARAÇÃO DO PARTICIPANTE abaixo.

- É aconselhável que você consulte um profissional de saúde qualificado para atuar com exercício físico, para ajudá-lo a desenvolver um plano de atividades físicas seguro e eficaz para atender às suas necessidades de saúde.
- É recomendável que você comece devagar e aumente o ritmo aos poucos – 20–60 minutos de exercícios de intensidade baixa a moderada, 3–5 dias por semana, incluindo exercícios aeróbios e de fortalecimento muscular.
- Ao progredir, tente acumular 150 minutos ou mais de atividades físicas de intensidade moderada por semana.
- Se você tiver mais de 45 anos e **NÃO** estiver acostumado a fazer exercícios intensos ou de esforço máximo, consulte um profissional de saúde qualificado para atuar com exercício físico, antes de participar de exercícios dessa intensidade.

Se você respondeu **SIM** a **uma ou mais das perguntas adicionais** sobre sua condição de saúde:

Você deve se informar melhor antes de se tornar mais ativo fisicamente ou de fazer uma avaliação física. Complete o programa on-line de recomendações para triagem e exercícios, especialmente projetado para esses casos, o eParmed-X+ (**www.eparmedx.com**) e/ou consulte um profissional de saúde qualificado para atuar com exercício físico, para trabalhar com você usando o ePARmed-X+ e para obter mais informações.

Deixe para ficar mais ativo depois se:

- Você tiver uma infecção aguda, como resfriado ou febre – é melhor esperar até se sentir bem.
- Você estiver grávida – fale com um profissional de saúde, um médico, um profissional de saúde qualificado para atuar com exercício físico, e/ou preencha o ePARmed-X+ (**www.eparmedx.com**) antes de se tornar mais ativa fisicamente.
- Sua saúde mudar – fale com um médico ou um profissional de saúde qualificado para atuar com exercício físico, antes de continuar com qualquer programa de atividade física.

- Incentivamos que você faça uma cópia do PAR-Q+. Você deve usar todo o questionário, e alterações NÃO são permitidas.
- Os autores, a PAR-Q+ Collaboration, as organizações parceiras e seus agentes, não assumem qualquer responsabilidade por pessoas que fazem atividades físicas e/ou utilizam o PAR-Q+ ou o ePARmed-X+. Em caso de dúvida após preencher o questionário, consulte um médico antes de fazer alguma atividade física.

DECLARAÇÃO DO PARTICIPANTE

- Pedimos a todos os que preencheram o PAR-Q+ que leiam e assinem a declaração abaixo.
- Se você for menor de idade ou precisar do consentimento de um responsável, seu pai, mãe, responsável legal ou cuidador também precisa assinar este formulário.

Eu, abaixo-assinado, li, compreendi satisfatoriamente e preenchi este questionário. Reconheço que esta liberação para a prática de atividade física é válida por no máximo 12 meses a partir da data do preenchimento, e será invalidada caso minha condição de saúde mude. Reconheço também que o estabelecimento onde irei praticar atividade física pode guardar uma cópia deste formulário para registro. Neste caso, ele manterá a confidencialidade do mesmo, respondendo às leis e regulamentações aplicáveis.

NOME _____ DATA _____

ASSINATURA _____ TESTEMUNHA _____

ASSINATURA DO PAI/MÃE/RESPONSÁVEL/CUIDADOR _____

Para mais informações, entre em contato com

www.eparmedx.com
E-mail: eparmedx@gmail.com

Citação para o PAR-Q+ em português:
Schwartz J, Oh P, Takito MY, Saunders B, Dolan E, Franchini E, Rhodes RE, Bredin SSD, Coelho JP, Santos P, Mazzuco M, and Warburton DER. Translation, cultural adaptation, and reproducibility of the Physical Activity Readiness Questionnaire for Everyone (PAR-Q+): the Brazilian Portuguese version. Front. Cardiovasc. Med. doi: 10.3389/fcvm.2021.712696. 2021

O PAR-Q+ foi criado usando o processo AGREE baseado em evidências (1) pela PAR-Q+ Collaboration, presidida pelo Dr. Darren E. R. Warburton com o Dr. Norman Gledhill, a Dra. Veronica Jamnik e o Dr. Donald C. McKenzie (2). A produção deste documento tornou-se possível graças a contribuições financeiras da Public Health Agency of Canada e do BC Ministry of Health Services. As opiniões aqui expressas não representam necessariamente os pontos de vista da Public Health Agency of Canada ou do BC Ministry of Health Services.

Principais referências:

1. Warburton DER, Jamnik VK, Bredin SSD, and Gledhill N on behalf of the PAR-Q+ Collaboration. The Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) and Electronic Physical Activity Readiness Medical Examination (ePARmed-X+). Health & Fitness Journal of Canada 4(2):3-23, 2011.
2. Jamnik VK, Warburton DER, Makarski J, McKenzie DC, Shephard RJ, Stone J, and Gledhill N. Enhancing the effectiveness of clearance for physical activity participation; background and overall process. APNM 36(S1):S3-S13, 2011.
3. Warburton DER, Gledhill N, Jamnik VK, Bredin SSD, McKenzie DC, Stone J, Charlesworth S, and Shephard RJ. Evidence-based risk assessment and recommendations for physical activity clearance; Consensus Document. APNM 36(S1):S266-s298, 2011.
4. Chisholm DM, Collis ML, Kulak LL, Davenport W, and Gruber N. Physical activity readiness. British Columbia Medical Journal. 1975;17:375-378.
5. Thomas S, Reading J, and Shephard RJ. Revision of the Physical Activity Readiness Questionnaire (PAR-Q). Canadian Journal of Sport Science 1992;17:4 338-345.

Traduzido por Bianca Bold (tradutora profissional) e Juliano Schwartz (CAPES/UBC), com apoio financeiro da University Health Network

 4 / 4

frontiers in Cardiovascular Medicine

CLINICAL TRIAL
published: 27 July 2021
doi: 10.3389/fcvm.2021.715207

Feasibility and Preliminary Effects of the BESMILE-HF Program on Chronic Heart Failure Patients: A Pilot Randomized Controlled Trial

Xiankun Chen[1,2,3], Wei Jiang[3,4], Thomas P. Olson[5], Cecilia Stålsby Lundborg[1], Zehuai Wen[2,6], Weihui Lu[3,4,7]* and Gaetano Marrone[1]*

[1] Health Systems and Policy, Department of Global Public Health, Karolinska Institutet, Stockholm, Sweden, [2] Key Unit of Methodology in Clinical Research, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, China, [3] The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China, [4] Department of Cardiology, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, China, [5] Division of Cardiovascular Diseases, Department of Internal Medicine, Mayo Clinic and Foundation, Rochester, MN, United States, [6] National Centre for Design Measurement and Evaluation in Clinical Research, Guangzhou University of Chinese Medicine, Guangzhou, China, [7] Heart Failure Center/Department of Cardiology, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, China

OPEN ACCESS

Edited by:
Jian Yang,
Fudan University, China

Reviewed by:
Jianqing She,
The First Affiliated Hospital of Xi'an Jiaotong University, China
Ferdinando Iellamo,
University of Rome Tor Vergata, Italy

***Correspondence:**
Weihui Lu
weihui.lu@163.com
Zehuai Wen
wenzh@gzucm.edu.cn

Specialty section:
This article was submitted to General Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

Received: *26 May 2021*
Accepted: *05 July 2021*
Published: *27 July 2021*

Citation:
Chen X, Jiang W, Olson TP, Lundborg CS, Wen Z, Lu W and Marrone G (2021) Feasibility and Preliminary Effects of the BESMILE-HF Program on Chronic Heart Failure Patients: A Pilot Randomized Controlled Trial. Front. Cardiovasc. Med. 8:715207. doi: 10.3389/fcvm.2021.715207

Aims: The *Baduanjin* Eight-Silken-Movements wIth Self-Efficacy building for Heart Failure (BESMILE-HF) program is a contextually adapted cardiac rehabilitation program. It uses a traditional Chinese exercise, *Baduanjin*, to solve the unmet demand of exercise-based cardiac rehabilitation programs due to their scarcity and unaffordability in China. This pilot study assesses BESMILE-HF's feasibility and preliminary effects.

Methods: Eighteen patients with chronic heart failure were included: 8 in a BESMILE-HF group (age: 67 ± 5 years, EF: 40.4 ± 13.6%) and 10 in a control group (age: 70 ± 13 years, EF: 42.9 ± 12.5%). Both received the usual medications, with the intervention group receiving additionally the BESMILE-HF program for 6 weeks. Feasibility was explored by participants' involvement in the intended intervention. Clinical outcome assessments were conducted at baseline and post-intervention, while adverse events were captured throughout the study period.

Results: The BESMILE-HF program was well-received by patients, and adherence to the intervention was good. The intervention group completed all required home exercises and total home-practice time was correlated with baseline self-efficacy ($r = 0.831$, $p = 0.011$). Moreover, after 6 weeks, self-efficacy increased in the BESMILE-HF group ($p = 0.028$) and the change was higher than in the control [mean difference (MD): 3.2; 95% confidence interval (CI) 0.6–5.9, $p = 0.004$]. For the exercise capacity, the control group demonstrated a significant decline in peak oxygen consumption ($p = 0.018$) whereas, the BESMILE-HF group maintained their exercise capacity ($p = 0.063$). Although the between-group difference was not statistically significance, there was clear clinical improvement in the BESMILE-HF group (1.5 mL/kg/min, 95% CI, −0.3 to 3.2 vs. minimal clinically important difference of 1 mL/kg/min). Throughout the study period, no adverse events related to the intervention were captured.

Conclusions: BESMILE-HF is feasible for patients with chronic heart failure in Chinese settings. A larger sample size and a longer follow-up period is needed to confirm its benefit on clinical outcomes.

Clinical Trial Registration: ClinicalTrials.gov: NCT03180320.

Keywords: exercise-based cardiac rehabilitation, chronic heart failure, pilot randomized controlled trial, self-efficacy for exercise, *Baduanjin* exercise

INTRODUCTION

A hallmark symptom of chronic heart failure (CHF) is impaired exercise tolerance and poor quality of life. Exercise-based cardiac rehabilitation (EBCR) is a proven therapy to improve exercise capacity and quality of life in these patients (1, 2). However, the sub-optimal use of EBCR remains troubling and warrants high priority in global healthcare (3).

While many countries have reported gaps in patient referrals to existing EBCR programs, China has faced an even greater "upstream" challenge—a lack of available EBCR programs (4). One national survey showed that only 24% of China's tertiary hospitals have EBCR programs (5). Unfortunately, the type of comprehensive EBCR programs delivered in high income countries are not feasible in China due to the dearth of rehabilitation facilities, trained professionals, as well as unaffordability (5).

Home-based exercises can empower patients to take responsibility and accountability for their own disease management (6). Most importantly, they increase patients' access to EBCR by confronting the challenge of limited healthcare resources. This includes the paucity of rehabilitation facilities, the lack of medical reimbursement, and sub-standard access to hospital services in rural areas in China (7).

One possible solution tailored to the Chinese setting is traditional *Baduanjin* exercise which is usually practiced at home. *Baduanjin*, translated as Eight Silken Movements, is a form of ancient martial arts that originated in China and has been culturally accepted as being beneficial to one's health in Chinese society (8). This practice has evolved based on traditional Chinese medicine theory and is characterized by interplay between flowing circular physical postures and movements, mindfulness, and breathing exercise in harmony (9). *Baduanjin* is easy to learn and has minimal physical and cognitive demands because it entails only eight simple movements.

A novel and contextually adapted EBCR program using *Baduanjin*, BESMILE-HF, has recently been developed at the Guangdong Provincial Hospital of Chinese Medicine (GPHCM)—a tertiary care hospital and one of the oldest and largest Chinese medicine hospital groups in China (10). **BESMILE-HF** is an acronym for the **B**aduanjin **E**ight-**S**ilken-**M**ovement w**I**th Se**L**f-**E**fficacy building for **H**eart **F**ailure (10). In this program, *Baduanjin* has been applied as the core constituent in a multi-component EBCR including evaluation, consultancy, and education, as well as a series of self-efficacy building strategies to increase adherence, and to maintain exercise compliance over time.

However, uncertainties remain regarding the use of *Baduanjin* in an EBCR program. Therefore, we conducted a pilot study to: (1) assess the feasibility of the BESMILE-HF program regarding patients' adherence to their intended intervention protocols; and (2) attain initial estimates of the effects of the program on clinical outcomes.

METHODS

The study was conducted in accordance with the Declaration of Helsinki, and the BESMILE-HF study has been approved by the Ethics Committee at the GPHCM (number: B2016–202-01) and registered (ClinicalTrials.gov: NCT03180320). All patients were informed about the study, were given the possibility to ask questions and provided consent before participating in the study. Participants were told they could withdraw at any time.

Design

This pilot study was a prospective, randomized controlled trial (RCT). This report includes the recommended elements elaborated upon in the reporting guidelines for pilot RCTs (**Appendix 1**: CONSORT checklist) (11).

Setting

Guangzhou is the capital of Guangdong province and the 3rd-largest city in China. It is located in Southeastern China and has a permanent population of 13.5 million with over 7 million permanent residents in its urban areas (12). GPHCM is a tertiary care public hospital and has four branches in different urban districts of Guangzhou. In this hospital, cardiac rehabilitation is delivered one-on-one to individuals in the hospital outpatient clinic and includes exercise training. The most commonly used exercise is cycle ergometer. However, this service relies on out-of-pocket payment systems. This leads to a financial burden for most patients and results in low participation rate in cardiac rehabilitation.

Abbreviations: BESMILE-HF, Baduanjin Eight-Silken-Movement wIth SeLf-Efficacy building for Heart Failure; CHF, Chronic heart failure; CI, Confidence interval; EBCR, Exercise-based cardiac rehabilitation; GPHCM, Guangdong Provincial Hospital of Chinese Medicine; hsCRP, High sensity C-reactive protein; LVEF, Left ventricular ejection fraction; MACEs, Major adverse cardiac events; MD, Mean difference; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NT-proBNP, N-terminal B-type natriuretic peptide; NYHA, New York Heart Association functional; RCT, Randomized controlled trial; SD, Standard deviation; SEE, Self-Efficacy for Exercise; VO_{2peak}, Peak oxygen consumption.

Participants

Recruitment took place at GPHCM from August to November 2017. Potential participants were identified for eligibility assessment by (1) on-site screening at clinic visits; (2) regular screening of potential participants using electronic medical records; and (3) referrals from physicians (10). Participants were included if they had clinically stable CHF with a New York Heart Association functional (NYHA) classification of II or III without restriction on left ventricular ejection fraction (LVEF) class. The complete list of inclusion and exclusion criteria has been reported previously (10) and is listed in **Appendix 2**.

Schematic Process of the Pilot Study

The schematic process of the pilot study is shown in **Figure 1**. It is in accordance with the study protocol described previously (10).

Randomization, Allocation Concealment, and Blinding

Patients were informed and provided the possibility to ask questions before they signed a consent form. Eligible patients were randomized into either a BESMILE-HF group or a control group. A block randomization sequence was generated by SAS 9.2 (SAS Institute Inc., Cary, NC, USA) in a 1:1 ratio. In the pilot RCT, treatment allocation was conducted using sealed and numbered envelopes. We had made 20 numbered envelopes (a target sample size of 20 participants). As we were able to include 18 participants, hence only the first 18 envelopes were used. Given the nature of the intervention, it was not possible to blind the patients and personnel involved in conducting the programs. Outcome assessors, laboratory technicians, data managers, and statisticians were blinded to treatment allocations.

Intervention and Control

A graphical depiction of the intervention is shown in **Figure 1** and the *Baduanjin* exercise video used in this study can be found online (13, 14). Both groups received the usual medications in accordance with national guidelines for 6 weeks (15). In the BESMILE-HF group, patients also received the pilot BESMILE-HF program. It included the core components of the full-scale 12-week BESMILE-HF program. Before the start of the 6-week home-exercise period, participants attended an exercise course to learn the eight postures at the hospital. A professional coach confirmed their performance. Following the exercise course, participants attended an educational course covering topics related to CHF, as well as exercise on the same day. Initial evaluation was conducted by the cardiologist by reviewing medical history, clinical examination results, and *Baduanjin* performance. Once the evaluation report was finalized, the initial consultation session was conducted by the cardiologist and the cardiology nurse. They would explain the exercise prescription and the results for the initial evaluation following pre-defined outlines. This was followed by 6-weeks of home exercise with guidance and instructions from a *Baduanjin* exercise demonstration video, a graphical exercise brochure, and weekly follow-up. Participants were generally required to do *Baduanjin* 30 min per day, 5 days per week, resulting in a total of 150 min per week. This was tailored according to individual evaluation results. Patients were asked to record their exercise performance in an exercise log (including duration in minutes and frequency) daily throughout the study period. After 6 weeks, participants were contacted to return to the hospital to attend the closure evaluation- and consultation-sessions.

Data Collection

Baseline Data

The following baseline data were collected by questionnaires and through medical chart review: (1) socio-demographics; (2) medical history; and (3) anthropometric variables.

Patient Adherence to the Intervention

Exercise compliance was collected from the self-reported exercise log. This information, along with course attendance rate, assessment- and consultation-session attendance rate, allowed characterization of patients' adherence to the intervention.

Clinical Outcome Measures From Both Groups

The following clinical outcomes proposed for a future full-scale study were collected at baseline and follow-up at the 6th week during an assessment appointment at GPHCM's Heart Failure Center. We used a cardiopulmonary exercise test to measure exercise capacity; a timed up-and-go test to measure balance and mobility; echocardiography to measure cardiac function; as well as biomarkers including N-terminal B-type natriuretic peptide (NT-proBNP), high sensitive C-reactive protein (hsCRP), hemoglobin, and lipid profile. For psychological aspects, we measured quality of life using both a validated disease-specific questionnaire, the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and a generic questionnaire, the EQ5D-visual analog scale; we used the Self-Efficacy for Exercise scale (SEE) to measure exercise self-efficacy; as well as the Hospital Anxiety and Depression Scale to measure depression and anxiety status. Clinical events, such as hospitalizations and major adverse cardiac events (MACEs) and safety outcomes (adverse events), were captured throughout the study period. Details of outcome measurements have been reported previously (10) and are listed in **Appendix 3**.

Statistical Analysis

Baseline socio-demographic and clinical characteristics were summarized for both intervention and control groups. Continuous data were summarized as mean and deviation (SD), or as median and interquartile range (IQR); categorical data were summarized as counts and percentages. For outcome variables, a Wilcoxon signed-rank tests was used to examine changes from baseline to the 6th week within the groups. In addition, the analysis of the baseline, the 6th week, and change from baseline to the 6th week in the intervention group vs. control group was conducted using the Mann–Whitney *U* test. Moreover, Spearman correlation was used to explore the relationship between baseline self-efficacy and patients' total exercise time. Statistical analysis was performed in PASW Statistics 18.0 (IBM SPSS

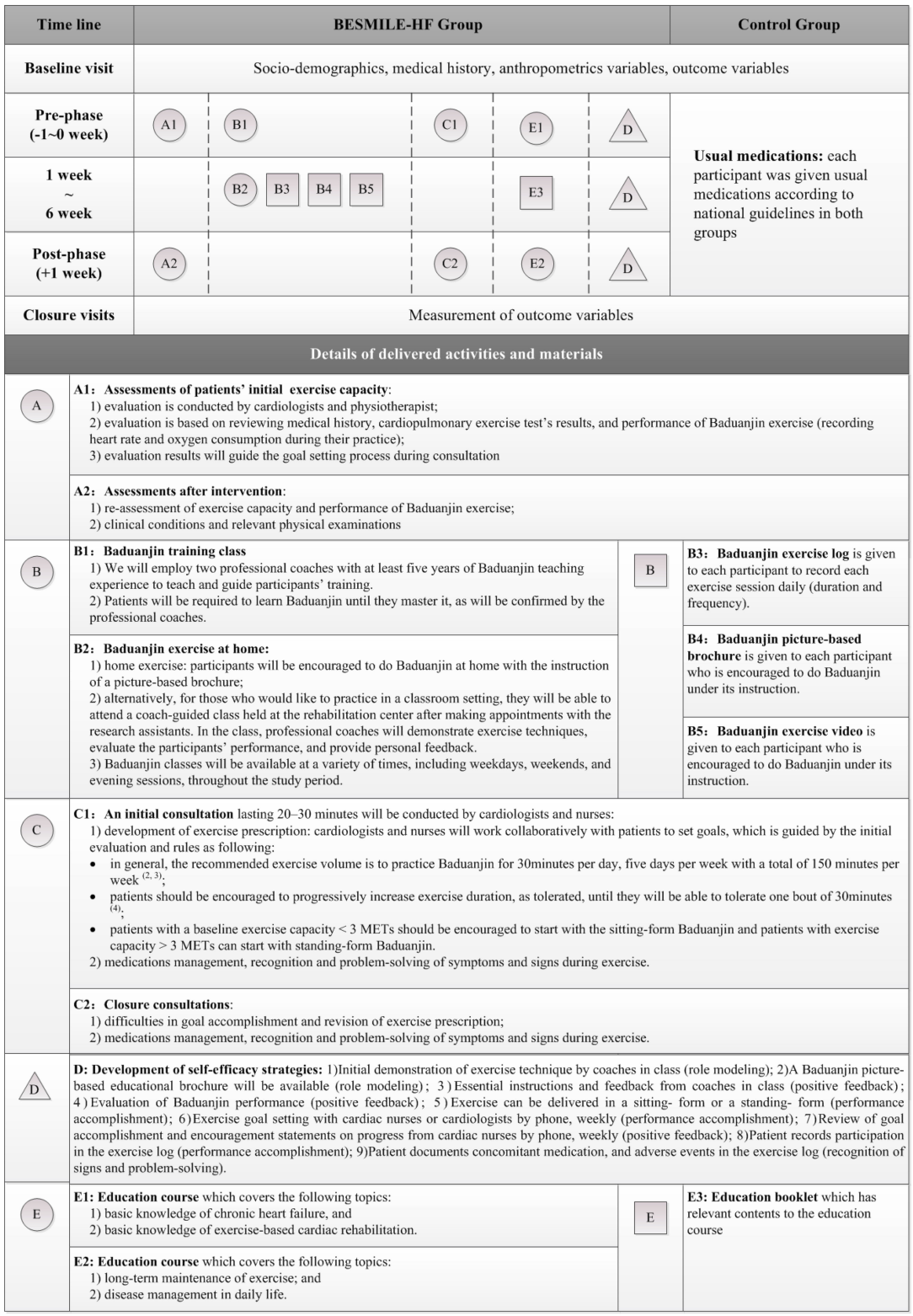


FIGURE 1 | Graphical depiction of the BESMILE-HF program and the research schematic process for both groups, and data collection. Each component of the BESMILE-HF program is depicted separately. We regard components either as activities or materials planned to deliver to the patients. Activities are represented by circles (to reflect their flexibility) and materials by squares (to reflect their fixed nature). Different components are labeled with different letters. Below the diagram, a legend gives a brief description of each component.

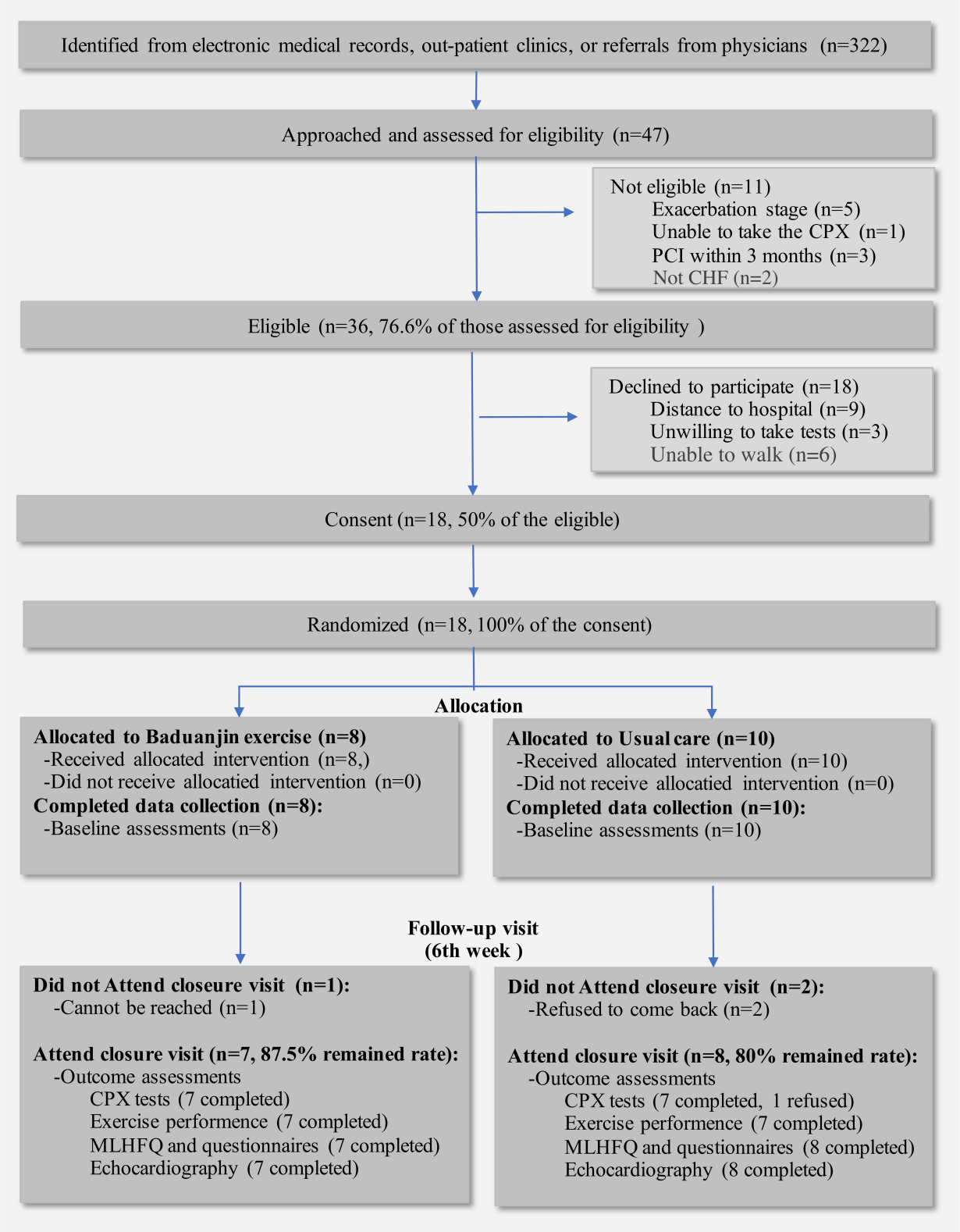


FIGURE 2 | Flowchart of the pilot study. CPX, Cardiopulmonary exercise test; MLHFQ, Minnesota Living with Heart Failure Questionnaire.

TABLE 1 | Baseline characteristics of 18 participating patients.

	All	Intervention	Control
	n = 18	*n* = 8	*n* = 10
Demographics			
Age, years	68 ± 10	67 ± 5	70 ± 13
Male, *n*	17 (94)	8 (100)	9 (90)
BMI, kg/m^2	23 ± 3	23 ± 3	24 ± 3
Smoking			
Never smoke, *n*	9 (50)	5 (63)	4 (40)
Previous smoker, *n*	7 (39)	2 (25)	5 (50)
Current smoker, *n*	2 (11)	1 (13)	1 (10)
Marital status			
Married, *n*	17 (94)	8 (100)	9 (90)
Widowed, *n*	1 (6)	0 (0)	1 (10)
Education			
Primary or less, *n*	6 (33)	3 (38)	3 (30)
High school or above, *n*	12 (67)	5 (62)	7 (70)
NYHA class			
NYHAII, *n*	9 (50)	5 (63)	4 (40)
NYHAIII, *n*	9 (50)	3 (38)	6 (60)
LVEF class			
HFrEF (EF < 40%), *n*	9 (50)	5 (63)	4 (40)
HFmrEF (EF 40–49%), *n*	4 (22)	0 (0)	4 (40)
HFpEF (EF ≥ 50), *n*	5 (28)	3 (38)	2 (20)
Cardiac interventional procedure/surgical treatment			
PCI, *n*	11 (61)	6 (75)	5 (50)
Pacemaker, *n*	4 (22)	1 (13)	3 (30)
ICD, *n*	1 (6)	0 (0)	1 (10)
CRT/CRT-D, *n*	1 (6)	0 (0)	1 (10)
Valvular surgery, *n*	1 (6)	1 (13)	0 (0)
Repairment of V-/A-septal defect, *n*	1 (6)	1 (13)	0 (0)
Comorbidity			
Average comorbidities per patient, mean	4 ± 2	5 ± 2	3 ± 1
Coronary heart diseases, *n*	13 (72)	8 (100)	5 (50)
Hypertension, *n*	11 (61)	6 (75)	5 (50)
Atrial fibrillation/flutter, *n*	6 (33)	3 (38)	3 (30)
Myocardial infarction, *n*	3 (17)	2 (25)	1 (10)
Stroke (Ischemic), *n*	2 (11)	2 (25)	0 (0)
Hyperlipoidemia, *n*	5 (28)	3 (38)	2 (20)
Type2-Diabetes, *n*	11 (61)	5 (63)	6 (60)
Hyperuricemia, *n*	11 (61)	5 (63)	6 (60)
COPD/Asthma, *n*	1 (6)	1 (13)	0 (0)
Current cardiac relevant medications			
ACEI/ARB, *n*	17 (94)	7 (88)	10 (100)
Beta-blockers, *n*	16 (89)	8 (100)	8 (80)
Aldosterone blockades, *n*	16 (89)	7 (88)	9 (90)
Statins, *n*	16 (89)	8 (100)	8 (80)
Platelet anti-aggregants, *n*	14 (78)	8 (100)	6 (60)
Diuretics, *n*	10 (56)	3 (38)	7 (70)
Digoxin, *n*	5 (28)	3 (38)	2 (20)
Calcium antagonists, *n*	4 (22)	1 (13)	3 (30)
Anticoagulant, *n*	3 (17)	0 (0)	3 (30)

Results are presented as mean ± SD or n (%).

BMI, Body Mass Index; NYHA, New York Heart Association; EF, ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range of ejection fraction; HFpEF, heart failure with preserved ejection fraction; PCI, percutaneous coronary intervention; ICD, implantable cardioverter defibrillators; CRT/CRT-D, cardiac resynchronization therapy/with defibrillator; V-/A-, ventricular-or atrial-; COPD, chronic obstructive pulmonary disease; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blocker.

Inc., Armonk, New York, USA). $p < 0.05$ was considered statistically significant.

RESULTS

A total of 322 individuals were identified. After exclusion of obvious exclusion criteria, such as contraindications to exercise or exercise test, not in the clinically stable stage, 47 (14.6%) were approached and screened for eligibility, and 36 (77%) met pre-defined criteria. They were all invited to participate in this pilot study and half of them ($n = 18$) refused to participate. Reasons were as followed: distance to the hospital ($n = 9$), unable to walk ($n = 6$), and unwilling to take the tests ($n = 3$). Female were more likely to refuse participations in our study (72.2% of the refused participants). Finally, a total of 18 (50% of those eligible) patients agreed to participate and were then randomized (**Figure 2**).

Baseline characteristics of the included participants are shown in **Table 1**. The majority of the participants were male (94%) with a mean age of 68 (SD: 10). Clinically, half were NYHA Class II, and the other half were NYHA Class III; 9 (50%), 4 (22%), and 5 (28%) patients had reduced, middle-ranged, and perceived LVEF, respectively. Beta-blockers were used by 89% of the participants. The intervention and control groups were comparable on all demographic and clinical characteristics, expect for history of coronary heart disease.

High Fidelity to Intervention

Participants involved in the BESMILE-HF program regarding the self-reported home exercise and attendant rates in other scheduled sessions are shown in **Figure 3**. Our results showed that the BESMILE-HF program was feasible with relatively high adherence. As a home-based EBCR program, the intervention group demonstrated good compliance with the required exercises. On average, participants exercised 27.5 (SD: 11.4) minutes/day and 5.6 (SD: 2.6) days/week for 6 weeks, reaching both the general required daily exercise time (30 min/day) and exercise frequency (5 days/week), respectively (**Figure 3**). Moreover, the total home-practice times (mins) had a significant

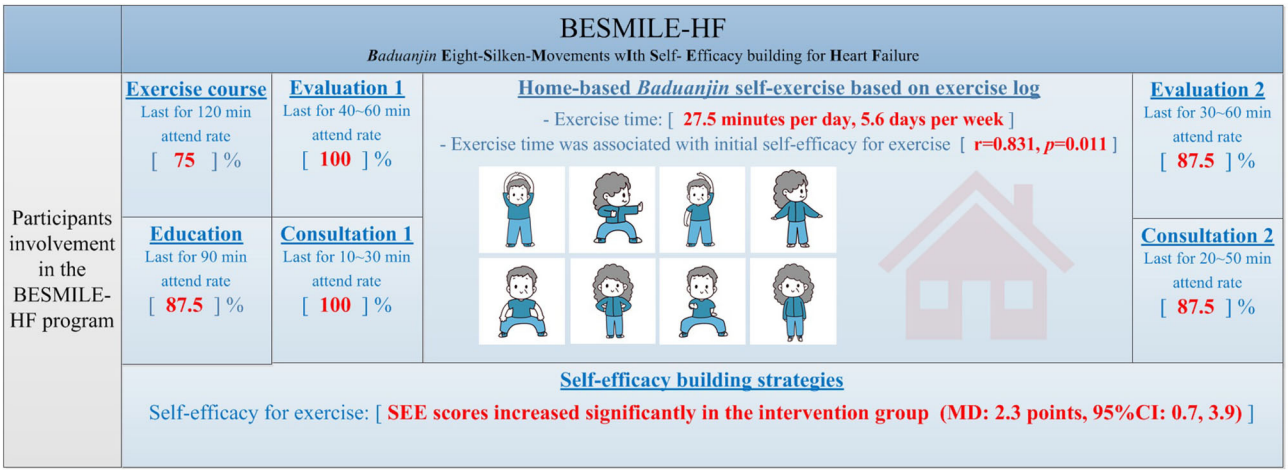


FIGURE 3 | Participants involvement in the BESMILE-HF program ($n = 8$). Participants' involvement in the BESMILE-HF program regarding the self-report home exercise and attendant rates in other scheduled sessions are shown in red. The intervention group had done the required home exercises and total home-practice time was significantly related to baseline self-efficacy. SEE, Self-efficacy for exercise; MD, mean difference.

positive relationship with their baseline self-efficacy scores ($r = 0.831$, $p = 0.011$).

In terms of other part of the BESMILE-HF program, all patients participated in the *Baduanjin* course which lasted for about 120 minutes and their performances were confirmed by the professional coach, except for 2 patients who preferred to learn the exercise via the video (attendance rate: 75%). All patients took the education course at baseline and at 6th week except one patient (overall attendance rate: 87.5%). All patients underwent baseline evaluation-session which included the collection of general assessments as well as individual cardiorespiratory data of *Baduanjin* exercise performance, except for two patients had only the general assessment data. All patients participated to the baseline consultation-session which mainly includes development of exercise prescription. For the closure evaluation- and consultation- sessions, all patients participated except one who died within 6-week (attendance rate: 87.5% for both sessions).

Effects of the BESMILE-HF Program

In terms of the exercise capacity, the control group demonstrated a significant decline in VO_{2peak} (MD: −2.6, 95% CI −4.3 to −0.9), whereas, the BESMILE-HF group maintained their exercise capacity (MD: −1.2, 95% CI −1.2 to 0). Although the between-group difference was not statistically significance, there was a clear clinical improvement in the BESMILE-HF group (1.5 mL/kg/min, 95% CI: −0.3 to 3.2 vs. minimal clinically important difference of 1 mL/kg/min; **Table 2.1**).

After 6 weeks, SEE scores improved significantly in the BESMILE-HF group [mean difference (MD): 2.3, 95% confidence interval (CI) 0.7–3.9, $p = 0.014$; **Table 2.2**], but decreased slightly in the control group (MD: −0.9, 95% CI −3.2 to 1.4, $p = 0.377$; **Table 2.2**). When comparing the score changes between the two groups, a significant difference was found (MD: 3.2; 95% CI 0.6–5.9, $p = 0.004$).

For other clinical outcomes, no significant differences between groups, for either post-intervention values or changes, were observed for: most of the echocardiography parameters (**Table 2.3**); biomarkers such as NT-proBNP and hsCRP (**Table 2.4**); balance/mobility as measured by Timed up-and-go test (**Table 2.5**); quality of life (**Table 2.6**), or status of depression/anxiety (**Table 2.7**).

Safety of the BESMILE-HF Program

Throughout the pilot RCT, no adverse events related to the intervention were captured. However, we documented several MACEs during the study period, one patient in the BESMILE-HF group died due to heart failure exacerbation, and two patients from the control group experienced acute heart failure exacerbation resulting in hospitalization.

DISCUSSION

The findings of this pilot study support the feasibility of the contextually adapted BESMILE-HF program using traditional *Baduanjin* exercise for patients with CHF in China. The BESMILE-HF program was well-received by patients. As a home-based EBCR program, the intervention group demonstrated exceptional compliance with the required exercises. We also found that one's initial self-efficacy had a positive effect on the total exercise time. More importantly, intervention can improve participants' exercise self-efficacy and may have benefit on exercise capacity.

The BESMILE-HF program's feasibility is primarily attributed to its in-home nature and the use of traditional *Baduanjin* exercise. According to a recent consensus statement on EBCR delivery in low-resource settings, safe, equipment-free, low-cost, and easy-to-implement exercise modalities provide the most practical options for Chinese settings (16). Compared to other low-cost outdoor activities such as walking, biking, running, and

TABLE 2 | Clinical outcomes in each group and between-group comparison ($n = 18$).

Outcomes	Control		Intervention		*P*-value[e]
	Baseline	6th week	Baseline	6th week	
1. CPX parameters					
Exercise test time, seconds	399 (309.8, 408.3)	329 (253, 419)	501 (400.8, 538.5)	404 (387, 488)	0.902
Wordload, watt	66 (53.3, 77.8)	70 (53, 85)	82.5 (65.8, 89.3)	82 (80, 85)	1
RER	55.5 (43.7, 59.5)	52.2 (40.3, 67.1)	60 (53.5, 68)	62.6 (62, 65.4)	1
VO_{2at}, mL/kg/min[a]	1 (1, 1.1)	1.1 (1, 1.3)	1.1 (1, 1.2)	1.1 (1, 1.2)	0.165
VO_{2peak}, mL/kg/min[a]	10.9 (8.9, 14.1)	9.7 (6.1, 11.6)[c]	12.9 (11, 13.6)	11 (10.3, 12.1)	0.128
VO_{2peak} %pred, %[a]	14.3 (10.2, 17.4)	13.6 (8.6, 15.2)[c]	15.9 (15.1, 16.8)	14.3 (13.6, 16.4)	0.295
HRR, bpm[a]	54.4 (49.4, 62.2)	47.6 (30.7, 51.7)[c]	59.2 (56, 62.6)	59.2 (50.6, 61.1)	0.128
Peak O_2 pulse, mL/beat[a]	29.5 (14.5, 42.5)	25 (11, 34)	35 (25.3, 47)	26 (16, 40)	0.097
V_E/VCO_2, slope[b]	8.1 (7, 10)	7 (6.4, 9)[c]	8.9 (7.6, 10.7)	10 (7.7, 11.1)	0.805
dVO_2/dWR, mL/min/W[a]	32.7 (29.1, 41.2)	36.7 (33.3, 42.9)[c]	32.9 (24.3, 35.9)	33.6 (28.2, 35.4)	0.073
FEV1 %pred, %[a]	7.4 (6.3, 8)	8.3 (4, 8.8)	7 (5.5, 8.7)	10.3 (9.4, 11.4)[d]	0.165
MVV %pred, %[a]	71 (60.8, 83.3)	68 (56, 87)	74 (54.5, 85)	78 (63, 82)	0.053
2. Self-efficacy for exercise					
SEE[a]	3.9 (3.1, 6.6)	4.3 (2.7, 5.1)	3.5 (1, 6.8)	7.2 (4, 9.9)[c,d]	0.04
3. Echocardiography					
LVEF, %[a]	41 (35, 47.8)	36.5 (34, 39.5)	34.5 (30.5, 50)	45 (36, 53)	0.281
FS, %[a]	24 (19.5, 30)	19 (17, 22.5)	21 (17.3, 28.8)	27 (18, 29)[d]	0.04
SV, mL/bit[a]	80 (64, 83.5)	82.5 (63.8, 92.8)	66 (57.8, 86.8)	83 (70, 97)	0.165
LVEDD, mm[a]	60 (51.8, 63.5)	64 (59, 67.5)	60 (49.5, 70)	59 (51, 67)	0.281
PASP, mmHg[b]	31 (19, 45)	26 (20.3, 36.5)	31 (25.8, 43.8)	27 (25, 32)	0.536
4. Biomarkers					
NT-proBNP, pg/L[b]	1,177 (717.8, 2351)	872.9 (489.7, 4191.5)	1,346 (268.5, 2686.3)	703 (289, 1062)	0.397
hsCRP, mg/L[b]	5.4 (1.1, 10.8)	6.2 (1.8, 15.9)	2.4 (0.5, 5.7)	1.6 (1, 4.4)	0.694
Total cholesterol, mmol/L[b]	4.3 (3, 4.6)	3.7 (3.3, 4.2)	4.2 (3.5, 4.4)	4.1 (3.6, 4.7)	0.072
LDL-C, mmol/L[b]	2.4 (1.7, 3)	2.2 (1.7, 2.7)	2.4 (2.2, 2.9)	2.7 (1.9, 3)	0.336
HDL-C, mmol/L[a]	1.2 (0.8, 1.6)	1.1 (0.8, 1.6)	1 (1, 1.2)	1 (0.9, 1.3)	0.152
Triglycerides, mmol/L[b]	1.3 (0.6, 1.8)	1.1 (0.7, 1.5)	1.5 (1.1, 2.2)	1.2 (1, 1.7)	0.536
Hemoglobin, g/L[a]	130.5 (124.3, 141.8)	137 (127, 147)[c]	134 (125.5, 142)	135 (131, 142)	0.731
5. Exercise performance					
Timed-Up and Go, seconds[b]	8.1 (6.5, 10.8)	8.6 (7.8, 10.7)[c]	7.1 (6.6, 9.8)	7.7 (6.9, 8.7)	0.094
Left-hand grip strength, kg[a]	28.6 (20.8, 35.5)	28.7 (22, 37.3)	29.7 (23.5, 32.2)	31.2 (26.1, 33.1)	0.536
Right-hand grip strength, kg[a]	31.8 (22.9, 37.6)	27.6 (23.9, 35.3)	29.9 (26.4, 33.1)	27.4 (23.6, 27.5)[c]	0.397
6. Quality of life					
MLHFQ total score[b]	20.5 (13.8, 65.5)	16.5 (3.3, 23.5)	12.5 (5.5, 31.8)	12 (1, 26)	0.779
EQ-5D-VAS score[a]	80 (73.8, 90)	86.5 (80, 98.8)	85 (64.8, 93.8)	75 (70, 100)	0.232
7. Depression and anxiety status					
HADS-anxiety score[b]	1.5 (1, 7)	1 (1, 3)	0.5 (0, 3)	1 (0, 6)	0.867
HADS-depression score[b]	1 (1, 3)	2.5 (1, 5.5)	1 (0, 6)	0 (0, 1)	0.072

Continuous data are summarized as median and interquartile range (IQR).

CPX, cardiopulmonary exercise test; RER, respiratory exchange ratio; METs, metabolic equivalents; VO_{2at}, oxygen uptake at AT; VO_{2peak}, peak oxygen uptake; HRR, heart rate reserve 1 min post exercise; V_E/VCO_2, minute ventilation-carbon dioxide production; dVO_2/dWR, the rate of increase in VO_2 relative to work rate;FEV1 %pred, percentage of predicted value of forced expiratory volume in 1 min; MVV %pred, percentage of predicted value of maximum voluntary ventilation; LVEF, Left ventricular ejection fraction; FS, fractional shortening; SV, stroke volume; LVEDD, left ventricular end-diastolic diameter; PASP, pulmonary artery systolic pressure; NT-proBNP, N-terminal B-type natriuretic peptide; hsCRP, high-sensitivity C-reactive protein; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; MLHFQ, Minnesota Living with Heart Failure Questionnaire; EQ-5D-VAS, EQ-5D-visual analog scale; HADS, Hospital Anxiety and Depression Scale; SEE, Self-efficacy for exercise questionnaire.

[a]*Higher value more favorable.*

[b]*Lower value more favorable.*

[c]$p < 0.05$, *refers to the comparison with baseline using Wilcoxon signed-rank tests.*

[d]$p < 0.05$, *refers to the comparison with the control group using Mann–Whitney U test at the 6th week.*

[e]*Comparison was conducted for the change from baseline to the 6th week in the intervention group vs. control group was conducted using the Mann–Whitney U test.*

swimming, a home-based modality might be a more attractive and sensible option for optimal EBCR flexibility, given the fact that one-third of Chinese HF patients had difficulty or were unable to leave their homes due to their symptoms (17). In addition, *Baduanjin* exercise is an adaptable form of exercise that can be practiced in any place, and at any time. It also requires no special equipment and is not time-consuming. Hence, it is easy to be incorporated into daily routines.

Generally, adherence to exercise programs is low among CHF patients, which may limit its effect on clinical outcomes (18). In practice, self-efficacy plays a crucial role in adherence (19). In this study, a statistically significant positive relationship was found between baseline self-efficacy scores and individual exercise time. This result is supported by emerging literature in which self-efficacy is reported as the dominant factor in exercise uptake and maintenance among the CHF population (20). Therefore, it is reasonable to assume that the BESMILE-HF program might increase participants' adherence and maintenance of exercise compliance over time.

It is important to highlight that there was a significant improvement in self-efficacy score in the intervention group, but not in the control group. The between-group difference was found to be statistically significant, even within the context of this pilot study. However, the lack of periodic contact with doctors or nurses in the control group could have resulted in bias since the frequent contact with rehabilitation staff may explain some of the improvement in the intervention group. Nevertheless, a recent RCT reported that the 16-week *Baduanjin* training could improve self-efficacy for managing chronic diseases in community-living adults, such as increased confidence to mitigate fatigue, physical discomfort/pain, and emotional distress, and to be able to accomplish various tasks and activities (21). Our results also dovetail with previous evidence which shows that Tai Chi, a similar style of exercise, can improve CHF patients' self-efficacy (22).

Self-efficacy is defined as "the perceived confidence in the ability to take successful action and perform a specific task." It is centered on four core elements: "role modeling," "positive feedback," "performance accomplishment," and "recognition of problems and problem-solving" (23). In the BESMILE-HF program, specific adherence strategies for each of the four elements of self-efficacy were adopted and delivered as adjuncts to the *Baduanjin* exercise. Examples include an exercise course with an initial demonstration of exercise techniques by a coach and a graphic exercise brochure (role modeling); an evaluation session with feedback on *Baduanjin* performance and a weekly phone-call follow-up to review the progress by cardiac nurses (positive feedback); an exercise log to record individuals' own daily home-exercise (performance accomplishment); an educational course about disease management in daily life (recognition of problems and problem-solving).

The BESMILE-HF program is a complex intervention with several interacting components. This means that there will be a certain number of behaviors required by those delivering or receiving the intervention, as well as difficulties. Moreover, flexibility and tailoring of the intervention was permitted, as ensuring strict fidelity to a protocol may have been inappropriate. Evaluations of clinical outcomes are often undermined by problems such as delivery of the intervention, recruitment and retention, and smaller-than-expected effect sizes (24). Our small sample size was under-powered to reach a statistically significant effect on clinical outcomes such as VO_{2peak}. However, there was a favorable trend with a clinically significant difference between two groups at the week 6 follow-up. In addition, our research team has recently confirmed that *Baduanjin* training intensity fulfilled ACSM's recommendations for bodily stimulation resulting in physiologically oriented outcomes (25). Moreover, previous studies have reported that *Baduanjin* improves exercise capacity (26–31). Therefore, the benefits of *Baduanjin* on exercise capacity should be expected from continued practice. Of note, *Baduanjin* can also be practiced in a sitting-form. Hece, for those patients with orthopedic limitations or other concomitant illness, the clinicians can also proposed this exercise to their patients to practice at home.

LIMITATIONS

As with all studies, there are potential limitations to note. Firstly, the generalizability of the results might be limited by the characteristics of the included patients: NYHA II and III CHF patients who are relatively young and suffer from heart failure of mild-moderate severity. However, we still believe that our main findings described above are mostly applied to other parts of China. This is because the demographic and clinical characteristics of the study participants are similar to the those CHF patients undergoing a cross-sectional survey in Guangzhou (32) and in China as a whole (17). In addition, although we only recruited CHF patients with NYHA classification of II or III, the findings on *Baduanjin* intensity also apply to CHF patients in general. This is because patients with NYHA classification of II or III account for 83% of the HF patients in the stable stage in this setting (17). Secondly, 94% of the pilot study population was male. Sex has been showed to be an influencing factor in the change of VO_{2peak} and time spent on exercise (18, 33). Additional studies should strive to include an equal distribution of men and women. Thirdly, due to the nature of the intervention, blinding of patients and implementors was impossible. Trials with inadequate blinding are likely to exaggerate treatment effects, especially with regard to subjective results (such as SEE) and with participants with knowledge of traditional Chinese culture (34). However, we have blinded outcome assessors to minimize the detection bias. Fourthly, although the intervention group completed the required home exercises as reported through exercise logs, it should be noted that self-reported practice exercise tends to be overestimated (20). Assessing and ensuring adequate levels of intervention adherence is a challenge in most self-directed home-based interventions. However, self-reported exercise records, because of their ease of use, remain one of the most common tools for recording exercise data (20). Future, full-scale clinical trials should consider use of objective data collection methods to validate self-reported exercise data. Finally, given the scope of the pilot study and limited resources, the sample size was small. Therefore, the pilot RCT was not powered to

test efficacy. However, the primary aim of the pilot study is to explore intervention feasibility, such as the recruitment rate, data collection process, and retention rate. Moreover, this small size study can still provide us some information regarding the preliminary efficacy of this intervention, as there is no data available regarding the BESMILE-HF program.

CONCLUSION

This pilot study indicates that the BESMILE-HF program using traditional *Baduanjin* exercise, is feasible for patients with CHF in the Chinese setting. This practice may also increase patients' long-term adherence to exercise by improving exercise self-efficacy. Its potential benefits on clinical outcomes need confirmation with a larger sample size and a longer follow-up period. A full-scale RCT has been launched to determine the efficacy and safety of the BESMILE-HF program in patients with CHF.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee at the Guangdong Provincial Hospital of Chinese Medicine (number: B2016–202-01). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XC, WJ, CL, ZW, WL, and GM contributed to the conception and design of the research. ZW and WL contributed to obtaining funding and supervising the work. XC drafted the first version of the manuscript and revised it based on other authors: WJ, TO, CL, ZW, WL, and GM contribution. All authors contributed important intellectual content to the critical revision of the manuscript and read and approved the final manuscript.

FUNDING

This work was supported by the General Research Fund of Traditional Chinese Medicine Science and Technology from Guangdong Provincial Hospital of Chinese Medicine (YN2018ML02), the Clinical Research Funding of Traditional Chinese Medicine Science and Technology (Project 1010) from Guangdong Provincial Hospital of Chinese Medicine (YN10101910), and the China Scholarships Council (201608440264).

ACKNOWLEDGMENTS

The authors wish to thank the professional coach (Haojian Yu) from the GPHCM Department of Cardiology in teaching the exercise; cardiology nurses (Yunxiang Fan) from the GPHCM Department of Cardiology for assistance with conducting the education-/evaluation-/consultation-sessions and collecting data; as well as research assistants from the GPHCM for assistance with collecting data. Results of the upload manuscript were partially presented as an abstract at the 23rd Annual Scientific Meeting of the Heart-Failure-Society-of-America (HFSA) and the American Association of Cardiovascular and Pulmonary Rehabilitation 34th Annual Meeting. Some parts of the results of the upload manuscript were included the doctoral thesis of XC and have been appeared online.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.715207/full#supplementary-material

REFERENCES

1. Fleg JL, Cooper LS, Borlaug BA, Haykowsky MJ, Kraus WE, Levine BD, et al. Exercise training as therapy for heart failure: current status and future directions. *Circ Heart Fail.* (2015) 8:209–20. doi: 10.1161/CIRCHEARTFAILURE.113.001420
2. Taylor RS, Sagar VA, Davies EJ, Briscoe S, Coats AJ, Dalal H, et al. Exercise-based rehabilitation for heart failure. *Cochrane Database Syst Rev.* (2014) 2014:CD003331. doi: 10.1002/14651858.CD003331.pub4
3. Turk-Adawi K, Sarrafzadegan N, Grace SL. Global availability of cardiac rehabilitation. *Nat Rev Cardiol.* (2014) 11:586–96. doi: 10.1038/nrcardio.2014.98
4. Sun XG. Rehabilitation practice patterns for patients with heart failure: the Asian perspective. *Heart Fail Clin.* (2015) 11:95–104. doi: 10.1016/j.hfc.2014.09.001
5. Zhang Z, Pack Q, Squires RW, Lopez-Jimenez F, Yu L, Thomas RJ. Availability and characteristics of cardiac rehabilitation programmes in China. *Heart Asia.* (2016) 8:9–12. doi: 10.1136/heartasia-2016-010758
6. Zwisler AD, Norton RJ, Dean SG, Dalal H, Tang LH, Wingham J, et al. Home-based cardiac rehabilitation for people with heart failure: a systematic review and meta-analysis. *Int J Cardiol.* (2016) 221:963–9. doi: 10.1016/j.ijcard.2016.06.207
7. David R. Thompson, Yu C-M. Cardiac Rehabilitation: China. In: Joep P, Helmut G, Irene H, Philippe S, Peter M, Catherine M, et al., edtiors. *Cardiovascular Prevention and Rehabilitation*. London: Springer (2007).
8. Koh TC. Baduanjin – an ancient Chinese exercise. *Am J Chin Med.* (1982) 10:14–21. doi: 10.1142/S0192415X8200004X
9. Wang N, Guo Y. Traditional Chinese practice, a promising integrative intervention for chronic non-infectious disease management. *Chin J Integr Med.* (2018) 24:886–90. doi: 10.1007/s11655-018-2572-7
10. Chen X, Jiang W, Lin X, Lundborg CS, Wen Z, Lu W, et al. Effect of an exercise-based cardiac rehabilitation program "Baduanjin Eight-Silken-Movements with self-efficacy building" for heart failure (BESMILE-HF study): study protocol for a randomized controlled trial. *Trials.* (2018) 19:150. doi: 10.1186/s13063-018-2531-9
11. Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *BMJ.* (2016) 355:i5239. doi: 10.1136/bmj.i5239

12. *2015 Population Scope and Distribution in Guangzhou Population Department of Guangzhou Statistics Bureau*. (2015). Available online at: www.gzstats.gov.cn (accessed November 11, 2016).
13. *Baduanjin Exercises [YouTube]*. Available online at: https://www.youtube.com/watch?v=i2YY6t1JhCY&list=PLPCWVScVb76hNWtgDyXyiI9tz4977_6N6 (accessed June 29, 2020).
14. *Baduanjin Exercise (Tutorial) [YouTube]*. Available online at: https://www.youtube.com/watch?v=UculAU8mWd8 (accessed June 29, 2020).
15. Chinese Society of Cardiology of Chinese Medical Association EBoCJoC. The Chinese guidelines for diagnosis and treatmen for heart failure 2018. *Chin J Cardio*. (2018) 46:760–89. doi: 10.3760/cma.j.issn.0253-3758.2018.10.004
16. Grace SL, Turk-Adawi KI, Contractor A, Atrey A, Campbell N, Derman W, et al. Cardiac rehabilitation delivery model for low-resource settings. *Heart*. (2016) 102:1449–55. doi: 10.1136/heartjnl-2015-309209
17. Jackson JD, Cotton SE, Bruce Wirta S, Proenca CC, Zhang M, Lahoz R, et al. Burden of heart failure on patients from China: results from a cross-sectional survey. *Drug Des Dev Ther*. (2018) 12:1659–68. doi: 10.2147/DDDT.S148949
18. Barbour KA, Miller NH. Adherence to exercise training in heart failure: a review. *Heart Fail Rev*. (2008) 13:81–9. doi: 10.1007/s10741-007-9054-x
19. Rajati F, Sadeghi M, Feizi A, Sharifirad G, Hasandokht T, Mostafavi F. Self-efficacy strategies to improve exercise in patients with heart failure: a systematic review. *ARYA Atherosclerosis*. (2014) 10:319–33.
20. Deka P, Pozehl B, Williams MA, Yates B. Adherence to recommended exercise guidelines in patients with heart failure. *Heart Fail Rev*. (2017) 22:41–53. doi: 10.1007/s10741-016-9584-1
21. Xiao X, Wang J, Gu Y, Cai Y, Ma L. Effect of community based practice of Baduanjin on self-efficacy of adults with cardiovascular diseases. *PLoS ONE*. (2018) 13:e0200246. doi: 10.1371/journal.pone.0200246
22. Yeh GY, McCarthy EP, Wayne PM, Stevenson LW, Wood MJ, Forman D, et al. Tai chi exercise in patients with chronic heart failure: a randomized clinical trial. *Arch Intern Med*. (2011) 171:750–7. doi: 10.1001/archinternmed.2011.150
23. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. *Psychol Rev*. (1977) 84:191–215. doi: 10.1037/0033-295X.84.2.191
24. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ*. (2008) 337:a1655. doi: 10.1136/bmj.a1655
25. Chen XK, Marrone G, Olson TP, Lundborg CS, Zhu H, Wen ZH, et al. Intensity level and cardiorespiratory responses to baduanjin exercise in patients with chronic heart failure (forthcoming). *ESC Heart Fail*. (2020) 7:3782–91. doi: 10.1002/ehf2.12959
26. Xiong X, Xu D. Therapeutic effect of Baduanjin on patients with coronary heart disease and chronic heart failure [in Chinese]. *China Modern Med J*. (2016) 18:55–6. doi: 10.3969/j.issn.1672-9463.2016.05.016
27. Yang X, Feixiang Huang, Yongchao Shi, Yanxia Wang, Ye L. Effect of aerobics training on exercise tolerance in patients with chronic heart failure [in Chinese]. *Chin J Nurs*. (2015) 50:193–7. doi: 10.3761/j.issn.0254-1769.2015.02.015
28. Yan X. Effects of Liuzi and Ba Duan Jin training on exercise tolerance in patients with chronic heart failure [in Chinese]. *Chin Trad Med Modern Distance Educ*. (2016) 14:126–8. doi: 10.3969/j.issn.1672-2779.2016.16.055
29. Jing Y. Effect of TCM aerobics on exercise endurance in patients with chronic heart failure [in Chinese]. *Chin Trad Med Modern Distance Educ*. (2015) 13:12–4. doi: 10.3969/j.issn.1672-2779.2015.21.006
30. Chen DM, Yu WC, Hung HF, Tsai JC, Wu HY, Chiou AF. The effects of Baduanjin exercise on fatigue and quality of life in patients with heart failure: a randomized controlled trial. *Eur J Cardiovasc Nurs*. (2017) 17:456–66. doi: 10.1177/1474515117744770
31. Li R. Observation on the improvement of cardiac function and quality of life in elderly patients with chronic heart failure by Ba Duan Jin [in Chinese]. *Massage Rehabil Med*. (2017) 8:23–5. doi: 10.3969/j.issn.1008-1879.2017.24.009
32. Lai SW. *The Investigation of the Current Status of the Use of Traditional Chinese Medicine (TCM) Exercise Regimen in Patients With Chronic Heart Failure* (PhD). Guangzhou University of Traditional Chinese Medicine (2014).
33. Tierney S, Mamas M, Woods S, Rutter MK, Gibson M, Neyses L, et al. What strategies are effective for exercise adherence in heart failure? A systematic review of controlled studies. *Heart Fail Rev*. (2012) 17:107–15. doi: 10.1007/s10741-011-9252-4
34. McCambridge J, Witton J, Elbourne DR. Systematic review of the Hawthorne effect: new concepts are needed to study research participation effects. *J Clin Epidemiol*. (2014) 67:267–77. doi: 10.1016/j.jclinepi.2013.08.015

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 28 July 2021
doi: 10.3389/fcvm.2021.682253

Differential Evaluating Effect on Exercise Capacity of Cardiopulmonary Exercise Testing and Treadmill Exercise Testing in Post-percutaneous Coronary Intervention Patients

Yifan Gao[1,2†], Bin Feng[2†], Rong Hu[1,2], YingYue Zhang[1,2], Yajun Shi[2], Yong Xu[2‡] and Jing Ma[2*‡]*

[1] Medical School of Chinese PLA, Beijing, China, [2] Department of Cardiology, Chinese PLA General Hospital, Beijing, China

OPEN ACCESS

Edited by:
Richard Yang Cao, Shanghai Xuhui Central Hospital, China

Reviewed by:
Yihua Bei, Shanghai University, China
Hong-Tao Liu, Shanghai Xuhui Central Hospital, China

***Correspondence:**
Yong Xu
13701141929@163.com
Jing Ma
crystalma@126.com

†*These authors share first authorship*

‡*These authors share last authorship*

Specialty section:
This article was submitted to General Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

Received: *18 March 2021*
Accepted: *24 June 2021*
Published: *28 July 2021*

Citation:
Gao Y, Feng B, Hu R, Zhang Y, Shi Y, Xu Y and Ma J (2021) Differential Evaluating Effect on Exercise Capacity of Cardiopulmonary Exercise Testing and Treadmill Exercise Testing in Post-percutaneous Coronary Intervention Patients. Front. Cardiovasc. Med. 8:682253. doi: 10.3389/fcvm.2021.682253

Background: Treadmill exercise testing (TET) is commonly used to measure exercise capacity. Studies have shown that cardiopulmonary exercise testing (CPET) is more accurate than TET and is, therefore, regarded as the "gold standard" for testing maximum exercise capacity and prescribing exercise plans. To date, no studies have reported the differences in exercise capacity after percutaneous coronary intervention (PCI) using the two methods or how to more accurately measure exercise capacity based on the results of TET.

Aims: This study aims to measure maximum exercise capacity in post-PCI patients and to recommend exercise intensities that ensure safe levels of exercise.

Methods: We enrolled 41 post-PCI patients who were admitted to the Cardiac Rehabilitation Clinic at the First Medical Center, the Chinese PLA General Hospital, from July 2015 to June 2016. They completed CPET and TET. The paired sample *t*-test was used to compare differences in measured exercise capacity, and multiple linear regression was applied to analyze the factors that affected the difference.

Results: The mean maximum exercise capacity measured by TET was 8.89 ± 1.53 metabolic equivalents (METs), and that measured by CPET was 5.19 ± 1.23 METs. The difference between them was statistically significant ($p = 0.000$) according to the paired sample *t*-test. The difference averaged 40.15% ± 2.61% of the exercise capacity measured by TET multiple linear regression analysis showed that the difference negatively correlated with waist-hip ratio (WHR).

Conclusion: For the purpose of formulating more accurate exercise prescription, the results of TET should be appropriately adjusted when applied to exercise capacity assessment.

Clinical Trial Registration: http://www.chictr.org.cn/ number, ChiCTR2000031543.

Keywords: cardiac rehabilitation, exercise test, coronary artery, exercise prescription, aerobic exercise

INTRODUCTION

Reasonable cardiac rehabilitation (CR), especially exercise training can effectively reduce heart-related symptoms in post-percutaneous coronary intervention (post-PCI) patients, improve long-term prognosis, and reduce the probability of recurrent myocardial infarction or unscheduled revascularization (1–3). The most important aspect of exercise training is identification of appropriate exercise intensity depending a lot on maximum exercise capacity, so as to accurately instruct patients with cardiovascular disease how to exercise safely. There are many ways to measure exercise capacity, including the 6-min walk test and treadmill exercise testing (TET). When patients are instructed to return to daily life, levels of exercise capacity correspond to various daily activities (4–6). It has been revealed that cardiopulmonary exercise testing (CPET), a method that accurately measures oxygen and carbon dioxide metabolism, measures true oxygen uptake and estimates maximum exercise capacity more accurately. Therefore, it is considered the "gold standard" for testing maximum exercise capacity and prescribing exercise plans (7, 8).

However, in most developing countries, CPET is not common, and doctors had to use the results of ordinary TET to estimate the maximum exercise capacity, so as to formulate exercise prescriptions for post-PCI patients (9). In developed countries, despite the decline in the use of TET for clinical purposes in recent years, there are still examples of exercise capacity estimation through it (10). Actually, ordinary TET lacks synchronous gas metabolism monitoring and can only estimate the exercise capacity at various stages. Moreover, the results estimated by different TET protocols were inconsistent (11). It has been pointed out that exercise capacity estimated by TET is greater than that measured by CPET (12–14). Consequently, using TET results to formulate exercise prescription may pose a risk of recommending exercise intensity that exceeds the patient's actual capacity and increase the risk of cardiovascular events.

Nevertheless, the similarities and differences between CPET and TET in evaluating the maximum exercise capacity in the post-PCI patients remain largely unknown. An in-depth study on the conversion relationship between TET and CPET would provide accurate, objective values for medical institutions without CPET, thereby improving the safety of post-PCI patients during exercise training. Therefore, the present study employed CPET and TET to measure the maximum exercise capacity of post-PCI patients and to examine the conversion factor relating the two means, so as to provide a basis for the assessment of relatively actual exercise capacity of post-PCI patients and the formulation of accurate exercise prescriptions, thereby improving the safety of exercise prescription.

MATERIALS AND METHODS

Subjects

A total of 41 patients were selected from those admitted to the Cardiac Rehabilitation Clinic, Chinese PLA General Hospital, from July 2015 to June 2016. Inclusion criteria include chronic coronary syndrome confirmed by coronary arteriography, status-post-stent implantation. Exclusion criteria were as follows: (1) acute myocardial infarction (within 2 days); (2) high-risk unstable angina pectoris; (3) uncontrolled symptomatic arrhythmia or hemodynamic instability; (4) decompensated symptomatic heart failure; and (5) mental or physical handicaps or inability to cooperate during exercise.

The study was approved by the ethics committee of the Chinese PLA General Hospital and registered in Chinese clinical trial registry (ChiCTR2000031543). All subjects gave written informed consent. The whole study conforms with the principles outlined in the Declaration of Helsinki.

Clinical Data Collection and Preparation

We established a clinical database to record basic information such as age, sex, height, and weight of all subjects. We calculated the body mass index (BMI) and waist-hip ratio (WHR) and recorded in detail the time of PCI treatment, the number of stents implanted, coexisting diseases such as hypertension, diabetes, and hyperlipidemia, and medications such as β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB), statins, diltiazem, and nitrates. Patients were asked not to eat within 3 h before starting the exercise testing; however, they could drink an appropriate amount of water. The subjects were asked to wear comfortable and suitable clothes, shoes, and socks. Other strenuous exercise was to be avoided within 24 h of exercise testing, and medications such as β-blockers, calcium antagonists, and nitrates should be held until immediately after the testing. All patients underwent CPET first, and then TET 1 week later, from which the relevant results were recorded.

Cardiopulmonary Exercise Testing

A cycle ergometer (CS-200, Schiller, Obfelden, Switzerland) was adopted as the exercise device. Calibration was performed before each testing. The calibrated gases were as follows: 4% CO_2, 16% O_2, and N_2 (the balance). A ramp protocol was applied to identify the symptom-limiting maximum exercise load. The specific protocol was as follows: 0 W: rest for 1 min; 0 W: warm-up for 2 min; the treadmill intensity started at 5 W. Thereafter, the intensity for men was ramped up at 25 W/min and for women it was 20 W/min. The speed was maintained at 60–70 rpm until the maximum exercise load was reached (i.e., no more exercise could be performed because of dyspnea or fatigue of the legs or the whole body, or rotational speed decreased to <50 rpm). The recovery phase intensity was 0 W until the heart rate, VO_2, VCO_2, and other indicators returned to baseline, whereupon testing was terminated. The measured METs was calculated using the following equation: METs = peak VO_2/3.5.

Treadmill Exercise Testing

Submaximal exercise testing was carried out according to the Bruce protocol using the exercise treadmill (T2100, GE Medical Systems, Milwaukee, WI, USA). The specific protocol began at a gradient of 10% and a speed of 1.7 mph. At the end of each stage, the gradient increased by 2%; the speed increased to 2.5, 3.4, 4.2, 5.0, and 5.5 mph for the subsequent stages. The patient exercised

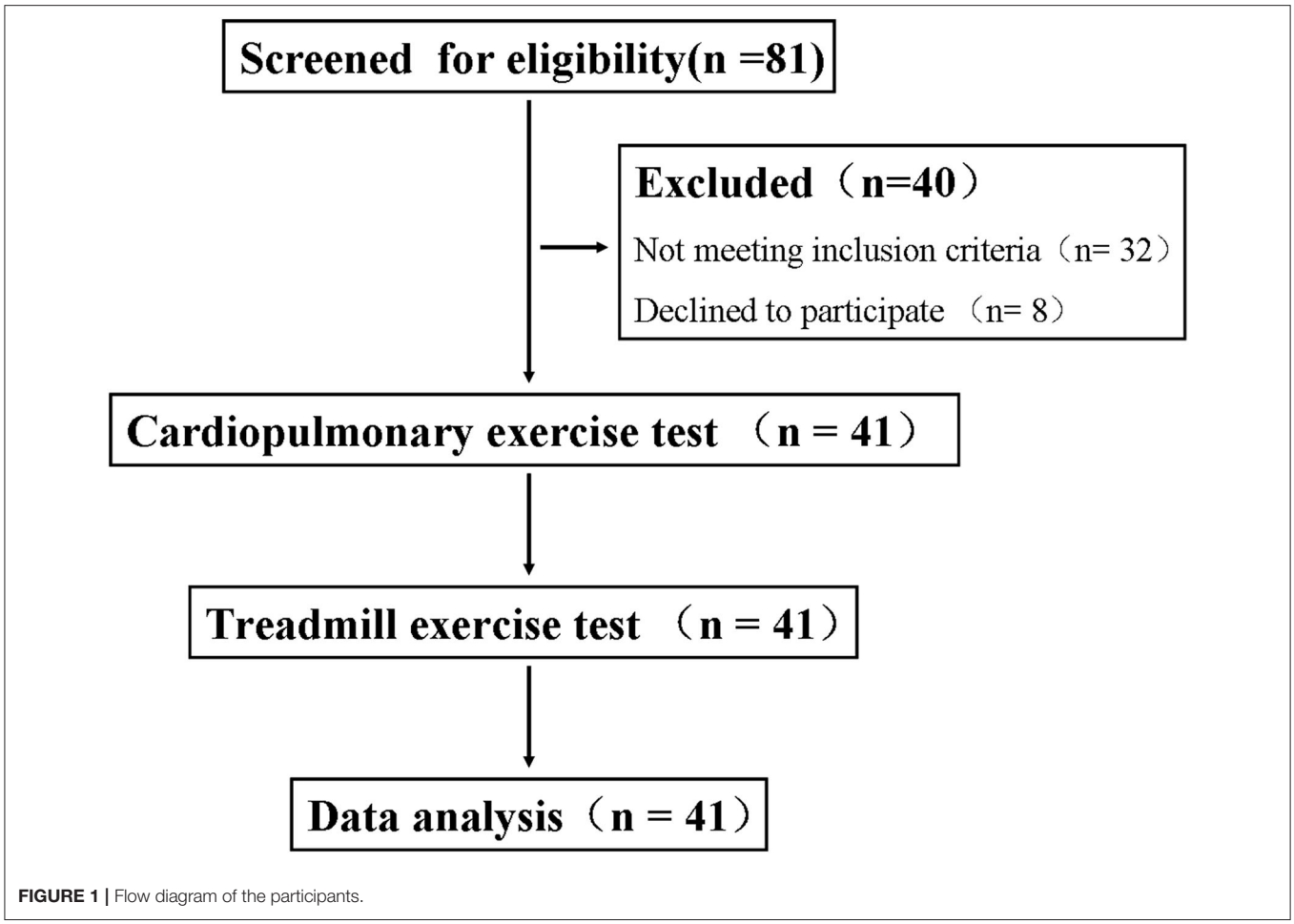


FIGURE 1 | Flow diagram of the participants.

at each grade for 3 min until the maximum exercise load was reached, then entered the recovery state and gradually decreased to grade I, grade 0, and warm-up (1.6 mph, 0%), with each grade being 2 min apart. The testing was terminated when heart rate, VO_2, VCO_2, and other indicators return to baseline. The patient's subjective level of exertion was qualified using the Borg 6–20 scale which is a simple method of rating perceived exertion (RPE) (6 means about 20% while 20 means exhaustion). The MET value was estimated by a software (GE Cardiac Assessment System for Exercise Testing, Milwaukee, WI, USA) using the following equation: METs = [3.5 + 26.8 ∗ 0.1 ∗ (speed in mph) + (speed in mph) ∗ 26.8 * (% gradient) ∗ 1.8]/3.5.

Statistical Methods

Statistical analysis was performed using SPSS version 23.0(IBM SPSS Statistics for Windows, New York, USA). Quantitative variables were first tested for normality. Those following normal distribution were expressed as mean ± standard deviation ($x \pm s$), whereas those that were not were expressed as median and interquartile range. The qualitative data were expressed as ratio or percentage. The paired t-test was used to compare the indicators of the two tests in the same patient. $p < 0.05$ determined statistical significance. Finally, count data were graded/classified, assigned values, and then converted into binary variables for statistical analysis (while excluding outliers) and multiple linear regression analysis. The variables were screened using a stepwise screening method.

RESULTS

General Clinical Data

A total of 41 subjects were enrolled in the study (**Figure 1**), patient characteristics are displayed in **Table 1**. All patients had undergone PCI revascularization before, of which 25 (61.0%) were due to acute myocardial infarction and 16 (39.0%) were due to unstable angina pectoris. The median number of stents implanted was 2 (1–4), and the median time between CPET and the last PCI was 6 (2.25–12 weeks). None of the patients had any discomfort such as chest pain 2 weeks before the test. in addition, biochemical and cardiac ultrasound indicators indicated that the disease was in a stable state.

Comparison of the Termination of Treadmill Exercise Testing and Cardiopulmonary Exercise Testing

All 41 subjects completed CPET and TET. During the interval between the two tests, no patients had angina pectoris attacks or respiratory symptoms. In the TET, all patients stopped the testing

TABLE 1 | Subject characteristics ($n = 41$).

Variables	*Mean* ± *SD* or median (P25, P75) or percentage
Male	34 (82.9)
Female	7 (17.1)
Age (years)	56.2 ± 9.2
Height (cm)	169.4 ± 7.6
Weight (kg)	75.3 ± 11.1
BMI (kg/m^2)	26.2 ± 2.9
Waist-hip ratio	0.78 ± 0.36
Smokers (%)	14 (34.1)
Previous myocardial infarction	25 (61.0)
No. of stenotic coronary arteries	
1	29 (70.7)
2	8 (19.5)
3	4 (9.8)
No. of stents	2 (1,4)
The time between CPET and the latest PCI (weeks)	6 (2.25, 12)
Coexisting disease	
Hypertension	25 (61.0)
Diabetes	11 (26.8)
Hyperlipidemia	26 (63.4)
Medication	
β-Blocker	27 (65.7)
ACEI/ARB	11 (26.8)
Stain	38 (92.7)
Diltiazem	4 (9.8)
Nitrates	20 (48.8)
Biochemical indicators (reference range)	
BNP (pg/ml)	270.1 ± 275.7 (0–150)
Cr (μmol/L)	80.7 ± 16.9 (30–110)
TnT (ng/L)	0.02 ± 0.03 (0–0.1)
CK-MB (ng/ml)	3.89 ± 4.19 (0–6.5)
TG (mmol/L)	3.78 ± 0.93 (3.1–5.7)
LDL (mmol/L)	2.21 ± 0.74 (0–3.4)
Cardiac ultrasound indicators (reference range)	
LVEF (%)	58.1 ± 7.6 (50–70)
LVIDd (mm)	46.3 ± 4.6 (37–53)
IVSd (mm)	10.7 ± 1.3 (8–11)
Regional wall motion	14 (34.1)

BMI, body mass index; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; LVEF, left ventricular ejection fraction; LVIDd, left ventricular diastolic dimension; IVSd, interventricular septal thickness.

after reaching the target heart rate, of which 87.8% (36/41) had negative results, 7.3% (3/41) had suspiciously positive results, and 4.9% (2/41) had positive results. In the CPET, 97.6% (40/41) of the 41 subjects terminated the testing because of fatigue, and very few terminated the testing because of chest distress (2.4%, 1/41). During the testing, only one patient had ST-segment changes (2.4%, 1/41). At the end of the testing, the mean Brog score of the subjects was 15.08, and the mean maximum amount of exercise reached 5.19 METs.

TABLE 2 | Comparison of the two kinds of exercise testing.

	CPET	TET	*t*-Value	*p*-Value
METmax	5.19 ± 1.23	8.89 ± 1.53	14.51	0.000
HRmax	126.22 ± 21.16	127.11 ± 13.08	−0.20	0.842
HRrest	70.56 ± 9.83	74.75 ± 12.98	1.98	0.056
ΔSBP	53 ± 19	39 ± 19	−3.15	0.003
ΔDBP	9 ± 14	11 ± 32	3.54	0.001

CPET, cardiopulmonary exercise testing; TET, treadmill exercise testing; MET, metabolic equivalent; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Comparison of Exercise Capacity Measured in Treadmill Exercise Testing and Cardiopulmonary Exercise Testing

The subjects showed a mean maximum exercise capacity of 8.89 METs during the testing (**Table 2**). There was no significant difference in maximum heart rate during the two testing ($p = 0.842$); however, there was a significant difference in the maximum exercise capacity ($p = 0.000$). **Figure 2** lists the maximum exercise capacity of all 41 patients. It can be seen that the maximum exercise capacity measured by TET was generally greater than that of CPET. The percentage of the METs measured by CPET to that estimated by TET averaged 59.85 ± 2.61%, with a confidence interval of 54.56–65.13%.

Factors Affecting the Difference in METs

The exercise capacity measured in the CPET was less than that of the TET, and the percentage of the difference in terms of treadmill exercise capacity averaged 40.15 ± 2.61%. Multiple linear regression analysis of the factors affecting the difference suggested that the difference of METs was related to WHR but was not significantly associated with age, sex, BMI, β-blockers, ACEI/ARB, statins, diltiazem, or nitrates (**Table 3**). The specific relationship is shown in the following regression equation:

$$Y1 = -1.591X1 + 5.088$$

where $Y1$ represents the maximum MET difference in the exercise capacity between the two testing, and $X1$ represents the WHR. From the equation, it can be seen that there is a negative correlation between MET difference and WHR.

When the dependent variable is changed to the percentage of MET difference in terms of treadmill exercise capacity, and the independent variable remains unchanged, the results of multiple linear regression analysis were similar to those of the previous results. The percentage of MET difference in treadmill exercise capacity was negatively associated with WHR; however, it was not significantly associated with age, sex, BMI, β-blockers, ACEI/ARB, statins, diltiazem, or nitrates (**Table 4**). The specific relationship is shown in the following equation:

$$Y2 = -16.244X2 + 54.847$$

where $Y2$ is the percentage of MET difference in treadmill exercise capacity, and $X2$ is WHR.

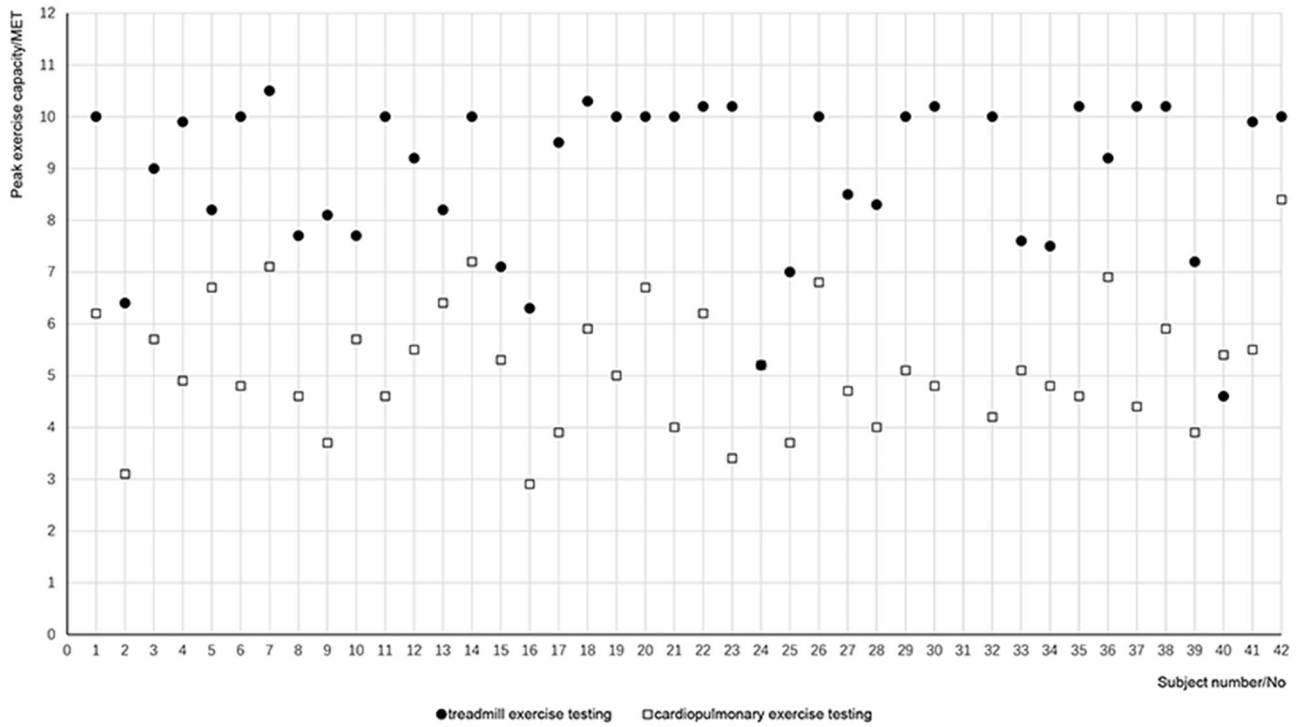


FIGURE 2 | Exercise capacity measured by the two tests for each patient. Solid dots refer to the METs calculated by treadmill exercise test for each patient, and open squares refer to the METs measured by cardiopulmonary exercise test.

TABLE 3 | Regression estimation 1.

Model	B	Std. Error	*β*	*t*	Sig.
Constant	5.088	0.640		7, 953	0.000
Waist-hip ratio	−1.591	0.739	0.356	−2.153	0.039

TABLE 4 | Regression estimation 2.

Model	B	Std. Error	*β*	*t*	Sig.
Constant	54.847	5.882		7, 953	0.000
Waist-hip-rate	−16.244	6.796	−0.389	−2.153	0.023

DISCUSSION

The present study is the first of its kind to measure the conversion factor between exercise capacity in post-PCI patients using CPET and TET, and we got two functions to estimate a more accurate MET by TET result.

We found a significant difference in maximum exercise capacity between CPET and TET in the same subject within 1 week. The estimated value in TET is likely to be greater than the actual value measured in CPET; in our study, the measured MET averaged (59.85 ± 2.61%) of the estimated value. Recent evidence demonstrated exercise capacity plays an important role for the prognosis of obviously healthy people or ill people. While 1 MET increase in exercise capacity is considered to decrease the risk of all-cause mortality by 13% (15). Reasonable CR exercise training not only improves the mobility and quality of life, but it also improves long-term prognosis and reduces the probability of recurrent cardiovascular events (16, 17). Cao et al. (18) demonstrated that only a certain intensity of exercise could improve the relevant parameters before and after CR. When an exercise plan is formulated, the exercise intensity is usually set to 50–80% of the patient's maximum exercise capacity (19). Low-intensity exercise cannot achieve the goal of improving cardiac function, whereas high-intensity exercise may exceed the adaptation range of the patient's cardiorespiratory fitness (20). Estimation by the results of simple TET may lead to overestimation of actual exercise capacity and therefore may incorrectly match rehabilitation training intensity with actual cardiac function, thereby increasing cardiovascular risk in cardiac rehabilitation training.

The results of this study are consistent with those of previous studies. The maximum exercise capacity measured by TET is higher than that of CPET using a cycle ergometer as a dynamometer (8). The stepwise power-increasing Bruce protocol is commonly adopted in TET, while the increasing ramp protocol is commonly adopted in CPET. According to Myers' study, whether using treadmill or cycle ergometer, there was a significant difference in exercise capacity in the same patient between a stepwise increasing exercise program and a ramp increasing exercise program (12, 21). The amount of exercise is

thought to be proportional to exercise time, which is the basis of the estimation formula of METs. However, the increment of a stepwise increasing exercise program is incontinuous actually. Post-PCI patients often suffer from cardiac insufficiency; as a consequence, their actual ejection fraction cannot increase linearly with the amount of exercise (20, 22, 23). Nevertheless, the estimation of the exercise capacity in TET is based on a linear formula. Therefore, for post-PCI patients, exercise capacity estimated by TET may be higher than the actual value (24). Another possible explanation might involve the effecting muscles. Cycle ergometer exercise is more dependent on lower limb muscles, while the handrails equipped with TET may produce additional resistance and allocate more muscle to work (25).

We found that the average percentage of the difference in the METs estimated by TET was 40.15%, (95% confidence interval: 35.03–45.27%). Multiple linear regression analysis showed yielded a function: $Y1 = -1.591X1 + 5.088$ ($Y1$ represents the maximum MET difference in the exercise capacity between the two testing, $X1$ represents the WHR). Considering the MET by TET was an estimated value, we changed the dependent variable to the percentage of MET difference in terms of treadmill exercise capacity and got a new function: $Y2 = -16.244X2 + 54.847$. These two functions indicate that the difference and the difference in the METs estimated by TET both negatively correlated with the WHR. A study that attempted to compare measured and estimated METs in TET found that the difference had a weak positive correlation to age (26). Considering that the main purpose of this study was to improve the accuracy of diagnosis, the subjects of the study were all patients with heart-related symptoms while the subjects of our study were all patients after PCI, which may result in the difference between the results. Some drugs routinely used after PCI, such as β-blockers and calcium channel blockers, may affect exercise capacity (27, 28). All drugs were temporarily suspended 24 h before the exercise testing; nevertheless, we included them among the independent variables for multivariate linear analysis. We found use of these medications had no bearing on the difference between the two testing methods or on the percentage of the difference in the METs estimated by TET.

Given that gas measurements and analysis devices are not common in developing countries, it is more feasible to estimate exercise capacity using TET; however, we suggest that the results of TET be reduced by 35–45% to be used for the consequent exercise prescription. Previous studies have indicated that self-assessment questionnaires such as the Duke Activity Status Index and the Veterans Specific Activity Questionnaire can provide a rough assessment of exercise capacity through questionnaires regarding daily activity capacity of various magnitudes (4, 29). The combination of the two estimation methods may improve the safety of exercise training and the accuracy of exercise prescription.

There are limitations in the present study. Although the study demonstrated significant different effects between two exercise tests, the sample size was relatively small and involved only a single center. A multicenter clinical trial with larger sample size is on the way to further explore the differential evaluating effect on exercise capacity of CPET and TET in post-PCI patients.

CONCLUSION

The basis of reasonable cardiac rehabilitation training for post-PCI patients is correct assessment of exercise capacity. Even though current international guidelines recommend CPET, when CPET or other metabolic testing were not available, exercise capacity can be estimated indirectly using simple TET, the results of which should be reduced by 35–45%. Two formulas could also be used to attain a more accurate METs. The results of this study might supply a more accurate means of evaluating the exercise capacity for the post-PCI patients when CPET is not available.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of the Chinese PLA General Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

The study was initiated by JM and YX. YG and BF performed the statistical analysis and drafted the manuscript. RH, YZ, and YS were helpful for data collection. JM and YX contributed substantially to its revision and took responsibility for the manuscript as a whole. All authors contributed to the article and approved the submitted version.

FUNDING

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Key R&D Program of China (2018YFC2000600).

ACKNOWLEDGMENTS

We recognize effort and great work from all team members and appreciate project coordinators, investigators, and data operators including Lian Tang, Long-Fang Xing, Hai-Yan Li, Yan-Yan Wei, Xiao-Yan Li, Yan-Yan Yao, and Xin Wang, as well as patients who participated in the study.

REFERENCES

1. Taylor RS, Brown A, Ebrahim S, Noorani H, Rees K, Skidmore B, et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *Am J Med.* (2004) 116:682–92. doi: 10.1016/j.amjmed.2004.01.009
2. Myers J, Prakash M, Froelicher V, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med.* (2002) 346:793–801. doi: 10.1056/NEJMoa011858
3. Oldridge N, Pakosh M, Grace SL, A. systematic review of recent cardiac rehabilitation meta-analyses in patients with coronary heart disease or heart failure. *Future Cardiol.* (2019) 15:227–49. doi: 10.2217/fca-2018-0085
4. Myers J, Bader D, Madhavan R, Froelicher V. Validation of a specific activity questionnaire to estimate exercise tolerance in patients referred for exercise testing. *Am Heart J.* (2001) 142:1041–6. doi: 10.1067/mhj.2001.118740
5. Chinese Society of Cardiology of Chinese Medical Association; Cardiovascular Committee of Chinese Association of Rehabilitation Medicine; Committee of Cardio-Cerebral-Vascular Diseases of Gerontological Society of China. [Chinese experts consensus on cardiac rehabilitation/secondary prevention for coronary artery disease]. *Chin J Cardiol.* (2013) 41:267–75. doi: 10.3760/cma.j.issn.0253-3758.2013.04.003
6. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA.* (2009) 301:2024–35. doi: 10.1001/jama.2009.681
7. Price KJ, Gordon BA, Bird SR. Benson AC. A review of guidelines for cardiac rehabilitation exercise programmes: is there an international consensus? *Eur J Prev Cardiol.* (2016) 23:1715–33. doi: 10.1177/2047487316657669
8. McElroy PA, Janicki JS, Weber KT. Cardiopulmonary exercise testing in congestive heart failure. *Am J Cardiol.* (1988) 62:35A−40A. doi: 10.1016/s0002-9149(88)80083-3
9. Na ZY Li B, Yin L, Han X, Zhang HS, Wang Y, et al. Significance of exercise treadmill testing for instructing exercise training in cardiac rehabilitation. *J Pract Electrocardiol.* (2009) 18:220–1. doi: 10.3969/j.issn.1008-0740.2009.03.041
10. Kelly, JP, Andonian, BJ, Patel, MJ, Huang, Z, Shaw, LK, McGarrah, RW, et al. Trends in cardiorespiratory fitness: the evolution of exercise treadmill testing at a single Academic Medical Center from 1970 to 2012. *Am Heart J.* (2019) 210, 88–97. doi: 10.1016/j.ahj.2019.01.001
11. Panza JA, Quyyumi AA, Diodati JG, Callahan TS, Epstein SE. Prediction of the frequency and duration of ambulatory myocardial ischemia in patients with stable coronary artery disease by determination of the ischemic threshold from exercise testing: importance of the exercise protocol. *J Am Coll Cardiol.* (1991) 17:657–63. doi: 10.1016/s0735-1097(10)80180-9
12. Myers J, Buchanan N, Walsh D, Kraemer M, McAuley P, Hamilton-Wessler M, et al. Comparison of the ramp versus standard exercise protocols. *J Am Coll Cardiol.* (1991) 17:1334–42. doi: 10.1016/s0735-1097(10)80144-5
13. Hambrecht RP, Schuler GC, Muth T, Grunze MF, Marburger CT, Niebauer J, et al. Greater diagnostic sensitivity of treadmill versus cycle exercise testing of asymptomatic men with coronary artery disease. *Am J Cardiol.* (1992) 70:141–6. doi: 10.1016/0002-9149(92)91265-6
14. Mitchell J, Kist WB, Mears K, Nalls J, Ritter K. Does standing on a cycle-ergometer, towards the conclusion of a graded exercise test, yield cardiorespiratory values equivalent to treadmill testing? *Int J Exerc Sci.* (2010) 3:117–25.
15. Myers J, Arena R, Franklin B, Pina I, Kraus WE, McInnis K, et al. Recommendations for clinical exercise laboratories: a scientific statement from the american heart association. *Circulation.* (2009) 119:3144–61. doi: 10.1161/CIRCULATIONAHA.109.192520
16. Lawler PR, Filion KB, Eisenberg MJ, Atallah R, Garfinkle M, Eisenberg MJ. Efficacy of exercise-based cardiac rehabilitation post-myocardial infarction: a systematic review and meta-analysis of randomized controlled trials. *Am Heart J.* (2011) 162:571–84. doi: 10.1016/j.ahj.2011.07.017
17. Oldridge N. Exercise-based cardiac rehabilitation in patients with coronary heart disease: meta-analysis outcomes revisited. *Future Cardiol.* (2012) 8:729–51. doi: 10.2217/fca.12.34
18. Cao RY, Zheng H, Hong Y, Zheng Y, Yang J. Cardiac rehabilitation with targeted intensity improves cardiopulmonary functions accompanying with reduced copeptin level in patients with coronary artery disease. *J Cardiovasc Transl Res.* (2020) 4:317–26. doi: 10.1007/s12265-020-10055-y
19. American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription, 9th ed*. Baltimore, MD: Lippincott Williams & Wilkins (2014). p. 166–179.
20. Hansen D, Bonné K, Alders T, Hermans A, Copermans K, Swinnen H, et al. Exercise training intensity determination in cardiovascular rehabilitation: should the guidelines be reconsidered? *Eur J Prev Cardiol.* (2019) 26:1921–8. doi: 10.1177/2047487319859450
21. Myers J, Buchanan N, Smith D, Neutel J, Bowes E, Walsh D, et al. Individualized ramp treadmill. Observations on a new protocol. *Chest.* (1992) 101:236S−41S.
22. Pymer S, Nichols S, Prosser J, Birkett S, Carroll S, Ingle L. Does exercise prescription based on estimated heart rate training zones exceed the ventilatory anaerobic threshold in patients with coronary heart disease undergoing usual-care cardiovascular rehabilitation? *A United Kingdom perspective Eur J Prev Cardiol.* (2020) 27:579–89. doi: 10.1177/2047487319852711
23. Reddy HK, Weber KT, Janicki JS, McElroy PA. Hemodynamic, ventilatory and metabolic effects of light isometric exercise in patients with chronic heart failure. *J Am Coll Cardiol.* (1988) 12:353–8. doi: 10.1016/0735-1097(88)90405-6
24. Berling J, Foster C, Gibson M, Doberstein S, Porcari J. The effect of handrail support on oxygen uptake during steady-state treadmill exercise. *J Cardiopulm Rehabil.* (2006) 26:391–4. doi: 10.1097/00008483-200611000-00009
25. Pinkstaff S, Peberdy MA, Kontos MC, Fabiato A, Finucane S, Arena R. Overestimation of aerobic capacity with the bruce treadmill protocol in patients being assessed for suspected myocardial ischemia. *J Cardiopulm Rehabil Prev.* (2011) 31:254–60. doi: 10.1097/HCR.0b013e318211e3ed
26. Ades PA, Savage PD, Brawner CA, Lyon CE, Ehrman JK, Bunn JY, et al. Aerobic capacity in patients entering cardiac rehabilitation. *Circulation.* (2006) 113:2706–12. doi: 10.1161/CIRCULATIONAHA.105.606624
27. Gullestad L, Manhenke C, Aarsland T, Skårdal R, Fagertun H, Wikstrand J, et al. Effect of metoprolol CR/XL on exercise tolerance in chronic heart failure - a substudy to the MERIT-HF trial. *Eur J Heart Fail.* (2001) 3:463–8. doi: 10.1016/s1388-9842(01)00146-5
28. Chugh SK, Digpal K, Hutchinson T, Chugh SK, Digpal K, Hutchinson T, et al. randomized, double-blind comparison of the efficacy and tolerability of once-daily modified-release diltiazem capsules with once-daily amlodipine tablets in patients with stable angina. *J Cardiovasc Pharmacol.* (2001) 38:356–64. doi: 10.1097/00005344-200109000-00004
29. Hlatky MA, Boineau RE, Higginbotham MB, Lee KL, Mark DB, Califf RM, et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). *Am J Cardiol.* (1989) 64:651–4. doi: 10.1016/0002-9149(89)90496-7

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 19 August 2021
doi: 10.3389/fcvm.2021.685673

Determinants and Prediction Equations of Six-Minute Walk Test Distance Immediately After Cardiac Surgery

Basuni Radi[1,2]*, *Ade Meidian Ambari*[1,2], *Bambang Dwiputra*[1,2], *Ryan Enast Intan*[3], *Kevin Triangto*[1], *Anwar Santoso*[1,2] *and Budhi Setianto*[1,2]

[1] Department of Cardiovascular Prevention and Rehabilitation, National Cardiovascular Center Harapan Kita, Jakarta, Indonesia, [2] Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia, [3] Adhyaksa Hospital, Jakarta, Indonesia

Background: To date, there is no reference for a 6-min walk test distance (6-MWD) immediately after cardiac surgery. Therefore, this study aimed to identify the determinants and to generate equations for prediction reference for 6-MWD in patients immediately after cardiac surgery.

Methods: This is a cross-sectional study of the 6-min walk test (6-MWT) prior to participation in the cardiac rehabilitation (CR) program of patients after coronary artery bypass surgery (CABG) or valve surgery. The 6-MWT were carried out in a gymnasium prior to the CR program immediately after the cardiac surgery. Available demographic and clinical data of patients were analyzed to identify the clinical determinants of 6-MWD.

Results: This study obtained and analyzed the data of 1,509 patients after CABG and 632 patients after valve surgery. The 6-MWD of all patients was 321.5 ± 73.2 m (60–577). The distance was longer in the valve surgery group than that of patients in the CABG group (327.75 ± 70.5 vs. 313.59 ± 75.8 m, $p < 0.001$). The determinants which significantly influence the 6-MWD in the CABG group were age, gender, diabetes, atrial fibrillation, and body height, whereas in the valve surgery group these were age, gender, and atrial fibrillation. The multivariable regression models generated two formulas using the identified clinical determinants for patients after CABG: 6-MWD (meter) = 212.57 + 30.47 (if male gender) − 1.62 (age in year) + 1.09 (body height in cm) − 12.68 (if with diabetes) − 28.36 (if with atrial fibrillation), and for patients after valve surgery with the formula: 6-MWD (meter) = 371.05 + 37.98 (if male gender) − 1.36 (age in years) − 10.61 (if atrial with fibrillation).

Conclusion: This study identified several determinants for the 6-MWD and successively generated two reference equations for predicting 6-MWD in patients after CABG and valve surgery.

Keywords: 6-minute walk test, CABG, valve surgery, cardiac surgery, cardiac rehabilitation

OPEN ACCESS

Edited by:
Sebastian Kelle,
Deutsches Herzzentrum Berlin, Germany

Reviewed by:
Warawut Chaiwong,
Chiang Mai University, Thailand
Knosalla Christoph,
German Heart Center Berlin, Germany

***Correspondence:**
Basuni Radi
basuni_radi@hotmail.com

Specialty section:
This article was submitted to General Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

Received: *25 March 2021*
Accepted: *16 July 2021*
Published: *19 August 2021*

Citation:
Radi B, Ambari AM, Dwiputra B, Intan RE, Triangto K, Santoso A and Setianto B (2021) Determinants and Prediction Equations of Six-Minute Walk Test Distance Immediately After Cardiac Surgery. Front. Cardiovasc. Med. 8:685673. doi: 10.3389/fcvm.2021.685673

INTRODUCTION

The 6-min walk test (6-MWT) is a simple, safe, and practical sub-maximum exercise test for patients with respiratory or heart diseases (1). It becomes an ordinary exercise test to measure the functional capacity and to evaluate the treatment or intervention. The 6-min walk test distance (6-MWD) can also be used as a predictor of hospitalization and death from cardiac or pulmonary diseases. This test is objective, independent, able to predict peak oxygen uptake, and well-tolerated by most patients (2–4). However, to the author's knowledge there is still no reference for 6-MWD which could be used to compare the 6-MWD in patients immediately after cardiac surgery.

In the case of post-cardiac surgeries, performing maximal stress testing is still contraindicated clinically. The first reason is the pain in the sternal region, which would then significantly cause arm-swing reduction and thus reduce the whole acceleration momentum during running uphill in the treadmill test. Another identified reason is that purposefully accelerating the heart rate after a surgery could potentially lead to safety issues, in which the heart is still undergoing a recovery phase. Therefore, submaximal stress testing through 6-MWT is generally acceptable and is recommended to be done prior to discharge in post-cardiac surgery patients. Additionally, the 6-MWT could also serve as a functional capacity testing if the patient could walk a distance of approximately 300 m, which serves an equivocal of 3.5 METs, reflecting the ability to walk and perform home activities with moderate effort. METs could be defined as the ratio of caloric consumption in an active person, compared to their basal metabolic rate at rest. METs are measured in kcal/kg/hour.

Henceforth, this study is aimed to both identify determinants of 6-MWD in patients after cardiac surgery and generate equations for 6-MWD of patients immediately after coronary artery bypass graft (CABG) and after valve surgery. The secondary objectives include exhibiting the baseline comparison between the CABG and valve surgery groups, owing to the fact that patient characteristics would differ in these two groups. It is then expected that these equations could be used to predict the level of functional capacity of patients immediately after cardiac surgery.

MATERIALS AND METHODS

This was a cross-sectional study which evaluated first 6-MWT prior to patients' participation in the cardiac rehabilitation (CR) program immediately after CABG surgery or valve surgery. Therefore, immediate 6-MWD is defined as the 6-MWT performed at initial visit to the CR program, in which the patients were recommended to attend CR within the first week after inpatient discharge. This was done in order to achieve the study aims through comparison of means and multivariable regression analysis.

Patients

The population of this study was a cohort of patients who registered to participate in a CR program held in the Cardiovascular Prevention and Rehabilitation Unit of the National Cardiovascular Center Harapan Kita Jakarta, within January 2014 and December 2016 immediately after CABG or cardiac valve surgeries. As for external validation of the generated equations, we used a population group of patients immediately after CABG and valve surgery who registered in the CR program in the year 2018.

All patients had given complete verbal and written information and gave written consent to participate in the CR program, which also includes exercise stress testing. Ethical approval for the CR patient registry was provided from the Committee on Institutional Review Board of the National Cardiac Center "Harapan Kita" Hospital with the following registration number: LB.02.01/VII/536/KEP 027/2021. The CR program and the 6-MWT in this research is a standard procedure in the institution for all patients after cardiac surgery. Individual data of patients were retrieved from the available medical records for analysis.

Patients will be excluded when they have limitation of motion that prevents them from performing physical activities such as walking for 6 min and also pain due to multiple causes. Moreover, since this is an analysis of secondary data, incomplete values from the patient database will also be excluded from the study.

All of these open heart surgeries used thoracotomy approach and cardiopulmonary bypass (CPB) machine with cardioplegia protection technique. The CABG technique includes grafting the left internal mammary artery to the left anterior descending artery or its main branches and grafting the saphenous vein from the aorta to the other coronary branches. Meanwhile, valvular surgery technique includes valve repair or valve replacement using a mechanical valve or a bio-prosthesis valve.

The prevalence of atrial fibrillations (AFs) in the samples was obtained through electrocardiography (ECG) that has been performed during either their pre-exercise or pre-operative setting. Any new AFs identified would warrant further examination before admission into the CR and thus were not included in this registry.

6-Minute Walk Test

After being registered, the patients attended a pre-participation orientation for the CR program, medical assessment, and educational session and performed the 6-MWT when no contraindication was observed. Extracardiac conditions that hinder active walking, such as acute pain, and neuromusculoskeletal disabilities are classified as relative contraindications to 6-MWT.

The 6-MWT were carried out once before the participation in the CR program in the gymnasium with a standardized protocol at a 30-m gymnasium corridor (1).

The patients were instructed to walk as far as possible within 6 min. Standard verbal encouragement was gently provided. The remaining time was announced every minute, and every 15 s within the last minute. The patients could stop walking if any symptoms appeared, such as severe dyspnea, dizziness, fatigue, angina, or severe skeletal muscle pain; afterwards they could resume walking as soon as possible until the 6-min test time is attained. Additionally, the test will also be halted when the

Borg rating of the perceived exertion scale is 15 out of 20, allowing the patient to rest and thus ensuring that these tests are performed on submaximal state. Their heart rate and rhythm were monitored using ECG telemonitor, while distance was recorded in meters.

Most patients attend the CR 1 week after discharge, and due to these relatively fast timings of CR initiation, the patients were instructed to perform 6-MWT only once. This was done in order to avoid over-exhaustion in these patients, as most patients tend to not resume daily activities before attending the CR program. Although some patients had performed 6-MWT pre-discharge when possible, these data were not included in this study, as these were done only to allow clinicians to prescribe better lifestyle modifications prior to CR participation and achieve better functional goals.

Statistical Analysis

The demographic data, atherosclerotic risk factors, body height, body weight, left ventricle ejection fraction (LVEF), heart rhythm, length of stay during hospitalization, current medications, 6-MWD, and other relevant data of the CR program were retrieved for the analysis. The distribution of numeric data was evaluated with the Kolmogorov–Smirnov test and expressed with mean ± standard deviation when normally distributed and median (minimum–maximum) when the data are non-parametric.

The available data of 6-MWD of all the patients were used to identify the determinants of 6-MWD and to generate equations of 6-MWD reference either in the CABG group or in the valve surgery group.

Variables with p-value < 0.1 in univariable analysis that were seen correlated with 6-MWD (ejection fraction, body height, and body weight) were included in the multivariable regression model to analyze the magnitude of influence of the variables to the 6-MWD.

All multivariable regression analysis assumptions were checked before inclusion into the final model. For the assumption, linear relationship between independent and dependent variables was tested by Pearson correlation and linear regression test, multicollinearity by correlation coefficient below 0.7, autocorrelation by calculated Durbin Watson test, standardized residual normal distribution by Kolmogorov–Smirnov test, and homoscedasticity of variance by Levene's test of equality of error variances.

The equations were generated from the model using determinants which significantly related with 6-MWD. For the comparison with healthy persons, we used a predictive equation for reference value of 6-MWD which was generated from a study by Zou et al. (5), who used a similar procedure with this study and from an Asian ethnic population.

For internal validation, we used the original population (year 2014–2016). Meanwhile, for external validation, we used a similar population group of patients after cardiac surgery who registered in the CR program in the year 2018 which consisted of 412 patients after CABG and 324 patients after valve surgery.

TABLE 1 | Baseline characteristic of patients after cardiac surgery.

Variables	Total ($n = 2,141$)	CABG surgery ($n = 1,509$)	Valve surgery ($n = 632$)	*P*
Age, years (median)	53 (16–80)	58 (20–80)	43 (16–71)	<0.001[a]
Male gender, *n* (%)	1,613 (75)	1,291 (86)	323 (51)	<0.001[c]
Systolic BP (median)	109 (72–197)	112 (72–197)	106 (73–172)	<0.001[a]
Diastolic BP (median)	65 (32–99)	66 (32–99)	65 (40–99)	0.121[a]
Body height, cm (median)	163 (135–185)	164 (138–185)	161 (135–183)	<0.001[a]
Body weight, kg (median)	58 (29–120)	66 (30–115)	53 (29–120)	0.001[a]
Diabetes, *n* (%)	702 (32.7)	665 (44)	37 (5.8)	<0.001[c]
Dyslipidemia, *n* (%)	846 (39.5)	813 (54)	33 (6.7)	<0.001[c]
Smoker, *n* (%)	903 (42.2)	804 (53)	99 (18.9)	<0.001[c]
LVEF, % (median)	58 (12–93)	56 (12–81)	60 (18–93)	<0.001[a]
ECG with AF, *n* (%)	298 (13.9)	34 (2.3)	264 (41.7)	<0.001[c]
Length of stay, day (mean)	9 ± 4.9	9 ± 5	9 ± 4.8	0.488[b]
6-MWD in meters (mean)	321.5 ± 73.2	313.6 ± 75.8	327.8 ± 70.5	0.001[b]

Values are mean ± SD, median (minimum–maximum) or frequency (%). CABG, coronary artery bypass graft; BP, blood pressure; LVEF, left ventricle ejection fraction; ECG, electrocardiography; AF, atrial fibrillation; 6-MWD, 6-min walk test distance; p, for comparison between the CABG surgery group and the valve surgery group.

[a] *Mann–Whitney U-test.*

[b] *Independent t-test.*

[c] *Chi square test.*

The mean difference was tested using Student's t-test for normally distributed variables and Mann–Whitney test if proven otherwise. Pearson's product moment correlation coefficient was applied to test the correlation between predicted and observed 6-MWD in the original population and in the other population from year 2018. A Bland–Altman plot was also used to describe the variance of difference and the limit agreement of difference between predicted and observed 6-MWD by plotting the mean difference against the observed 6-MWD.

RESULTS

Clinical Characteristics of the Patients

A total of 2,302 patients registered consecutively to participate in the exercise-based CR program; among those, the data of 161 patients were incomplete, accruing for 127 CABG patients and 32 valve surgery patients being excluded from the study. Therefore, this study consisted of 2,141 patients with complete data who underwent 6-MWT after CABG surgery ($n = 1,509$) or after valve surgery ($n = 632$) in January 2014 to December 2016. The patients were hospitalized for 9 ± 5 days for their surgical procedures. Most of the patients were male (75%), with normal systolic function (median left ventricle ejection function 58%) and sinus rhythm (86.1%) on their ECG.

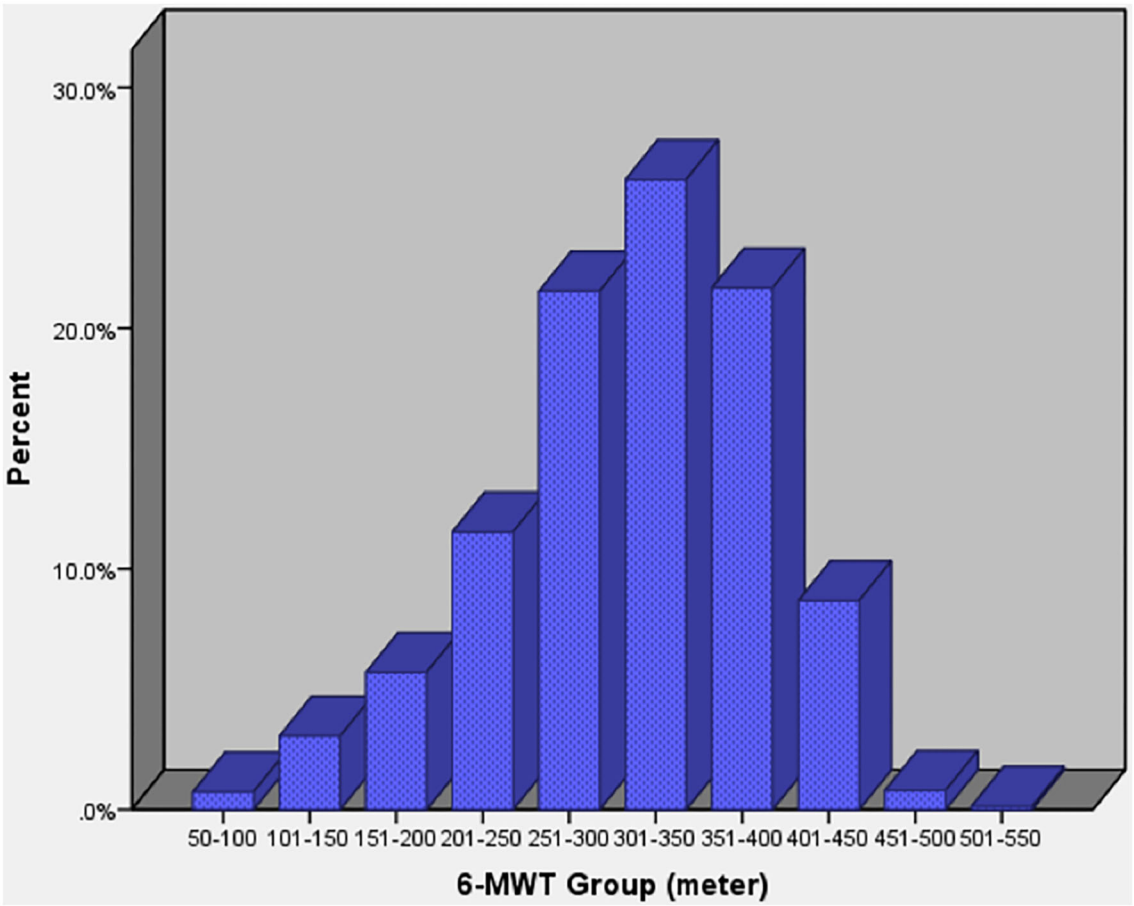


FIGURE 1 | Distribution of 6-MWD of patients after cardiac surgery. 6-MWD, 6-min walk test distance.

The 6-MWTs were carried out prior to the exercise program without adverse event. The baseline characteristics (**Table 1**) revealed a comparable length of stay between groups. However, the patients in the CABG group were older and male dominant, had lower ejection fraction and lower prevalence of AF, but had a higher prevalence of co-morbidities regarding atherosclerotic risks as compared to the patients in the valve surgery group.

6-Minute Walk Test Performance

The mean 6-MWD of all patients was 321.5 ± 73.2 m, which ranged from 60 to 488 m as seen in **Figure 1**. It was 57.4 ± 12.8% (range: 13–91%) of the predicted reference distance of the healthy population (5). It could be evidently seen that post CABG subjects had lower 6-MWDs as compared to those after valve surgery (313.6 ± 75.8 vs. 327.8 ± 70.5, $p = 0.001$).

In multivariable regression analysis, we entered the variables which were assumed to have influence on functional capacity, and variables from univariable analysis which significantly correlated with the 6-MWD with $p < 0.1$ (**Supplementary Table 1**). This analysis revealed that gender, age, diabetes status, body height, and heart rhythm were significantly related with 6-MWD in the patients after CABG; meanwhile, for patients after valve surgery, slightly variable differences were observed in gender, age, and heart rhythm.

Predictive equations of 6-MWD in both patient groups were generated from the determinants (**Table 2**) and were seen to be significantly related with 6-MWT ($p < 0.05$).

For the patients after CABG, the equation is as follows:

$$6-\text{MWD(in meters)} = 212.57 - 1.62(\text{age in year}) + 1.09(\text{body height in cm}) + 30.47(\text{if male gender}) - 12.68(\text{if with diabetes}) - 28.36(\text{if with atrial fibrillation})$$

And for the patients after valve surgery, the equation is as follows:

$$6-\text{MWD(in meters)} = 371.05 - 1.36(\text{age in year}) + 37.98(\text{if male gender}) - 10.61(\text{if with atrial fibrillation})$$

Internal and External Validation

We applied the equation to calculate predicted 6-MWD and compared the result with the observed 6-MWD in the original population (2014–2016) and in the population from 2018 for internal and external validation. The comparison seemed to

TABLE 2 | Multivariable linear regression model of 6-MWD post cardiac surgery.

Model	CABG surgery			Valve surgery		
	Unstandardized coefficients		*P*	Unstandardized coefficients		*P*
	B	Standard error		B	Standard error	
(Constant)	212.57	49.55	<0.001	371.05	9.99	<0.001
Male gender	30.47	5.19	<0.001	37.98	5.57	<0.001
Age	−1.62	0.23	<0.001	−1.36	0.22	<0.001
Diabetes	−12.68	3.59	<0.001	-	-	-
Body height	1.09	0.29	<0.001	-	-	-
AF	−28.36	11.05	0.027	−10.61	5.60	0.049
Adjusted R^2		15.3%			14.6%	
ANOVA *p*-value		<0.001			<0.001	
Durbin Watson		2.040			2.037	
Standardized residual Kolmogorov–Smirnov		0.342			0.479	
Levene's test equality of error variances		0.751			0.848	

This multivariable regression model explained 15.3 and 14.6% of 6-MWD after CABG and valve surgery, respectively. Homogeneity of residual and homoscedasticity assumption by Kolmogorov-Smirnov test and Levene's test are fulfilled ($p > 0.05$).
6-MWD, 6-min walk test distance, CABG, coronary artery bypass graft; gender, male = 1, female = 0; age, year; diabetes, no = 0; body height, cm; AF, atrial fibrillation = 1; sinus rhythm = 0.

TABLE 3 | Comparison between predicted and observed 6-MWD for internal and external validation.

	Population (year)	Mean observed 6-MWD	Mean predicted 6-MWD	*P*-value
CABG	2014–2016	313.59	313.23	0.87
	2018	337.28	331.89	0.11
Valve surgery	2014–2016	327.75	327.91	0.93
	2018	328.13	326.70	0.59

p-value of difference between observed and predicted 6-MWT distance. 6-MWD, 6-min walk test distance.

show no significant difference between predicted and observed distances (**Table 3**).

The correlation scatter plot for each population and each group are presented in **Figure 2**; Pearson's product moment correlation shows significant result ($p < 0.05$) with coefficient correlation approximately 30–40%. The Bland–Altmann plot (**Figure 3**) also shows that the average differences between predicted and observed 6-MWD is close to 0 for the CABG group and the valve surgery group (0.36 and −0.16 m, respectively), which indicates no significant difference between the predicted 6-MWD from the equations and the observed 6-MWTdistance.

The upper and lower limit variance agreement of the difference in this study was between −103.95 and +104.67 m for the CABG group and between −118.86 and +118.34 m for the valve surgery group. There was a tendency of proportional bias with bigger difference variance at lower and higher observed 6-MWD.

DISCUSSION

This study was conducted in an institution where the number of cardiac surgeries was the largest in the country. In this institution, the 6-MWT was used as the main functional capacity test before commencing or after finishing the early phase II of the CR program, with exceptions if the medical assessment indicated that the patients could safely perform maximum exercise stress test. The 6-MWT is selected because it is a safe, easy to perform, suitable, and reliable test for the patients after cardiac surgery or heart failure or patients who are unable to perform maximum treadmill or ergocycle test (6–8). Additionally, the 6-MWT also has a good correlation with measured oxygen uptake (VO_2) (2, 9), so that it could be used to obtain a predictive value when cardiopulmonary exercise testing is unavailable. Besides those reasons, the patients in the institution register early to the CR program after the surgery (within the first week after hospital discharge) when a maximum exercise test is more challenging to perform.

This study has a mean 6-MWD that was 57.4 ± 12.8% of the predicted distance of the healthy population reference (5), which indicates a reduced functional capacity after cardiac surgery compared with the normal population. But when these values were compared to similar patients, it would be challenging to grade their functional capacity as there are still no available reference. From our knowledge, there are no published studies regarding the minimum clinically important difference (MCID) in 6-MWD after cardiac surgery. However, as these results were compared to a study by Spertus et al. (10) about 6-MWD MCID for chronic heart failure patients for moderate decline of global rating of change scale (mean 6-MWD of 90 m), majority (78% for the CABG group, 82% for the valve surgery group) of the 6-MWD differences between the predicted and observed distances in our population are still below the MCID limit mentioned.

Reduced functional capacity, as observed in this study, is a common condition in patients after cardiac surgery especially in older age and in women when measured using 6-MWT or direct gas analysis (11). Presumably, it might be caused by the summative effect of existing chronic diseases, the

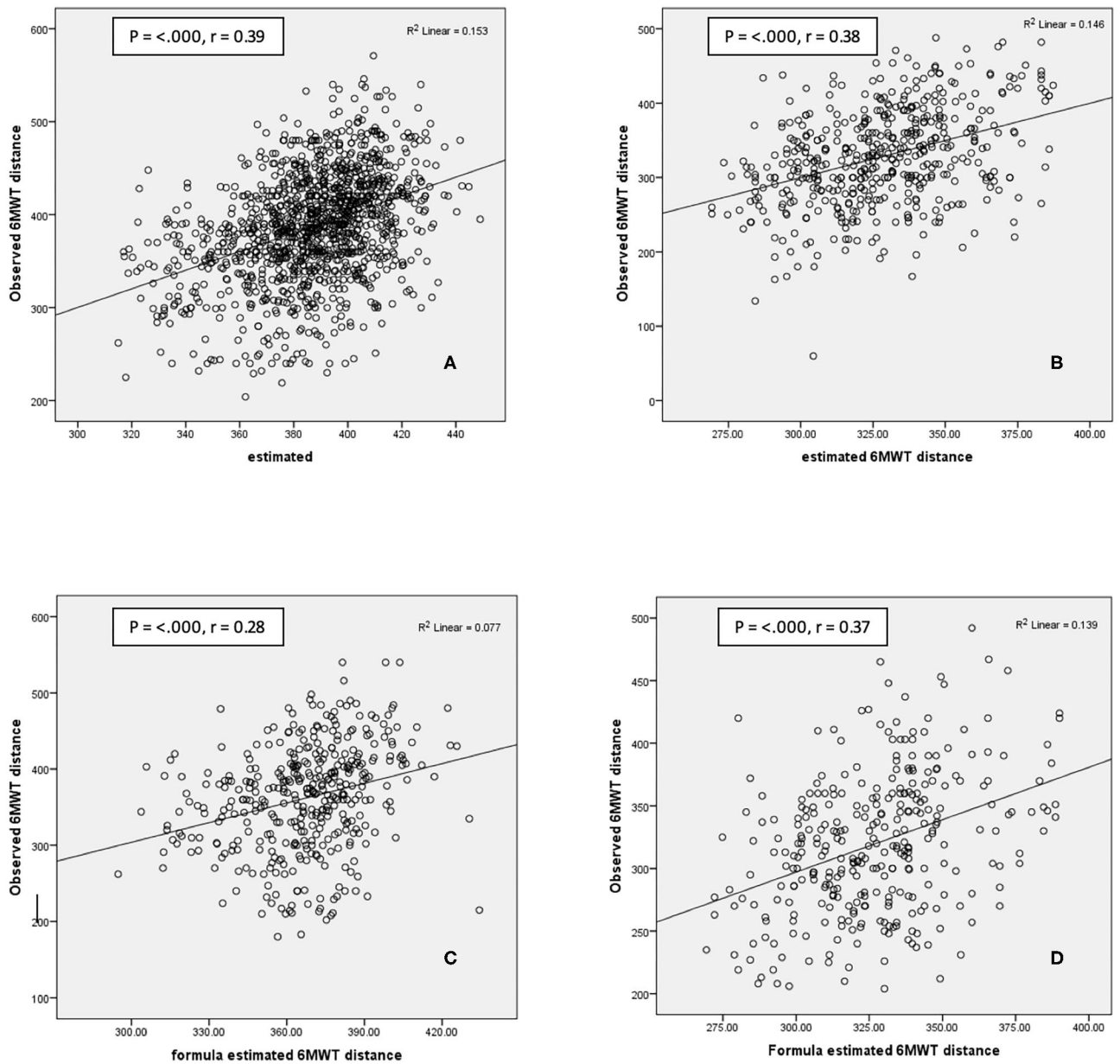


FIGURE 2 | Scatterplot of predicted value with actual 6-MWT. Internal validation: **(A)** CABG surgery group 2014–2016 population; **(B)** valve surgery group 2014–2016 population. External validation: **(C)**. CABG surgery group 2018 population. **(D)** Valve surgery group 2018 population. *p,* Pearson correlation significant; *r* = Pearson coefficient; 6-MWT, 6-min walk test; CABG, coronary artery bypass graft.

impacts of surgical procedure (chest and leg discomfort due to the surgical wound), long-term coronary artery disease (systolic or diastolic dysfunction), pulmonary hemodynamic changes due to valvular heart diseases, previous speed of habitual walking or cultural aspects related to lifestyle, mood, attitude, and motivation of the patients or technicians (2, 12). However, it is evident that there will be a significant increase of functional capacity after the comprehensive CR program (13). This functional capacity reduction cannot be interpreted whether they are higher or lower for patients after cardiac surgery, since there is no available reference. Ultimately, the equations from this study can be used to grade a patient's functional capacity after CABG or valve surgery.

The baseline characteristic of the patients in the CABG group and the valve surgery group were different (**Table 1**). In the CABG group, the patients were significantly older, and they had more atherosclerosis risk factors such as diabetes mellitus, being an active smoker, dyslipidemia, higher systolic blood pressure, and body weight. Meanwhile, in the valve surgery group, the mean ejection fraction is higher than in the patients in the CABG group, and they had more incidences of AF. The 6-MWD soon

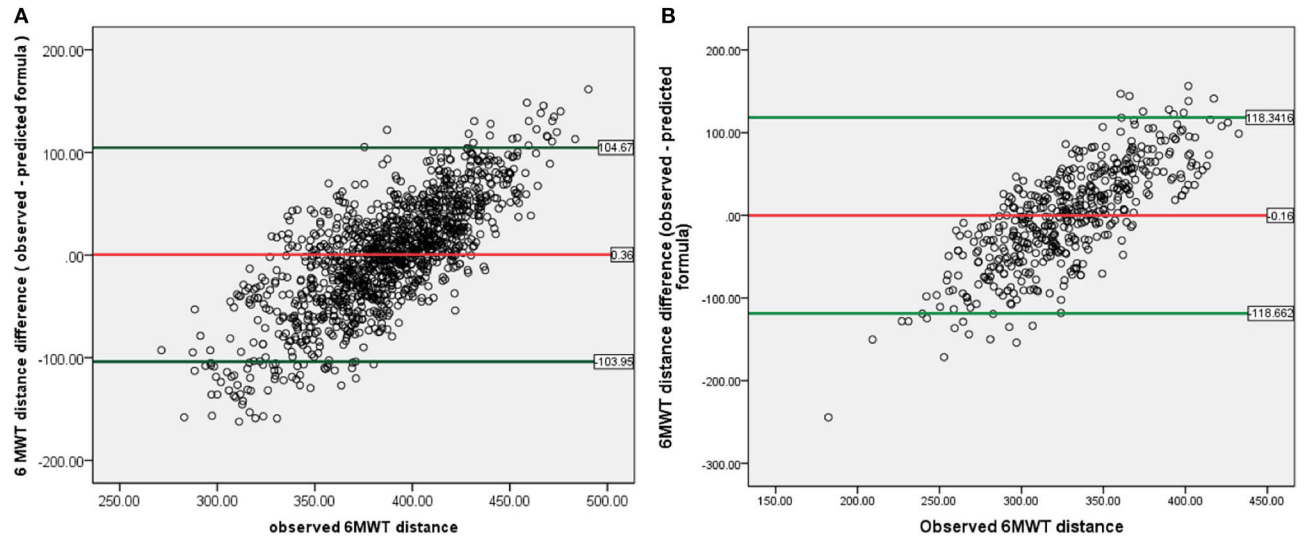


FIGURE 3 | Bland–Altman plot of 6-MWT distance difference between observed and predicted formula, against actual observed 6-MWT distance for 2014–2016 population: **(A)** CABG group. **(B)** Valve surgery group. *Red line indicates mean difference between 6-MWT distance predicted and observed and showed values close to 0 for both groups. Green line indicates upper and lower limit agreement of difference in the population. 6-MWT, 6-min walk test; CABG, coronary artery bypass graft.

after surgery was also longer in the valve surgery group than in the CABG group. This condition is caused by the nature of the different processes between coronary artery disease and valvular disease.

The univariable analysis revealed that female gender, older age, and lower body height, together with AF, were related to shorter 6-MWD early after CABG and heart valve surgery. Diabetes also had a negative effect on 6-MWD soon after CABG but not for the valve surgery group.

The multivariable linear regression analysis revealed that in patients of the CABG group, the determinants of the prediction equation were gender, age, body height, diabetes, and AF. Meanwhile, for the valve surgery group, the determinants were gender, age, and AF. Our prediction models explained only approximately 15% (R^2) of the observed variation of 6-MWD after surgery, which is moderately satisfactory.

The strongest predictor of 6-MWD in this study was gender, followed by heart rhythm (AF or sinus). The influence of gender group on the 6-MWD in our study is consistent with previous studies in the healthy population (12, 13). However, our finding differs from a study of Oliveira et al. where gender was not the determinant variable of the predicted 6-MWD after cardiac surgery (14). This difference might be caused by the difference in the population characteristic and ethnicity, where in the previous study mentioned the population comprised non-Asian patients.

Several studies revealed some determinants probably influenced functional capacity early after surgery such as CPB time, type of surgeries, previous functional capacity, body mass index, age, gender, or co-morbidity (11, 14, 15).

It is important to have a 6-MWD reference from various groups of patients to compare and to consider whether a value resulting from a measurement is within normal range or subnormal. This study successfully generates two reference equations for 6-MWD for patients after cardiac surgery (CABG or valve surgery) which can be used for a similar population group.

The limitation of this study is that the data only came from a single center, so that additional data from other centers in the country must be collected to establish a national reference, including the 6-MWD reference for healthy persons. There were no data regarding the patient's functional capacity prior to the surgeries so that their functional capacity improvements as the direct effect of surgeries could not be explored. Another limitation is that the predicted functional capacity measurement is very much affected by individual motivation and other psychological factors, which were beyond the scope of the current study. However, from the authors' knowledge, this is the first study about reference equation prediction models of patients after cardiac surgery in an Asian population with satisfactory internal and external validation. Further studies could then revolve among other determinants which were not discussed yet in this study, in which the current discovered formula could be used as a baseline and thinking foundation in more advanced future studies.

CONCLUSION

In conclusion, several determinants for the 6-MWD were identified, and two reference equations for predicting 6-MWD in patients after CABG and valve surgery were generated. Regarding patient characteristics, CABG is performed on older subjects, males, and more prevalent on diabetes; on the other hand, the prevalence of AF seems to be significantly higher in the valve surgery group. Although different variables are seen to influence 6-MWT in these two groups, the male gender seems to be the strongest predictor in both groups, while older age and AF were negative predictors. Additional exclusive predictors

were seen in the CABG group; these include higher body height as a mild positive predictor and presence of diabetes as a negative predictor. It is expected that the equations generated in this study would assist clinicians in predicting the level of functional capacity of patients immediately after cardiac surgery.

DATA AVAILABILITY STATEMENT

The datasets generated for this article are not readily available because the data is a part of Indonesian National Cardiovascular Center registry of Cardiac Rehabilitation, data would be provided in the presence of acceptable purposes, such as multicenter study. Requests to access the datasets should be directed to basuni_radi@hotmail.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Committee on Institutional Review Board/Health Research Ethics of National Cardiac Center Harapan Kita Hospital with the following registration number: LB.02.01/VII/536/KEP 027/2021 on Cardiac Rehabilitation Patient Registry. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BR contributed in providing research ideas and leading the research team. The full article writing and study operations were completed by AA, BD, RI, KT, and AS. Statistical consultations were provided by BS. All authors have equal and significant contributions toward the final accomplishments of this study.

ACKNOWLEDGMENTS

The authors would like to thank all the members of the National Cardiovascular Center Harapan Kita, Indonesia, and all individuals that have been involved toward the completion of this study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.685673/full#supplementary-material

REFERENCES

1. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med.* (2002) 166:111-7. doi: 10.1164/ajrccm.166.1.at1102
2. Papathanasiou JV, Ilieva E, Marinov B. Six-minute walk test: an effective and necessary tool in modern cardiac rehabilitation. *Hellenic J Cardiol.* (2013) 54:126-30.
3. Rasekaba T, Lee AL, Naughton MT, Williams TJ, Holland AE. The six-minute walk test: a useful metric for the cardiopulmonary patient. *Intern Med J.* (2009) 39:495-501. doi: 10.1111/j.1445-5994.2008.01880.x
4. Wright DJ, Khan KM, Gossage EM, Saltisi S. Assessment of a low-intensity cardiac rehabilitation programme using the six-minute walk test. *Clin Rehabil.* (2001) 15:119-24. doi: 10.1191/026921501671364449
5. Zou H, Zhu X, Zhang J, Wang Y, Wu X, Liu F, et al. Reference equations for the six-minute walk distance in the healthy Chinese population aged 18-59 years. *PLoS ONE.* (2017) 12:e0184669. doi: 10.1371/journal.pone.0184669
6. Bellet RN, Adams L, Morris NR. The 6-minute walk test in outpatient cardiac rehabilitation: validity, reliability and responsiveness—a systematic review. *Physiotherapy.* (2012) 98:277-86. doi: 10.1016/j.physio.2011.11.003
7. Pollentier B, Irons SL, Menedeto CM, DiBenedetto CM, Loton D, Seyler RD, et al. Examination of the six-minute walk test to determine functional capacity in people with chronic heart failure: a systematic review. *Cardiopulm Phys Ther J.* (2010) 21(1):13-21. doi: 10.1097/01823246-201021010-00003
8. De Feo S, Tramarin R, Lorusso R, Faggiano P. Six-minute walking test after cardiac surgery: instructions for an appropriate use. *Eur J Cardiovasc Prev Rehabil.* (2009) 16:144-9. doi: 10.1097/HJR.0b013e328321312e
9. Ross RM, Murthy JN, Wollak ID, Jackson AS. The six-minute walk test accurately estimates mean peak oxygen uptake. *BMC Pulm Med.* (2010) 10:31. doi: 10.1186/1471-2466-10-31
10. Spertus J, Peterson E, Conard MW, Heidenreich PA, Krumholz HM, Jones P, et al. Monitoring clinical changes in patients with heart failure: a comparison of methods. *Am Heart J.* (2005) 150:707-15. doi: 10.1016/j.ahj.2004.12.010
11. Fiorina C, Vizzardi E, Lorusso R, Maggio M, De Cicco G, Nodari S, et al. The 6-min walking test early after cardiac surgery. Reference values and the effects of rehabilitation programme. *Eur J Cardiothorac Surg.* (2007) 32:724-9. doi: 10.1016/j.ejcts.2007.08.013
12. Casanova C, Celli BR, Barria P, Casas A, Cote C, de Torres JP, et al. The 6-min walk distance in healthy subjects: reference standards from seven countries. *Eur Respir J.* (2011) 37:150-6. doi: 10.1183/09031936.00194909
13. Spiroski D, Andjic M, Stojanovic OI, Lazovic M, Dikic AD, Ostojik M, et al. Very short/ short-term benefit of inpatient/outpatient cardiac rehabilitation programs after coronary artery bypass grafting surgery. *Clin Cardiol.* (2017) 40:281-6. doi: 10.1002/clc.22656
14. Opasich C, De Feo S, Pinna GD, Furgi G, Pedretti R, Scrutinio D, et al. Distance walked in the 6-minute test soon after cardiac surgery: toward an efficient use in the individual patient. *Chest.* (2004) 126:1796-801. doi: 10.1378/chest.126.6.1796
15. Oliveira GU, Carvalho VO, de Assis Cacau LP, Filho AA, Netto ML, Junior WM, et al. Determinants of distance walked during the six-minute walk test in patients undergoing cardiac surgery at hospital discharge. *J Cardiothorac Surg.* (2014) 9:95. doi: 10.1186/1749-8090-9-95

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Cardiovascular Medicine

STUDY PROTOCOL
published: 26 August 2021
doi: 10.3389/fcvm.2021.705972

Efficacy and Safety of Different Aerobic Exercise Intensities in Patients With Heart Failure With Reduced Ejection Fraction: Design of a Multicenter Randomized Controlled Trial (HF-EI Trial)

Ting Shen[1†], Xiaoling Liu[1†], Bo Zhuang[1], Qian Luo[1], Yishan Jin[1], Guanghe Li[1], Yumei Jiang[1], Dejie Li[1], Xianchuan Chen[2], Nuo Tang[3], Zhimin Xu[4], Lemin Wang[1], Liang Zheng[5] and Yuqin Shen[1*]*

[1] Department of Rehabilitation, Tongji Hospital Affiliated to Tongji University, Tongji University School of Medicine, Shanghai, China, [2] Department of Geriatrics, Yueyang Integrated Traditional Chinese Medicine and Western Medicine Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China, [3] Department of Cardiology, Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China, [4] Department of Cardiovascular Medicine, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China, [5] Department of Cardiovascular Medicine, Research Center for Translational Medicine, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China

Background: Heart failure (HF) is one of the major causes of mortality worldwide, representing the terminal stage of several cardiovascular diseases. Exercise-based rehabilitation is a beneficial therapy for patients with chronic heart failure (CHF). However, there is a lack of specific guidance on clinical decision-making regarding optimal exercise intensity. It is necessary to optimize the clinical recommendations for HF exercises. We will evaluate the efficacy and safety of different aerobic exercise intensities in patients with heart failure with reduced ejection fraction (HFrEF): the HF-EI trial. This trial aims to assess the appropriate exercise intensity for patients with HFrEF.

Methods: After a baseline assessment to determine the safety of exercise, 180 patients will be randomly assigned to supervised high-intensity exercise training (ET) group, supervised moderate intensity training (MIT) group, and control group at a ratio of 1:1:1. Patients randomly receiving high intensity training (HIT) undergo supervised ET (3 times/week, 30 min) for aerobic endurance at 70% peak oxygen consumption (peak VO_2) intensity for 12 weeks. The MIT patients will perform supervised aerobic ET (3 times/week, 35–42 min) at the anaerobic threshold (AT) intensity for 12 weeks. The control group will continue to maintain their daily activities and will not receive ET. During the baseline and follow-up period, physical examination, laboratory tests, cardiology diagnostic tests, cardiopulmonary exercise tests (CPET), 6-min walk distance (6MWD), scale scores, exercise steps, medications, and clinical events will be monitored. Throughout the research, sport bracelets and patient diaries will be used to monitor and record overall physical activity, training courses, and compliance.

OPEN ACCESS

Edited by:
Richard Yang Cao,
Shanghai Xuhui Central Hospital, China

Reviewed by:
Xiankun Chen,
Karolinska Institutet (KI), Sweden
Randal Thomas,
Mayo Clinic, United States

***Correspondence:**
Liang Zheng
zhengliang@tongji.edu.cn
Yuqin Shen
sy_1963@126.com

[†] These authors have contributed equally to this work and share co-first authorship

Specialty section:
This article was submitted to General Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

Received: 06 May 2021
Accepted: 04 August 2021
Published: 26 August 2021

Citation:
Shen T, Liu X, Zhuang B, Luo Q, Jin Y, Li G, Jiang Y, Li D, Chen X, Tang N, Xu Z, Wang L, Zheng L and Shen Y (2021) Efficacy and Safety of Different Aerobic Exercise Intensities in Patients With Heart Failure With Reduced Ejection Fraction: Design of a Multicenter Randomized Controlled Trial (HF-EI Trial). Front. Cardiovasc. Med. 8:705972. doi: 10.3389/fcvm.2021.705972

Discussion: The HF-EI trial will evaluate the effects of different aerobic exercise intensities on peak VO_2, quality of life (QoL), and clinical events among patients with HFrEF. The findings of this trial will provide a basis for formulating exercise prescriptions for patients with HFrEF.

Clinical Trial Registration: http://www.chictr.org.cn/, identifier: ChiCTR2000036381.

Keywords: exercise intensities, HFREF, randomized controlled trial, anaerobic threshold, exercise training

INTRODUCTION

Chronic heart failure (CHF) is a severe and end-stage manifestation of several cardiovascular diseases. It is a syndrome with a high hospitalization rate, high disability rate, and high mortality rate, causing an economic and social burden on families (1). According to statistics, there are 64.3 million heart failure (HF) patients worldwide. In developed countries, the prevalence of adult HF is 1–2% (2). The China Hypertension Survey (CHS) showed that 1.3% of Chinese people aged ≥35 years, or an estimated 13.7 million individuals had HF (3). At present, there are many treatment option [s]s for HF, including general therapy, medication, and non-drug treatment (4). Despite active exploration of new medical and non-drug treatments for HF, the final effect is still unsatisfactory. The challenges facing HF intervention include optimizing HF treatment and reducing overall costs associated with long-term management.

Exercise training (ET) is a safe and effective treatment for HF. As shown in previous randomized controlled trials, it can significantly improve exercise capacity and quality of life (QoL) (5). Furthermore, ET is associated with reductions in mortality and hospitalization and recommended in the current guidelines on CHF management (6).

A massive amount of evidence suggests that ET is beneficial for patients with HF (7–16). A study by Belardinelli et al. in 2012 showed that exercise rehabilitation for up to 10 years could significantly reduce the readmission rate and the risk of cardiovascular death (17). A Cochrane review in 2019 found that exercise-based cardiac rehabilitation (CR) may have little effect on short-term all-cause mortality but may improve long-term all-cause mortality (>12 months follow up).CR probably reduces overall hospitalization rates in the short term (6).

However, data from the Exercise Training Meta-Analysis of Trials in Chronic Heart Failure (ExTraMATCH) II trial with at least 3 weeks of ET in HF showed that exercise-based CR had no significant effect on the risk of mortality and hospitalization in heart failure with reduced ejection fraction (HFrEF) (18).

Studies on the effects of exercise-based CR on the mortality and hospitalization rate of patients with HF show conflicting results, possibly attributed to differences in exercise pattern, exercise intensity, patient population selection, compliance, and follow-up time. All factors, especially exercise intensity, may affect the endpoint effect. Therefore, further research is needed to determine optimal exercise intensity to reduce the mortality and HF hospitalization rate.

Since the 1980s, numerous studies have demonstrated the safety and effectiveness of moderate intensity training (MIT) (19, 20). However, recent data suggest that high intensity training (HIT) may offer some advantages over MIT (21–32). Within a specific intensity range, exercise intensity is proportional to the effect. However, higher exercise intensity is associated with higher risk, and a higher need for adjusted to ensure safety and effectiveness in patients with HF. The mainstream sports rehabilitation model in developed countries of Europe and the United States is based on rehabilitation centers and ET under electrocardiogram (ECG) monitoring. A 12-week, three times a week treadmill exercise is used as a classic exercise prescription (33). The advantage is that it considers the efficacy and safety of ET, providing tremendous benefits to patients with HF in the short term. Keteyian et al. found that a moderate amount of exercise (3–7 metabolic equivalent hours per week) in patients with HF reduces the risk of clinical events, and within this range, an increase in the amount of exercise is associated with increased benefits (34). Swank et al. also obtained similar results. After exercise rehabilitation in patients with HF, increased peak oxygen consumption (peak VO_2) was associated with improved prognosis (35).

According to the grading standards for exercise intensity proposed by the 2020 European Society of Cardiology (ESC) Guidelines on sports cardiology and exercise in patients with cardiovascular disease, the anaerobic threshold (AT) intensity is moderate, 70% PeakVO_2 intensity is high intensity (36). We will design a three-arm randomized controlled experiment to explore the effectiveness and safety of moderate exercise intensity (AT intensity) in the treatment of HFrEF. The HIT (70% PeakVO_2 intensity) group served as the active control group, and the

Abbreviations: 6MWD, 6-min walk distance; 6MWT, 6-min walking test; AT, anaerobic threshold; BMI, body mass index; CHF, chronic heart failure; CHS, China hypertension survey; CPET, cardiopulmonary exercise testing; CR, cardiac rehabilitation; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; ET, Exercise training; ExTraMATCH, Exercise Training Meta-Analysis of Trials in Chronic Heart Failure; GAD-7, General Anxiety Disorder-7; HF, heart failure; HF-EI trial, the efficacy and safety of different aerobic exercise intensities in patients with heart failure with reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; HIT, high intensity training; ICD, implantable cardioverter-defibrillator; LVEF, left ventricle ejection fraction; MET, metabolic equivalent; MIT, moderate intensity training; MLHFQ, Minnesota Living with Heart Failure Questionnaire scores; NT pro-BNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; Peak VO_2, peak oxygen consumption; PHQ-9, the Patient Health Questionnaire-9; QoL, quality of life; RCT, randomized controlled trial; RR, relative risk; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials.

daily activity group served as the placebo control group. Mainly compare MIT and HIT, or MIT and daily activities, and explore the dose-effect relationship of exercise intensity on changes in clinical outcomes through regression analysis. We assume that MIT has a greater impact in the main results than HIT and daily activities.

We will evaluate the efficacy and safety of different aerobic exercise intensities in patients with HFrEF: the HF-EI trial. This study is the first multicenter randomized controlled trial (RCT) on the effects of different aerobic exercise intensities in patients with HFrEF in China. By collecting data on exercise capacity and exercise rehabilitation, we will evaluate the clinical efficacy of exercise-based CR in Chinese patients with HFrEF. Finally, suitable exercise intensity will be recommended for the popularized HFrEF aerobic exercise program for Chinese patients with HFrEF.

The primary objective of the HF-EI trial is to investigate the effects of different exercise intensities on exercise capacity and quality of life in patients with HFrEF. As secondary objectives, the HF-EI trial will evaluate AT oxygen uptake, 6-min walk distance (6MWD), left ventricle ejection fraction (LVEF), N-terminal prohormone of brain natriuretic peptide (NT pro-BNP), the Patient Health Questionnaire-9 (PHQ-9), General Anxiety Disorder-7(GAD-7), all-cause mortality, HF hospitalization, major cardiovascular events, and adverse events.

METHODS/DESIGN

Design

This will be a multi-center, parallel, three-group RCT to evaluate the efficacy and safety of MIT for HFrEF. Eligible participants will be randomly assigned to the HIT intervention group receiving a 12-week supervised training sessions (70% PeakVO_2 intensity) plus usual medications, MIT intervention group receiving a 12-week supervised training sessions (AT intensity) plus usual medications, or a control group receiving only the usual medication and maintain daily activity. This study has a 12-week intervention and a 12-month follow-up period. **Figure 1** shows the study design flow chart. This protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines and fulfills the SPIRIT checklist (**Supplemental File 1**); A SPIRIT checklist is provided in **Figure 2** (37).

Setting and Participants

The HF-EI trial aims to recruit 180 stable HFrEF patients in three study sites (Tongji Hospital Affiliated to Tongji University,

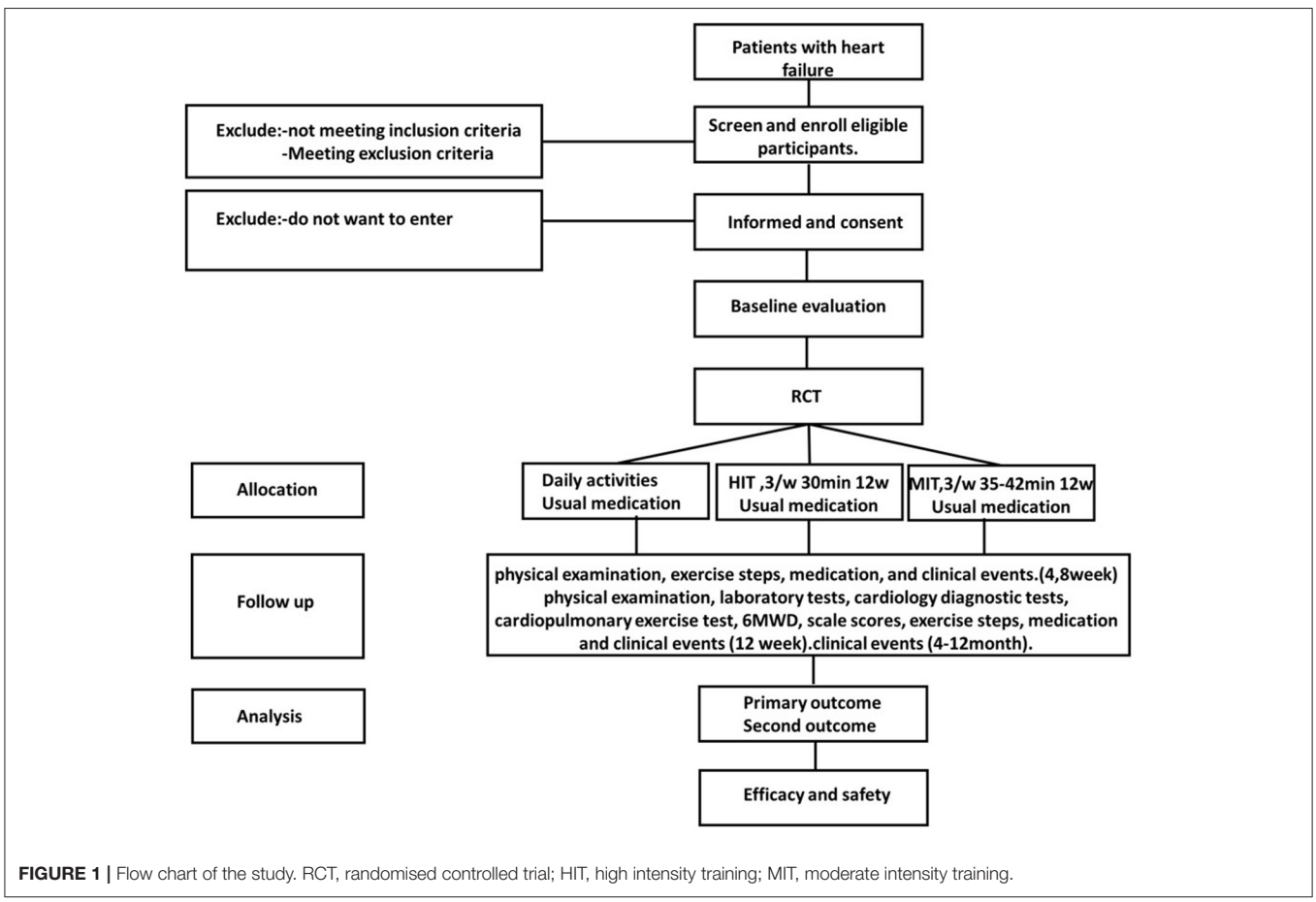


FIGURE 1 | Flow chart of the study. RCT, randomised controlled trial; HIT, high intensity training; MIT, moderate intensity training.

	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation				Close-out
TIMEPOINT**	$-t_1$	0	t_1 +0-4week	t_2 +8week	t_3 +12week	t_4 +4-12Month	t_x
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS:							
High intensity training-group			←	—	→		
Moderate intensity training-group			←	—	→		
Usual care-group			←	—	→		
ASSESSMENTS:							
Baseline dataset	X	X					
peak VO2		X			X		
Minnesota Living with Heart Failure Questionnaire		X			X		
anaerobic threshold oxygen uptake.		X			X		
6-minute walking distance		X			X		
Left ventricular ejection fraction (EF%),		X			X		
NT-proBNP		X			X		
PHQ-9		X			X		
GAD-7		X			X		
all-caused mortality			X	X	X	X	X
hospitalization events for heart failure			X	X	X	X	X
major cardiovascular events			X	X	X	X	X
adverse events			X	X	X	X	X
Safety endpoints			X	X	X	X	X

FIGURE 2 | Standard protocol items. Peak VO_2, peak oxygen consumption; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PHQ-9, Patient Health Questionnaire-9;GAD-7, General Anxiety Disorder-7.

Yueyang Integrated Traditional Chinese Medicine and Western Medicine Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, and Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine) in China and apply standard therapy in accordance with the ESC HF guidelines. We have predefined a set of inclusion and exclusion criteria (**Table 1**) to ensure the feasibility and safety of ET. The main method of recruiting patients is to screen the patients on-site when visiting a doctor.

Randomization and Allocation

We will use a block- randomization, stratified in groups for center to assign participants to the high- intensity exercise group, moderate- intensity exercise group and the control group in a 1:1:1 ratio. For the hierarchical random assignment operation, the statistical unit responsible adopted the SAS version 9.2 statistical software (procedure 'PROC PLAN') to complete program writing and randomization operations. The random distribution results will be released through the network of a central random distribution system. The results of random allocation will be managed by a person designated by the research group, and the results will be executed independently by clinicians. Due to the interventional study design, blinding is impossible for patients and clinical operators. However, the examiners, researchers collecting data on outcome indicators, data managers, and statisticians will be blinded.

Intervention and Control

The training program of intervention groups and the control group is shown in **Figure 2**. The HF-EI trial aims to ensure that patients receive appropriate and stable guide-based care before entering the trial. Throughout the trial, the three groups of patients will receive the usual medications, monthly follow-ups and the same number of visits. This study has a 12-week intervention and a 12-month follow-up period. All interventions and follow-ups will be completed by doctors (obtained a licensed physician qualification) in the Heart Rehabilitation Center.

Control Group

Patients in the control group will continue to maintain their daily activities (daily activities monitor the number of exercise steps through a sport bracelet) and will not provide additional ET.

Intervention Group

Patients randomized to receive HIT or MIT training receive 36 supervised training sessions, thrice weekly, in addition to usual care for 12 consecutive weeks of aerobic ET. Patients will be regularly encouraged to exercise on other days. The duration of each exercise session in the high intensity training group is 30 min, and the duration of each exercise session in the moderate intensity training group is 35–42 min. It is estimated that the high intensity training group and the moderate intensity training group have similar energy expenditure (38, 39). **Table 2** summarizes the training program for the HF-EI trial. Participants who have serious adverse clinical events during the intervention will immediately stop the intervention measures and withdraw from this clinical study.

TABLE 1 | HF-EI trial inclusion and exclusion criteria.

Inclusion criteria

1. Aged 18 to 75 years old
2. BMI 18–30 kg/m^2
3. LVEF<0.4
4. NYHA I-III.
5. Clinical symptoms are stable for at least 2 weeks
6. The dose of angiotensin-converting enzyme inhibitor/angiotensin receptor antagonist/angiotensin receptor enkephinase inhibitor, beta-blocker, aldosterone inhibitor and other drugs was stabilized for at least 2 weeks.
7. Written informed consent.

Exclusion criteria

1. Have a history of heart implant device in the last 6 weeks, or have a heart implant device plan or heart transplant plan within the next 12 months
2. Acute coronary syndrome within 6 weeks
3. Severe valvular heart disease, congenital heart disease, severe hypertrophic obstructive cardiomyopathy, acute myocarditis/pericarditis, intracardiac thrombosis, primary pulmonary hypertension, perinatal cardiomyopathy, thyroid heart disease;
4. Implanted pacemaker with no frequency response function, or set the discharge threshold of ICD lower than the heart rate during exercise.
5. Contraindications to exercise training: uncontrolled hypertension (systolic blood pressure >200 mmHg and/or diastolic blood pressure >110 mmHg); Severe arrhythmias such as ventricular tachycardia, frequent multi-source premature ventricular beats, high atrioventricular block and significant QT interval prolongation occurred during exercise test.
6. Progressive dyspnea or loss of exercise endurance in the last 3–5 days at rest;
7. Myocardial ischemia under low power exercise load (<2MET, or <50W);
8. Uncontrolled diabetes;.
9. Recent embolism;
10. Thrombophlebitis;
11. New atrial fibrillation or atrial flutter, etc., and other conditions not suitable for sports training;
12. Severe liver and kidney dysfunction, liver function more than three times the normal value, eGFR <30 mL/min/1.73 m2;
13. Currently suffering from severe mental illness, severe respiratory disorders, severe hematological diseases, severe nervous and neuromuscular diseases, severe metabolic and endocrine diseases, malignant neoplasms, severe autoimmune diseases, complicated with systemic infections and other acute systemic diseases.
14. Other clinical studies have been included to influence the results of this study;
15. Women who are pregnant or preparing to become pregnant, and women who are breastfeeding;
16. The researchers determined that the patients were not suitable for the study.

BMI, body mass index; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; ICD, implantable cardioverter-defibrillator; MET metabolic equivalent; eGFR, estimated glomerular filtration rate.

Adherence

Adherence refers to the degree to which trial participants comply with the intervention plan. Patients need to complete at least 66% of possible supervised training courses before consideration for treatment. The HF-EI trial uses several methods to promote compliance. First, researchers and trainers should regularly encourage patients randomized to ET to participate in supervised training courses. Second, a diary is

TABLE 2 | Training program.

Group	Intervention			
	Frequency	**Duration**	**Intensity**	**Form**
High intensity training group	3 times per week	30 min	70% peak VO_2	Centre-based rehabilitation: treadmill. Home-based cardiac rehabilitation: walk.
Moderate intensity training group	3 times per week	35–42 min	AT	Centre-based rehabilitation: treadmill. Home-based cardiac rehabilitation: walk.
Control group	Daily activities.			

peak VO_2, peak oxygen consumption; AT, anaerobic threshold.

used to track patient attendance and training to monitor patient compliance throughout the trial.

Outcome Measures

The primary outcome for the HF-EI trial is the change in peak VO_2 and Minnesota Living with Heart Failure Questionnaire scores (MLHFQ)after 12 weeks. We choose the common primary outcomes in order to obtain the comprehensive effect of different exercise intensities on HFrEF treatment. Aerobic exercise has a well-known positive effect on patients with HFrEF in exercise capacity and quality of life, and peakVO_2 is an important indicator for evaluating the prognosis of HF (22, 40).

Secondary outcomes included, AT oxygen uptake, 6MWD, LVEF, NT pro-BNP, PHQ-9, GAD-7, all-cause- mortality, hospitalization events for HF, major cardiovascular events, and adverse events.

The test indicators require patients to be measured at the hospital rehabilitation center. The test details are as follows:

Cardiopulmonary Exercise Testing(CPET)

According to the recommendations of international guidelines, CPET will be performed before randomization to determine exercise safety in patients. We will evaluate patient exercise endurance using CPET peak power, exercise duration, peak oxygen uptake, and AT. The core laboratory trains and certifies all researchers performing CPET before recruiting personnel.

6-min Walking Test (6MWT)

Perform 6MWT according to the guidelines of the American Thoracic Society (41). In the room, follow a long and straight corridor and instruct patients to walk back and forth at their chosen walking speed. The corridor is 30 m long, with a mark every 3 m, and turning points are marked with cones. During the test, all patients are guided by a unified standard record.

Echocardiography

Echocardiographic images and loops will be digitally recorded and stored on-site for analysis in an assessor-blinded reference echocardiography core lab, using color Doppler ultrasound diagnostic equipment, probe frequency 2.5–3.5HZ. During the examination, the patient assumes the left lateral decubitus position to obtain, the left ventricular long-axis view and the left ventricular short-axis view. The sampling lines are collected at the papillary muscle levels, the level of the mitral valve, and the aortic root to acquire two-dimensional images and an M-shaped spectrum. Echocardiography is repeated 12 weeks after randomization.

Laboratory Measurements and Biobanking

After resting for at least 5 min, blood samples will be collected under standardized conditions. According to standard operating procedures, all samples will be centrifuged immediately, aliquoted, and stored at −80 °C. Blood tests will be performed by a locally accredited laboratory.

Psychometric Analysis

A validated standard questionnaire will be used to assess the quality of life at baseline with repeat assessments within 12 weeks of patient randomization.

Data Collections

The HF-EI research data collection process is shown in **Figure 2**.

Baseline Data

We will monitor the demographic data, medical history, physical status, laboratory tests (NT pro-BNP), cardiology diagnostic tests (LVEF), cardiopulmonary exercise tests (peak VO_2, AT oxygen uptake), 6MWD, scale score(MLHFQ, PHQ-9, and GAD-7)and medications during the baseline period. Baseline data will be collected through outpatient consultation and medical record review.

Outcome Assessments

Physical examination, exercise steps, medication use, and clinical events (all-cause-mortality, hospitalization events for HF, major cardiovascular events, and adverse events) will receive outpatient follow-up in the 4th and 8th weeks after random assignment. At 12 weeks after randomization, physical examination, laboratory tests, cardiology diagnostic tests, cardiopulmonary exercise test, 6MWD, scale scores, exercise steps, medication, and clinical events will receive outpatient follow-up visits. 4–12 months after randomization, clinical events will be followed up by telephone every month. Both the baseline survey and follow-up will be conducted by two physicians.

Statistical Methods

The calculation of the sample size will be based on the primary outcome of the RCT. The sample size calculation was performed using PASS V11.0 (NCSS Company of the United States) with the

following calculation formula:

$$n = \Psi^2[\sum_{i=1}^{k} s_i^2/k]/[\sum_{i=1}^{k}(\overline{X}_i - \overline{X})^2/(k-1)](k = 3)$$

The parameters are set to double-sided $\alpha = 0.05$, $\beta = 0.1$, Power $= 1-\beta = 90\%$, the average difference in peak VO_2 of the three groups were 0, 2, 4(ml/kg/min) and the average difference in MLHFQ of the three groups were 2, 12, 10. The corresponding standard difference values of peakVO_2 were 6, 4, 6 (ml/kg/min) and MLHFQ were 5, 18, 16.

The parameter estimation is based on the results of previous researches (22, 42, 43).

A total of 180 cases were required for the three groups, 60 patients in each group, considering the 20% loss to follow-up rate and stratification factors. Because each of the primary endpoints can be individually reflected in clinical significance. Therefore, if one of the two primary endpoints of the intervention group improves significantly, the study is successful.

Blinded statistical analysis will be performed by qualified statisticians using PASW Statistics 18.0 (IBM SPSS Inc., Armonk, New York, USA). The measurement data will be expressed as mean ± standard deviation (x ± s), measurement data by *t* test, and count data by chi-square test. The clinical events of the treatment groups will be statistically compared, according to the principle of intention-to-treat. The Kaplan–Meier method will be used to calculate the cumulative event rate. The event time of all patients will be measured starting from the randomization time (time zero). We will collect all available information on clinical events until the last patient contact, including patients who withdraw consent or those lost to follow-up. Relative risk (RR) will be calculated using the Cox proportional hazard model. If a sufficient number of events occur, the Kaplan–Meier curve will be used for stratified analysis of the exercise group, and the log-rank test will be used to test the difference in survival. The significance level will be set at $p < 0.05$.

Trial Management and Quality Control

The management structure includes a trial management team, a data monitoring committee, and a trial steering committee.

The trial management team (including two physicians and three investigators) is responsible for the implementation of the trial and will meet weekly to discuss the progress of the trial. The data monitoring committee is composed of three clinicians and two biostatisticians, and independently evaluates the safety, scientific validity and completeness of clinical trials. The data monitoring committee will convene a meeting before the start of patient recruitment and once a month after the patient begins to intervene. The person in charge of the center monitors the intermediate results during the clinical trial. Once serious side effects occur, the trial should be stopped immediately. If there are significant differences in the efficacy of the three groups (HIT group, MIT group, and control group), the trial will be considered to be terminated. Responsibility of the test steering committee is to approve the main research plans and revisions, supervise the test, guide the test, and solve the problems of the test management team. The committee will be composed of four experts and will meet at least once every 6 months.

Before recruitment, the entire research team needs to participate in a training seminar. The data collected in this trial will include questionnaire information, medical chart review and test results. Professionals double-enter the data and store the data confidentially in the electronic database. The person in charge of the sub-center has the right to access the data set of the sub-center, and the person in charge of the project has the right to access the final data set of all the centers. Researchers and sponsors will inform participants and other relevant personnel of the results of the trial by publishing articles. The data quality will be regularly checked by the research assistant and supervised by the supervisor.

Trial Organization

Before enrolling patients, the protocol will be approved by the relevant institutional review boards, research ethics boards, and ethics committees of all the participating centers and the coordination center.

The clinical trial will be conducted in accordance with local laws. The study has been approved by Regional Committees for Medical Research Ethics of all participating centers (2020-KYSB-177). The study is registered at http://www.chictr.org.cn/ and the registration number is ChiCTR2000036381. The trial started in December 2020 and is currently recruiting.

DISCUSSION

The exercise-based CR is recommended in the guidelines for HFrEF but is still in infancy in China, where exercise-based CR services are rare in most regions, and the most suitable intensity ET for HFrEF patients remains unknown. Compared with global HFrEF exercise rehabilitation, HFrEF exercise rehabilitation in China started late and is still developing. Affected by factors, such as Chinese health and medical conditions and patients' exercise preferences, the overall level of CR in HFrEF still has some gaps compared with foreign countries. However, CR is a healthy behavior intervention affected by the social environment, cognition, and humanities. Simply introducing foreign experience cannot solve China's practical problems. The guidelines that are widely accepted abroad are referenced in China, but they need to be used in conjunction with China's actual adjustments. In this case, China currently lacks reference standards and effectiveness data on exercise intensity for HFrEF rehabilitation. The results of multi-center, randomized controlled registration studies from China are urgently needed to provide high-quality evidence and data from China.

To our knowledge, this is the first multicenter randomized controlled trial protocol to explore the appropriate exercise intensity for patients with HFrEF in China. The HF-EI trial will assess the impact of aerobic exercise intensity on the peak VO_2 and QoL in patients with HFrEF. It also provides a rationale for improving functional capacity and cardiovascular prognosis in patients with HFrEF. We hope that this research fills the gap in the literature and offers high-quality evidence on the recommendations for the treatment of HFrEF.

AT relates to the point when the exercise load increases to a certain amount and the tissue demand for oxygen exceeds the amount that the circulation can provide, and the tissues undergo anaerobic metabolism to provide more energy. The critical point from aerobic metabolism to anaerobic metabolism is called AT, expressed as the threshold oxygen consumption of anaerobic metabolism (VO_2 AT), equivalent to 50–60% of peak oxygen consumption, and directly detected by CPET (44). The advantages of using AT as the basis for formulating exercise prescriptions are sub-maximal exercise intensity, which can prevent the continuous increase of lactic acid levels, avoid hyperventilation and shortness of breath, avoid metabolic alkalosis, reduce the occurrence of overload on the heart and arrhythmia, and ensure high safety. Aerobic exercise with the intensity of the AT has protective effects on CHF, confirmed by the literature (45). For patients with HFrEF, exercise intensity is a range, not a point; AT belongs to sub-maximum medium intensity. Although 70% of peakVO_2 is high- intensity, it is not ultra-high intensity. This study will explore the effects of these two different intensities.

AT intensity has not been widely accepted internationally. This study compares the effectiveness and safety of AT intensity and high intensity in patients with HF, and aims to reflect the superiority of AT intensity exercise. It has reference value for other colleagues in the world.

Limitations of the study should be recognized as follows: lost to follow-up, influencing factors including patient age, difficulties attending appointments, concurrent illnesses, and the nature of the intervention that made blinding impossible. We made every effort to ensure that evaluators, laboratory technicians and statisticians remain unaware of the treatment allocation.

Altogether, the results of the HF-EI trial may provide evidence on the effective delivery of a contextually adapted exercise-based CR program in China. At the same time, it provides evidence of AT exercise intensity for the world's CR field.

CONCLUSIONS

The HF-EI trial will assess the effects of different aerobic exercise intensities on peak VO_2 and QoL in patients with HFrEF. It will provide a rationale for improving functional capacity and cardiovascular outcomes in patients with HFrEF.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Shanghai Tongji Hospital Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TS and XL prepared the manuscript and all the authors participated in the design of clinical and related research. All authors gave final approval and agreed to be accountable for the integrity and accuracy of all aspects of the work.

FUNDING

National Natural Science Foundation [81974359 and 81700316]. Advanced proper technology promotion project of Municipal Health and Health Commission in Shanghai, China [2019SY014].

ACKNOWLEDGMENTS

We would like to thank all the authors who provided important contributions to the drafting of this protocol.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.705972/full#supplementary-material

REFERENCES

1. Adams KF, Lindenfeld J, Arnold JMO, Baker DW, Barnard DH, Baughman KL, et al. Executive summary: HFSA 2006 comprehensive heart failure practice guideline. *J Cardiac Failure.* (2006) 12:10–38. doi: 10.1016/j.cardfail.2005.12.001
2. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. *Eur J Heart Fail.* (2020) 22:1342–56. doi: 10.1002/ejhf.1858
3. Hao G, Wang X, Chen Z, Zhang L, Zhang Y, Wei B, et al. Prevalence of heart failure and left ventricular dysfunction in China: the China Hypertension Survey, 2012-2015. *Eur J Heart Fail.* (2019) 21:1329–37. doi: 10.1002/ejhf.1629
4. Jiang H, Ge J. Epidemiology and clinical management of cardiomyopathies and heart failure in China. *Heart.* (2009) 95:1727–31. doi: 10.1136/hrt.2008.150177
5. Aronow WS, Shamliyan TA. Exercise for preventing hospitalization and readmission in adults with congestive heart failure. *Cardiol Rev.* (2019) 27:41–48. doi: 10.1097/CRD.0000000000000210
6. Long L, Mordi IR, Bridges C, Sagar VA, Davies EJ, Coats AJ, et al. Exercise-based cardiac rehabilitation for adults with heart failure. *Cochrane Database Syst Rev.* (2019) 1: CD003331. doi: 10.1002/14651858.CD003331.pub5
7. Cops J, Haesen S, De Moor B, Mullens W and Hansen D. Exercise intervention in hospitalized heart failure patients, with emphasis on congestion-related complications: a review. *Heart Fail Rev.* (2020) 25:257–68. doi: 10.1007/s10741-019-09833-x
8. Stolen T, Shi M, Wohlwend M, Hoydal MA, Bathen TF. Ellingsen O, Esmaeili M. Effect of exercise training on cardiac metabolism in rats with heart failure. *Scand Cardiovasc J.* (2020) 54:84–91. doi: 10.1080/14017431.2019.1658893
9. Schmidt C, Moreira-Goncalves D, Santos M, Leite-Moreira A, Oliveira J. Physical activity and exercise training in heart failure with preserved ejection fraction: gathering evidence from clinical and pre-clinical studies. *Heart Fail Rev.* (2020). doi: 10.1007/s10741-020-09973-5. [Epub ahead of print].
10. Fukuta H. Effects of Exercise Training on Cardiac Function in Heart Failure with Preserved Ejection Fraction. *Card Fail Rev.* (2020) 6: e27. doi: 10.15420/cfr.2020.17
11. Leggio M, Fusco A, Loreti C, Limongelli G, Bendini MG, Mazza A, et al. Effects of exercise training in heart failure with preserved ejection fraction: an updated systematic literature review. *Heart Fail Rev.* (2020) 25:703–711. doi: 10.1007/s10741-019-09841-x
12. Bjarnason-Wehrens B, Nebel R, Jensen K, Hackbusch M, Grilli M, Gielen S, et al. Exercise-based cardiac rehabilitation in patients with reduced

left ventricular ejection fraction: The Cardiac Rehabilitation Outcome Study in Heart Failure (CROS-HF): A systematic review and meta-analysis. *Eur J Prev Cardiol.* (2020) 27:929–952. doi: 10.1177/2047487319854140

13. Roh JD, Houstis N, Yu A, Chang B, Yeri A, Li H, et al. Exercise training reverses cardiac aging phenotypes associated with heart failure with preserved ejection fraction in male mice. *Aging Cell.* (2020) 19: e13159. doi: 10.1111/acel.13159
14. Bean G, Mou J, Pflugeisen B, Olsen L, Hoag S, Silva A, et al. Exercise training in patients with heart failure with preserved ejection fraction: A community hospital pilot study. *J Cardiovasc Nurs.* (2021) 36:124–30. doi: 10.1097/JCN.0000000000000737
15. Tucker WJ, Angadi SS, Haykowsky MJ, Nelson MD, Sarma S, Tomczak CR. Pathophysiology of exercise intolerance and its treatment with exercise-based cardiac rehabilitation in heart failure with preserved ejection fraction. *J Cardiopulm Rehabil Prev.* (2020) 40:9–16. doi: 10.1097/HCR.0000000000000481
16. Redwine LS, Pung MA, Wilson K, Bangen KJ, Delano-Wood L and Hurwitz B. An exploratory randomized sub-study of light-to-moderate intensity exercise on cognitive function, depression symptoms and inflammation in older adults with heart failure. *J Psychosom Res.* (2020) 128:109883. doi: 10.1016/j.jpsychores.2019.109883
17. Belardinelli R, Georgiou D, Cianci G and Purcaro A. 10-year exercise training in chronic heart failure: a randomized controlled trial. *J Am Coll Cardiol.* (2012) 60:1521–8. doi: 10.1016/j.jacc.2012.06.036
18. Taylor RS, Walker S, Smart NA, Piepoli MF, Warren FC, Ciani O, et al. Impact of exercise-based cardiac rehabilitation in patients with heart failure (ExTraMATCH II) on mortality and hospitalisation: an individual patient data meta-analysis of randomised trials. *Eur J Heart Fail.* (2018) 20:1735–43. doi: 10.1002/ejhf.1311
19. Abdelbasset WK, Alqahtani BA, Elshehawy AA, Tantawy SA, Elnegamy TE, Kamel DM. Examining the impacts of 12 weeks of low to moderate-intensity aerobic exercise on depression status in patients with systolic congestive heart failure - A randomized controlled study. *Clinics (São Paulo).* (2019) 74:e1017. doi: 10.6061/clinics/2019/e1017
20. Abdelbasset WK, Alqahtani BA, Alrawaili SM, Ahmed AS, Elnegamy TE, Ibrahim AA, et al. Similar effects of low to moderate-intensity exercise program vs moderate-intensity continuous exercise program on depressive disorder in heart failure patients: A 12-week randomized controlled trial. *Medicine (Baltimore).* (2019) 98:e16820. doi: 10.1097/MD.0000000000016820
21. Ding R. Exercise-Based Rehabilitation for Heart Failure: Clinical Evidence. *Adv Exp Med Biol.* (2017) 1000:31–49. doi: 10.1007/978-981-10-4304-8_3
22. Gomes Neto M, Duraes AR, Conceicao LSR, Saquetto MB, Ellingsen O, Carvalho VO. High intensity interval training versus moderate intensity continuous training on exercise capacity and quality of life in patients with heart failure with reduced ejection fraction: A systematic review and meta-analysis. *Int J Cardiol.* (2018) 261:134–41. doi: 10.1016/j.ijcard.2018.02.076
23. Dun Y, Smith JR, Liu S, Olson TP. High-intensity interval training in cardiac rehabilitation. *Clin Geriatr Med.* (2019) 35:469–87. doi: 10.1016/j.cger.2019.07.011
24. Giallauria F, Piccioli L, Vitale G, Sarullo FM. Exercise training in patients with chronic heart failure: A new challenge for Cardiac Rehabilitation Community. *Monaldi Arch Chest Dis.* (2018) 88:987. doi: 10.4081/monaldi.2018.987
25. Moreno-Suarez I, Scheer A, Lam K, Dembo L, Spence AL, Hayward C, et al. High-intensity interval training in patients with left ventricular assist devices: A pilot randomized controlled trial. *J Heart Lung Transplant.* (2020) 39:1380–8. doi: 10.1016/j.healun.2020.08.005
26. Keyhani D, Tartibian B, Dabiri A, Teixeira AMB. Effect of high-intensity interval training versus moderate-intensity aerobic continuous training on galectin-3 Gene expression in postmenopausal women: a randomized controlled trial. *J Aging Phys Act.* (2020) 1-9. doi: 10.1123/japa.2019-0213
27. Besnier F, Labrunee M, Richard L, Faggianelli F, Kerros H, Soukarie L, et al. Short-term effects of a 3-week interval training program on heart rate variability in chronic heart failure. A randomised controlled trial. *Ann Phys Rehabil Med.* (2019) 62:321–8. doi: 10.1016/j.rehab.2019.06.013
28. Angadi SS, Jarrett CL, Sherif M, Gaesser GA, Mookadam F. The effect of exercise training on biventricular myocardial strain in heart failure with preserved ejection fraction. *ESC Heart Fail.* (2017) 4:356–9. doi: 10.1002/ehf2.12149
29. Wu LH, Chang SC, Fu TC, Huang CH, Wang JS. High-intensity interval training improves mitochondrial function and suppresses thrombin generation in platelets undergoing hypoxic stress. *Sci Rep.* (2017) 7:4191. doi: 10.1038/s41598-017-04035-7
30. Giallauria F, Smart NA, Cittadini A and Vigorito C. Exercise training modalities in chronic heart failure: does high intensity aerobic interval training make the difference? *Monaldi Arch Chest Dis.* (2016) 86:754. doi: 10.4081/monaldi.2016.754
31. Fleg JL. Salutary effects of high-intensity interval training in persons with elevated cardiovascular risk. *F1000Res.* (2016) 5:F1000 Faculty Rev-2254. doi: 10.12688/f1000research.8778.1
32. Ellingsen O, Halle M, Conraads V, Stoylen A, Dalen H, Delagardelle C, et al. High-intensity interval training in patients with heart failure with reduced ejection fraction. *Circulation.* (2017) 135:839–49. doi: 10.1161/CIRCULATIONAHA.116.022924
33. Piepoli MF, Conraads V, Corra U, Dickstein K, Francis DP, Jaarsma T, et al. Exercise training in heart failure: from theory to practice. A consensus document of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation. *Eur J Heart Fail.* (2011) 13:347–57. doi: 10.1093/eurjhf/hfr017
34. Keteyian SJ, Leifer ES, Houston-Miller N, Kraus WE, Brawner CA, O'Connor CM, et al. Relation between volume of exercise and clinical outcomes in patients with heart failure. *J Am Coll Cardiol.* (2012) 60:1899–905. doi: 10.1016/j.jacc.2012.08.958
35. Swank AM, Horton J, Fleg JL, Fonarow GC, Keteyian S, Goldberg L, et al. Modest increase in peak VO2 is related to better clinical outcomes in chronic heart failure patients: results from heart failure and a controlled trial to investigate outcomes of exercise training. *Circ Heart Fail.* (2012) 5:579–85. doi: 10.1161/CIRCHEARTFAILURE.111.965186
36. Pelliccia A, Sharma S, Gati S, Back M, Borjesson M, Caselli S, et al. ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J.* (2021) 42:17–96. doi: 10.1093/eurheartj/ehaa605
37. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K, Hrobjartssonet al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med.* (2013) 158:200–207. doi: 10.7326/0003-4819-158-3-201302050-00583
38. Ohkawara K, Tanaka S, Miyachi M, Ishikawa-Takata K, Tabata I. A dose-response relation between aerobic exercise and visceral fat reduction: systematic review of clinical trials. *Int J Obes (Lond).* (2007) 31:1786–97. doi: 10.1038/sj.ijo.0803683
39. Rognmo O, Hetland E, Helgerud J, Hoff J and Slordahl SA. High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease. *Eur J Cardiovasc Prev Rehabil.* (2004) 11:216–222. doi: 10.1097/01.hjr.0000131677.96762.0c
40. Paolillo S, Veglia F, Salvioni E, Corra U, Piepoli M, Lagioia R, et al. Heart failure prognosis over time: how the prognostic role of oxygen consumption and ventilatory efficiency during exercise has changed in the last 20 years. *Eur J Heart Fail.* (2019) 21:208–17. doi: 10.1002/ejhf.1364
41. Laboratories ATSCoPSfCPF. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med.* (2002) 166:111–7. doi: 10.1164/ajrccm.166.1.at1102
42. Chen YW, Wang CY, Lai YH, Liao YC, Wen YK, Chang ST, et al. Home-based cardiac rehabilitation improves quality of life, aerobic capacity, and readmission rates in patients with chronic heart failure. *Medicine (Baltimore).* (2018) 97: e9629. doi: 10.1097/MD.0000000000009629
43. Wisloff U, Stoylen A, Loennechen JP, Bruvold M, Rognmo O, Haram PM, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study.

Circulation. (2007) 115:3086–94. doi: 10.1161/CIRCULATIONAHA.106.675041

44. Tanisho K, Hirakawa K. Training effects on endurance capacity in maximal intermittent exercise: comparison between continuous and interval training. *J Strength Cond Res.* (2009) 23:2405–10. doi: 10.1519/JSC.0b013e3181bac790
45. Shen YQ, Jiang JF, Wang LM, Che L, Qi XQ, Xu WJ, et al. [Effects of aerobic exercise on exercise tolerance in patients with chronic heart failure]. *Zhonghua Yi Xue Za Zhi.* (2011) 91:2678–82. doi: 10.3760/cma.j.issn.0376-2491.2011.38.005

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Cardiovascular Medicine

REVIEW
published: 30 August 2021
doi: 10.3389/fcvm.2021.730373

A Critical Review on New Approaches for Chronic Disease Prevention in Brazil and Canada: From Wholistic Dietary Guidelines to Physical Activity Security

*Juliano Schwartz[1,2], Paul Oh[3], Maira B. Perotto[4], Ryan E. Rhodes[5], Wanda Firth[6], Shannon S. D. Bredin[1,7], Alejandro Gaytán-González[1,7,8] and Darren E. R. Warburton[1,2,7]**

[1] Physical Activity Promotion and Chronic Disease Prevention Unit, University of British Columbia, Vancouver, BC, Canada, [2] Experimental Medicine Program, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada, [3] Cardiovascular Prevention and Rehabilitation Program, Toronto Rehabilitation Institute, University Health Network, Toronto, ON, Canada, [4] West Toronto Diabetes Education Program, LAMP Community Health Centre, Toronto, ON, Canada, [5] School of Exercise Science, Physical and Health Education, University of Victoria, Victoria, BC, Canada, [6] Hearts & Health in Motion Program, Nova Scotia Health, QEII Health Sciences Centre, Halifax, NS, Canada, [7] School of Kinesiology, Faculty of Education, University of British Columbia, Vancouver, BC, Canada, [8] Institute of Applied Sciences for Physical Activity and Sport, University of Guadalajara, Guadalajara, Mexico

OPEN ACCESS

Edited by:
Richard Yang Cao,
Shanghai Xuhui Central Hospital, China

Reviewed by:
Leila Itani,
Beirut Arab University, Lebanon
Flavia Mori Sarti,
University of São Paulo, Brazil

***Correspondence:**
Darren E. R. Warburton
darren.warburton@ubc.ca

Specialty section:
This article was submitted to General Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

Received: 24 June 2021
Accepted: 10 August 2021
Published: 30 August 2021

Citation:
Schwartz J, Oh P, Perotto MB, Rhodes RE, Firth W, Bredin SSD, Gaytán-González A and Warburton DER (2021) A Critical Review on New Approaches for Chronic Disease Prevention in Brazil and Canada: From Wholistic Dietary Guidelines to Physical Activity Security. Front. Cardiovasc. Med. 8:730373. doi: 10.3389/fcvm.2021.730373

In light of new evidence on the prevention of chronic diseases and the elevated rates of overweight and obesity in Brazil and Canada, this critical review aims to interpret and synthesize current aspects regarding dietary and physical activity initiatives in both countries and make future recommendations. The pioneering work presented in the last Brazilian dietary guidelines has been called a model that can be applied globally, given its conceptualization of healthy eating that translates easily to practical guidance. The new Canadian Food Guide has incorporated similar aspects, also putting the country as a leader in dietary guidance. With these new recommendations, citizens in both Brazil and Canada have access to impactful evidence-informed nutritional guidelines. Both documents propose eating patterns that focus not only on health benefits, such as chronic disease prevention, but also incorporate well-being concerning cultural, economic, sociodemographic, biological, and ecological dimensions. A similar approach is required for physical activity to allow individuals to have attainable health and life goals and thereby fully enjoy their lives, regardless of geographical location, health status, and socioeconomic condition, a concept recently described as physical activity security. The wholistic dietary guidelines from both countries represent a change in paradigm in public health. Likewise, national evidence-based policies are warranted to reduce disparities in physical activity, allowing healthier and more active lifestyles for everyone.

Keywords: lifestyle, health, physical inactivity, diet, Brazil, Canada, prevention

INTRODUCTION

As a result of significant improvements in health conditions management, most populations across the world have experienced a decrease in premature mortality related to infectious diseases in the last century (1). At the same time, there has been a rise in different chronic diseases and an increase in consequent morbidity and mortality associated with these medical conditions (2). This shift, called epidemiological transition, is linked to societies' progressive industrialization and extensive automation of manual tasks. Overall, there has been a marked reduction in the requirement for human movement in daily activities, along with widespread availability and active promotion of inexpensive and low-quality food around the world (3). Consequently, in the last decades, high-income as well as low- and middle-income countries (LMIC) have seen their populations engaging in unhealthy lifestyle behaviors, which represent the major cause of chronic diseases and early death (1).

Chronic medical conditions are a leading health problem in high-income countries, such as Canada, which has an estimated population of 37 million people (1, 4). These medical conditions affect LMIC in an even higher proportion—with more than 75% of worldwide deaths from such diseases occurring in these nations (5). This is the case of Brazil, a middle-income country with more than 200 million people, where chronic diseases are also the leading cause of mortality (1, 6).

When the World Health Organization (WHO) launched its global action plan for the prevention and control of chronic diseases 2013–2020, such conditions were responsible for around 63% of worldwide deaths (7). According to the newest report, the last decade has not seen much improvement, and this rate is now about 10% greater (8). Part of this situation is due to the lack of success in tackling these diseases' risk factors, mainly physical inactivity (usually identified when one does not engage in at least 150 min of moderate to vigorous physical activity (PA) per week); unhealthy diet (often characterized when one eats less than five servings of fruits and vegetables per day); smoking (tobacco use in any dose or route); and harmful alcohol intake (commonly observed in irregular or chronic heavy drinking) (3, 4, 6).

Tobacco use has received the most attention among governments and researchers worldwide, resulting in a significant decrease in this behavior in most countries, including Brazil and Canada (1, 9, 10). Global alcohol intake has also had some improvement, leading to stable levels of consumption in the last years—a trend also observed in both the Brazilian and Canadian populations (1, 6, 11, 12). Conversely, there has been an increase in the prevalence of obesity across the globe, which is directly related to unhealthy diet and physical inactivity, thus requiring effective national and international public health measures to tackle these burdens (1, 6, 13). In this respect, new evidence-based documents, such as the current dietary guidelines of both countries and the 2020 global guidelines on PA present cutting-edge advances and along with the newly proposed concept of PA security will be discussed in the following sections.

According to the WHO's latest report, in 2016 there were around 1.9 billion overweight adults worldwide, out of which 650 million were obese (14). While 39% of the adults across the globe have overweight or obesity, in Brazil and Canada this combined overweight/obesity prevalence is 55.4 and 59.8%, respectively (6, 13). As expected, according to official indicators, both countries also face high rates of physical inactivity and unhealthy dietary patterns. In Canada, 83.6% of adults do not engage in at least 150 min of moderate to vigorous PA per week, whereas in Brazil this prevalence is of 44.8% of the adult population (4, 6). This substantial difference is likely due to the lack of agreement between the methods of assessment used in each country. In Canada, PA was measured with accelerometers, which present better reliability and sensitivity, whereas Brazil used self-reports, which usually overestimate PA (15). To illustrate this difference, Colley et al. (16) compared both methods, which were used in a Canadian survey in 2016, showing that almost half of the Canadian adults reported engaging in 150 or more minutes of moderate to vigorous PA per week, whereas the accelerometer-measured data showed that this was the case for only 17% of these individuals. Regarding diet, 71.3% of Canadian adults and 87.1% of adults in Brazil do not eat five or more fruits and vegetables daily (4, 6).

Considering these realities, and in light of the new concept of PA security as well as innovative approaches introduced in the latest Canadian and Brazilian dietary guidelines and in the latest WHO guidelines on PA, this critical review aims to present and discuss current aspects regarding chronic disease prevention in adults in Brazil and Canada. Specifically, we analyze and synthesize current preventive approaches in terms of PA and diet carried out in each country, with a particular focus on PA, and make future recommendations.

PREVENTION APPROACHES IN BRAZIL AND CANADA

Given the alarming prevalence of unhealthy diets and insufficient levels of PA in Brazil and Canada, both countries have implemented population health programs and protocols to address these risk factors, including some novel initiatives (17–20). An innovative action taken by both countries was the update of their dietary guidelines. Brazil led the way, with their revolutionary approach to inform healthy eating (21). Canada followed with the launch of their new Food Guide, which incorporated similar concepts (22). Both documents address the context of eating rather than the usual focus on nutrients and food groups, which was a turning point in the field of nutrition and public health (23, 24). A common specific area of concern relates to the science regarding the negative impact on health from processed and ultra-processed food (22). With such evidence, the latest version of each guide addresses the importance of avoiding highly processed food and prioritizing minimally processed and unprocessed options (25, 26). These recommendations are directly aligned with the focus on chronic disease prevention, a primary goal in both documents (17, 20).

Without the food industry's participation in their development, both guidelines provide clear alternatives to processed and ultra-processed food, using simple and direct messaging (25, 26). Good examples are the recommendations to eat plenty of fruits and vegetables and to have water as the beverage of choice. Instead of the widely used nutrition-based guides, these food-based guidelines focus on healthy eating and, at the same time, make a direct ecological impact by encouraging a sustainable eating pattern (17, 21).

Another aspect present in both guides is the emphasis on meal planning and the connection with others during the act of eating, which contemplates sociocultural values, and are also considered strategies to support a healthy diet (23). With its emphasis on sustainability, this food- and meal-based wholistic approach put Brazil and Canada in the global leadership of dietary recommendations for optimal health of both human beings and the planet (27).

As is the case with all population-based guidelines, there is incremental work to be done beyond their release (28). There is a need for accompanying implementation tools for the guide, policy development, and multiple layered initiatives and support to target health behavior change (26). There are many barriers to be overcome, and it can be challenging to make healthy food choices (21). The Brazilian and Canadian dietary guidelines recognize the influence of social and physical environments, household income and the many determinants of health, educational and health programs, along with government food policies for the successful implementation of these guidelines (25, 26, 29).

While Brazil's latest dietary guidelines have been widely praised (30), by the time of its publication the country took a surprisingly different approach in respect of PA guidelines, despite the opinion of Brazilian researchers involved with the promotion of PA and health. The efforts and costs involved in creating national guidelines as a policy for health promotion were considered unjustified, and the country instead chose to adopt the general WHO PA recommendations (31).

Conversely, investments in PA policies are a priority in Canada (32, 33), which has led the country to be a leader in the promotion of the health benefits of PA and the development of evidence-informed PA recommendations for healthy individuals and persons living with chronic medical conditions (34–39). This includes leading international initiatives and conferences, such as the first and second "International Conference on PA, Fitness and Health" (held in 1988 and 1992), the "Dose-Response Symposium" (October 2000), the "Communicating PA and Health Messages Science into Practice" meeting (2001), the Toronto Charter for PA (2010), and the International Society for PA and Health Congress (2010 and 2021) (36, 40, 41). Also, the Canadian government was one of the main supporters of the 2020 WHO PA guidelines, which was launched in light of substantial advances in the field after the release of the previous version (42).

Besides an emphasis on participation and inclusivity, aiming at a broader reach, the latest WHO guidelines on PA address the new science on activities' intensity and duration (43). Specifically, the document highlights the importance of light-intensity PA and states that some activity is better than none. This echoes previous statements made by Canadian and international experts highlighting the importance of simply becoming more active (44–46). Also, due to insufficient supporting findings, these guidelines have removed the requirement for PA to be performed in bouts of at least 10 min of moderate to vigorous intensity to obtain health benefits (43). This new evidence is critical for less affluent settings since regular recreational PAs are inaccessible for many in these locations, as is the case in some areas in Canada as well as LMIC in general, including Brazil (47–49). Indeed, discrepancies in PA participation have been widely observed, with socioeconomically advantaged individuals having more opportunities to be physically active (50, 51). The inclusive approach presented in the 2020 WHO PA guidelines therefore has the potential to impact health outcomes in both Canada and Brazil, since inequalities in PA, besides contributing to the pandemic of physical inactivity, were found, for example, to be predictive of obesity in middle- as well as in high-income countries (51, 52). Further work is warranted, however, owing to the limited uptake of PA guidelines internationally and the deficits-based nature of PA messaging that focuses on the health perils of too little PA (i.e., increased risk for cardiometabolic disease) rather than the diverse benefits of simply moving more (53, 54).

Numerous disparities across the world require PA to be approached in terms of equity. This view is presented in the new Brazilian and Canadian dietary guidelines (25, 26). Just as these documents should lead to the development of strategies to address inequity and food insecurity, PA policies should also lead to recommendations on equity. This concept was recently described as PA security—when everyone, everywhere, would have unrestricted access to PA, meeting all needs for an active and healthy life (55). Aligned with this are two research priorities established in the latest WHO guidelines on PA (43). One of these concerns is the need for more evidence from LMIC and economically disadvantaged communities since most of the science on PA is based on findings from high-income settings. Another research topic to be prioritized refers to the health benefits of the aforementioned light-intensity PA. Both aspects relate to realities in Brazil and Canada since much of the PA carried out in different locations of these countries is of light intensity (48, 56). In fact, there is a pressing demand for PA security in certain areas of Canada and in much of Brazil's territory, where utilitarian PA, such as active commuting, is one of the main forms of PA (57, 58). Importantly, although some of these regions present a high prevalence of PA, many times such engagement happens due to a lack of alternatives, rather than simply choice, including walking and cycling to and from work/school in unsafe traffic areas as well as in locations with a high perception of criminality (55, 59, 60).

An important point corroborating this new approach is the evidence demonstrating significant health benefits with lower levels of PA than suggested in different guidelines (49). It has been demonstrated that such benefits can be attained even with half of the usual recommendation, particularly among previously inactive individuals (46). These findings hence show the lack of a minimum threshold in the amount of PA for health gains—a position which has just been endorsed by the WHO (42). This has

a great impact in terms of public health, since engaging in regular PA, regardless of the intensity and the duration, can promote change in other health behaviors, such as diet and smoking, thereby significantly contributing to the prevention of chronic diseases (61, 62).

Moreover, despite the well-known health benefits of regular PA (46), additional positive effects on the immune system, mental health, and quality of life have also been reported in the context of the COVID-19 pandemic, thus providing further support for PA to be made accessible to everyone (63). Therefore, the current moment is a window of opportunity to emphasize PA as a human right, calling for actions from local policy- and decision-makers (55, 64). In light of this recent evidence, the following section addresses aspects of different dimensions that should be considered in contemporary initiatives in Brazil and Canada aimed at population PA promotion. In addition, the Discussion section addresses more in-depth different initiatives carried out in each country.

MACRO-ENVIRONMENTAL DIMENSIONS OF PHYSICAL ACTIVITY

PA dimensions are commonly addressed only in terms of individual and physiological characteristics, such as energy expenditure, as well as activities' duration, frequency, and intensity, characterizing a strictly biomedical relationship (65, 66). At the same time, internal aspects such as motivation and self-regulation are frequently identified as significant barriers to PA in high-income nations (47, 67). However, given the low rates of physically active individuals in countries like Canada (68), it is unlikely that lack of motivation alone explains the level of physical inactivity in industrialized countries, and consequently other characteristics of population subgroups should also be considered. In fact, PA interventions focusing only on personal factors were excluding for many, particularly in disadvantaged areas, regardless of the geographic location (47, 59). These findings suggest the need for a more socially contextualized approach to make PA an attainable and enjoyable purpose for everyone, including those in middle- and high-income countries (51, 69). In that regard, some of the aspects employed in the current Brazilian and Canadian dietary guidelines could be used as references, aiming at establishing a wholistic approach to PA guidance that would influence research and policy development for equitable interventions for PA promotion (70, 71). The name of each of the following dimensions under which PA should be seen is not necessarily the only option since some have interchangeable characteristics for adults. The emphasis here is on the overall content presented rather than the specific label of each dimension.

Cultural

The interest in understanding the influence of culture on PA behavior is not new, however, to date, still little is known about this topic (72, 73). Commonly, health promotion interventions, including those aiming to increase PA participation, are based on outcomes from studies conducted with certain ethnicities and are then generalized to all cultures. As a consequence, since not all these interventions are universally transferable, individuals with different traditions, such as those in specific ethnic groups, religious communities, immigrant clusters, and indigenous peoples often present lower levels of PA (74–76). Even when resources are available and the built environment is conducive to PA, the absence of cultural care can limit changes in this behavior (77, 78). Accordingly, an increasing number of studies report that initiatives aiming at raising PA levels should take cultural backgrounds into consideration (64, 76, 79).

Despite Brazil's culture being a result of the integration of distinct nationalities and ethnic backgrounds, which implies a population full of diverse cultural roots (80, 81), only a few studies have investigated Brazilian initiatives that incorporated cultural contexts. These include an extensive intervention considering differences between cities in one specific state (82), and one community-based program addressing traditional components of specific PAs (83). Given the large and very heterogeneous population of the country, there is a need for a broader emphasis on cultural aspects in PA interventions. This is supported by studies showing a high prevalence of overweight and obesity in indigenous peoples, a higher risk of obesity among immigrants with higher levels of acculturation, and a high prevalence of physical inactivity in black individuals (81, 84, 85).

Conversely, in Canada, where only one third of the population reported being of Canadian origin (86), more studies have investigated PA interventions considering cultural backgrounds than in Brazil (87–90). However, there has been a growing movement calling for a more systematic approach in the country to implement culturally safe PA programs, similar to measures already in place in other health promotion initiatives (91). Although such approach focuses initially on indigenous peoples, it could be extended to other ethnicities, since the indigenous population corresponds to around 5% of Canadians (86), and some individuals from different ethnicities report not feeling culturally supported in PA initiatives (74, 92). For instance, Culp (93) highlighted the importance of addressing immigrants' and ethnic minorities' cultural norms in order to reduce PA barriers. Also, Brooks-Cleator and Giles (94) showed that even PA programs aiming at being culturally relevant for indigenous people have some aspects not meeting this purpose. This demonstrates the overall importance of research and promotion of culturally sensitive PA interventions contemplating all ethnicities (76).

Economic

Following PA guidelines requires different investments that are not affordable for various individuals (47, 95). Despite the direct expenditure of money required to participate in some activities, related for example to the purchase of clothes, allocating a certain number of minutes per day or week exclusively to engage in PA is an investment not compatible with the routine of many (63, 96–98). It is not surprising that modifying one's routine to include PA was shown to be impractical due to different reasons, such as tiresome jobs, long commutes, holding more than one job and/or also studying, and competing housework chores and/or family responsibilities (47, 99). Although different barriers to PA

are found in specific regions (95, 100), low income is associated with PA insecurity in high- as well as lower-income countries (47, 101).

Whereas, in some high-income countries the main obstacle for leisure-time PA is lack of time and possibly motivation—mainly for individuals of high socioeconomic status—in Brazil the main barrier is lack of money (98, 99, 102). Despite presenting some advances in economic welfare, Brazil is still one of the world's most unequal countries (59). This is reflected, for example, in higher levels of physical inactivity in low-income groups than in the economic elite, which has more means to afford being physically active (99). To address this and other inequalities related to chronic disease prevention, important actions were taken, mainly between 2004 and 2013, such as the inclusion of PA in the national health promotion agenda (29). However, although more than 40 million people were lifted out of poverty during this period (103), the challenge to reduce economic inequality in PA is substantial. In 2013 about 50 million Brazilians were still poor or extremely poor (104), and in 2019 around 60 million individuals were living in poverty (105).

Currently, economic aspects can be considered the main obstacle to be overcome in order to reduce disparities in Brazil, as evidenced by the significant hardship faced by some sectors, such as health and science (106). This is a result of changes that have been implemented in the national economy since 2016, with direct effects on physical inactivity and its consequences (59, 107). In 2017, for example, after years of stability, there was an increase in hospitalizations due to affective disorders, coinciding with stagnant PA levels in the same year, after increasing between 2006 and 2016 (108). Such economic changes deepened national discrepancies in PA, with less economically advantaged regions presenting a higher burden of mortality related to chronic diseases due to low PA levels (107). Other findings demonstrate the complexity around the difficulties faced by financially disadvantaged Brazilians. For instance, according to Galvim et al. (96), even when free PA programs are offered to economically vulnerable communities, adherence is low. They also report a significant number of dropouts, mainly due to participants finding new employment. Additionally, in contrast to high-income areas, solely building free of cost fitness facilities in low-income neighborhoods appears to be insufficient to favor PA in these communities (109). Therefore, more innovative initiatives are required, allowing for broader and more effective participation (2, 59). In that regard, several investigations have shown how increases in PA levels can lead to considerable savings in the country, thus justifying that investments in policies for the promotion of an active lifestyle must be a priority, even in this adverse context (5, 107, 110, 111).

As a high-income country, economic factors may be regarded as less limiting for PA engagement in Canada. However, longitudinal data starting in the twentieth century has shown that, through the decades, individuals with low income were constantly engaging less in leisure-time PA, and therefore this group should be prioritized in terms of efforts to increase population PA in the country (112). This is corroborated by findings showing that natural and free options for engagement in PA during the winter in Canada, such as an urban trail on a frozen waterway, which could help minimize weight gain during this season, are usually not used by low-income adults, likely due to access limitations using public transit as well as lack of adequate clothing (113). Additionally, Luan et al. (114) showed that even utilitarian PA, such as active transportation and its associated benefits—including decreases in body weight—is less accessible for low-income Canadians, highlighting the fact that some interventions to increase active travel may actually increase inequalities since many initiatives favor financially advantaged individuals in a higher proportion.

Overall, economic disparities in PA are present in different parts of Canada, such as recently reported by physicians and policy experts who serve low-income communities (47). These stakeholders stated that, given the difficulties in meeting national PA guidelines, such recommendations were not relevant for the 3.5 million Canadians living in poverty. Thereby, since there is a clear need for more actions to make PA accessible to members from low-income households in the country, such initiatives could take advantage of the savings that a more active population cause in health care (115). This is corroborated by the fact that in Canada, physical inactivity was found to be the primary unhealthy behavior leading to costs in the health sector (116).

Sociodemographic

Several studies have reported gender inequalities in PA programs, with a higher overall prevalence of inactivity in women than in men, thus signaling the need for gender-neutral interventions and actions that properly contemplate each gender (50, 79, 117, 118). For instance, according to Althoff et al. (52), obesity is more strongly predicted by gender disparities in PA than by physical inactivity alone. Similarly, using data from 142 countries, Mielke et al. (118) showed that small decreases in physical inactivity in women would lead to an overall 10% reduction in this unhealthy behavior, achieving a global target set by the WHO (79), even without changing the prevalence in men. Besides these disparities between men and women, education and marital status were other sociodemographic aspects investigated in different studies, presenting interesting associations with PA. Although most studies found that more highly educated individuals have higher levels of PA (6, 119–122), some investigations found opposite results (117, 123). The association between marital status and PA seems to be more complex, with some studies showing that married individuals are more active (50, 100, 124), some research showing the opposite (121, 122, 125), and some studies indicating no significant difference (117, 119, 126).

Some gender differences are present in PA engagement of the general Canadian population (68), as well as of specific groups, such as indigenous peoples (127) and immigrants (75), with studies consistently reporting that men were more physically active than women. In regards to education, similarly to most international findings, Canadians tend to be more physically active with increasing education levels (119, 122). With regards to marital status, two studies found that married people are more physically active (128, 129) while two studies showed the opposite (119, 130).

In Brazil, sociodemographic inequalities in PA are considerable, particularly with regards to recreational activities.

In terms of gender, men engage more in PA than women. This trend is observed not only in the general population (6) but also in rural communities (131) and among black individuals (81). Brazilians are also more physically active the more years of schooling they have (6), but the findings are mixed with regards to marital status. Whereas, one study showed that married individuals were more active (100), two studies showed the opposite (132, 133), and three others did not find any difference between married and not married individuals (131, 134, 135).

Biological

Many of the first population-based initiatives on PA targeting adults did not contemplate certain groups, such as the elderly, pregnant women, and individuals living with chronic diseases (136, 137). Overall, the first interventions focused on adulthood used to address only young and middle-aged adults (138, 139). However, with the inversion in the age pyramid, the older population has been receiving increasing attention, with several guidelines and other PA initiatives being tailored to older adults (140, 141). The WHO guidelines on PA have a specific chapter for this population (43). Besides recommending a minimum of 150 min of moderate to vigorous PA, the document mentions the importance of light-intensity activities and states that some PA is still of benefit for health in case the recommendations are not fully met by this group.

Additionally, for the first time, the 2020 WHO guidelines have addressed pregnancy and morbidities (42). The document provides specific recommendations for pregnant and postpartum women, and has dedicated sections for both chronic medical conditions and disabilities (43). The first section addresses cancer, hypertension, type 2 diabetes, and HIV, which is also considered a chronic condition given its treatment's advances and availability. And the other section focuses on multiple sclerosis, spinal cord injury, and cognitive function impairments, including Parkinson's disease, stroke, depression, schizophrenia, and intellectual disabilities.

Individuals in these groups need comprehensive and permanent initiatives, to allow a safe and continuous engagement in PA. In this regard, good examples of simple and effective strategies to reduce barriers for these individuals are the Canadian evidence-based pre-participation screening tools Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) and the electronic Physical Activity Readiness Medical Examination (ePARmed-X+), which are currently being translated and adapted to different languages (142, 143). The Brazilian version of the PAR-Q+ has just been validated (144).

Ecological

The effects of different human actions have posed severe risks to the planet, and the consequences can be disastrous (145). Therefore, measures to mitigate these effects and avoid further harm are deeply needed. In that regard, recent evidence has revealed the positive impact that interventions to increase PA levels can have on the natural environment (62). This is aligned with a global action plan on PA, highlighting the contributions of an increase in active recreation, sports, walking, and cycling to a sustainable and prosperous world (145). Reductions in traffic volumes and speeds, along with improving infrastructure to provide safe and welcoming spaces for active transportation, lead to a decrease in traffic accidents and pollution (146). Other incentives to active commuting, such as bike-sharing programs, reduce automobile use and decrease fossil fuel consumption, thereby contributing to the mitigation of climate change (69).

Another influence of PA on planetary health is related to dietary patterns. Given the deleterious effects of packaged highly-processed food on the environment, a reduction in its consumption is greatly warranted (24). In this respect, replacing these options with unprocessed foods, such as fruits and vegetables, contributes to a healthier weight and preserves planetary resources (147). Besides the fact that eating these plant-based alternatives in combination with PA leads to better weight management, physically active individuals usually eat more fruits and vegetables (62).

Additionally, aside from investigations addressing the built environment in the last decades, recent studies have analyzed the relationship between PA and the natural environment in Brazil and Canada. This topic is critical in both countries since they are among the top 10 nations in greenhouse gas emissions (148). A positive aspect in that regard is that Canadians cited their concern with the planet as one of the reasons to engage in PA (149). However, Galway et al. (149) also identified some issues that need to be addressed in the country, such as the underutilization of cycling as a mode of transportation and the barriers related to winter weather. In their review on cycling usage, including studies from Canada and Brazil, Jahanshahi et al. (150) highlight some issues, such as the need for initiatives addressing inequalities in accessing bike-sharing systems. On the other hand, according to Benedini et al. (151), bicycle infrastructure expansions has led underrepresented groups in Brazil to cycle more. As mentioned before, this is likely related to the fact that active transportation is the only commuting option for several individuals in low-income settings, which can be linked to the precarious transit system and spatial segregation in several regions of the country (58).

DISCUSSION

Mirroring the remarkable progress regarding national dietary guidelines and related policy development in Brazil and Canada, emergent evidence indicates that similar approaches are necessary in terms of PA (2, 55, 57). Findings from the last decades have also highlighted the importance of strategies to target sedentary behavior, which is different from physical inactivity (152). Whereas, physical inactivity is usually defined as not meeting international PA recommendations, sedentary behavior relates to the time spent in activities that require very low levels of energy expenditure in prolonged sitting, reclining or lying postures, such as watching TV, using the computer, and playing video games (43, 46, 153). Accordingly, the updated global guidelines have acknowledged the relevance of this theme, and the new document addresses both PA and sedentary behavior in several sections as well as in the title of the document: WHO Guidelines on PA and Sedentary Behavior (43).

The WHO also recognizes that broader and more inclusive initiatives are needed to increase proper access to PA and reduce sedentary time, addressing internal and external barriers, regardless of cultural background, education level, gender, age, socioeconomic conditions, and health status, while promoting sustainable development (145, 154).

Since the health risks associated with too much sedentary time add to the risks related to insufficient PA, specific strategies are required to decrease the engagement in activities such as passive screen-time (155). Strategies applied to break long sitting periods include the use of electric adjustable-height desks that alternate between sitting and standing positions (156), as well as treadmill desks (157) and bike desks (158). However, the aforementioned options are not accessible for many, are not environmentally sustainable, and are not practical and/or appealing enough for several people (62, 159, 160). This situation requires alternative approaches, such as for example, walking meetings, which has been reported to also lead to social benefits (161), as well as some recently proposed solutions with promising results, including intermittent upper body ergometry, an attractive option for those who prefer to remain in the seated position (162), and low-cost standing desks, which are made out of cardboard, are suitable for use in different locations such as at home, and can have an inexpensive and environment-friendly recycling process (163, 164). Despite the challenges involved in implementing public policies that contemplate widespread access to PA promotion and sedentary behavior reduction initiatives, especially in low-income settings, localized comprehensive interventions have been recently implemented in many countries, including Canada and Brazil, and must be scaled up (60, 101, 146, 165).

Although disparities in PA are still present in Canada, different efforts have been made to tackle this situation, including the development and implementation of several provincial and national PA policies (33, 166). An example was the inclusion of accelerometer-measured PA in the Canadian Health Measure Survey (68). PA monitoring systems allow the identification of target groups, the assessment of the population impact of policies, and the detection of changes in PA related to policies, thereby guiding effective actions to increase PA levels (167). Country-wide initiatives to reduce sedentary behavior and increase physical activity levels have addressed physical literacy—knowledge and skills necessary to take responsibility for a long-term engagement in PAs—as well as health literacy—the capacity of an individual to make proper health decisions (168, 169). This is the case of the ParticipAction program, a non-profit organization aimed at making daily physical activity a vital part of Canadians' lives (166), and the federal initiative Let's Get Moving—A Common Vision for Increasing Physical Activity and Reducing Sedentary Living in Canada (33). Both initiatives promote education material and activities to increase health literacy in relation to physical activity, as well as campaigns and products for community mobilization and engagement, such as the case of a recent free mobile phone app (19, 170). Specifically, the Let's Get Moving initiative encourages municipalities, volunteer associations, faith-based groups, and service clubs to take into account the experiences of individuals and their perspectives on what being active means, an approach directly related to health citizenship (33, 171). Another example is the Physical Activity Line (PAL), developed by researchers at the University of British Columbia to provide telehealth support (172). Residents from anywhere in the province were able to receive free evidence-based PA guidance from a qualified exercise professional via the telephone or internet. The PAL led to a major advancement in the promotion of health benefits of PA and served as a role model in the area of telehealth across Canada. The PAL was incorporated into HealthLink BC where it is now a part of the Government of British Columbia's menu of telehealth services (173). Other initiatives include the National Health & Fitness Day, and the Canadian Health & Fitness Institute, aimed at promoting active citizenship (174), as well as the National Indigenous PA Awareness Week, organized by the Indigenous PA and Cultural Circle, with a specific focus on this population (175).

Unlike in Canada, inequalities in Brazil are much more widespread and have lately been increasing (59). Nevertheless, with several cutting-edge researchers on PA promotion, some initiatives in the country have received worldwide recognition (176, 177). Examples include the World PA Day, adopted in the five continents, and the Agita São Paulo program (18). The latter is a permanent PA intervention focused on chronic disease prevention, known for its campaigns targeting sedentary behavior and physical inactivity, and for the participation of numerous and diverse communities, which led the WHO to considered it a model for other LMIC (176). More recent programs in primary health care for PA promotion and sedentary behavior reduction have interesting proposals. The Health Gym Program and the Expanded Family Health Center are national health promotion strategies that make use of public spaces to offer physical activity in different communities (178, 179). These actions are commissioned to health professionals along with the community in each location, and include education activities such as lectures, and different groups of PA sessions, such as walking and other aerobic activities as well as resistance training (179, 180). The Sport and Leisure in the City is a more inclusive program, which includes individuals with disabilities (181). Another example is the Family Health Strategy, which provides multidisciplinary teams to promote counseling for physical activity among other health aspects (182). Although the implementation of these different initiatives has faced substantial challenges, significant positive outcomes have been reported, including savings in the public health system and increases in physical activity levels (183–185).

The first version of the present study recommended the establishment of PA recommendations specifically tailored for the Brazilian population, highlighting that, based on the aforementioned experiences, Brazilian researchers had the required expertise for the development and implementation of effective national guidelines on PA. Exactly five days after the current study has been submitted for publication we learned that the PA Guidelines for the Brazilian Population had just been launched (186). The review process of our manuscript allowed us to acknowledge this publication, which brings significant messages, such as the emphasis on keeping in mind that engaging in any PA, whenever and wherever possible is better than nothing and can lead to health benefits. Additionally, the document

makes clear that engaging in PA does not depend solely on one's decision, and that several factors may act as barriers or facilitators, such as personal, environmental, cultural, financial, and political factors. The guidelines recommend Brazilians to have conversations about these topics, and to approach municipal, state, and federal politicians from different sectors, to enquire about how their communities can be more propitious to PA engagement (186). Thereby, these guidelines explore health citizenship, by addressing entitlements and responsibilities in the political and social developments of public health practices, involving each citizen as well as the government for the successful uptake of the guidelines (171).

This approach is in agreement with the WHO document Global Action Plan on Physical Activity 2018–2030: More Active People for a Healthier World, which states that not recognizing and investing in PA as a priority is a serious mistake, leading to harmful consequences on the health system, economic development, and the environment, as well as quality of life and community well-being (145). Indeed, despite the importance of the aforementioned initiatives, considering Brazil's large population and the current context of significant inequalities, developing national PA guidelines and providing the support of appropriate public policies for its implementation is crucial to prevent setbacks and to enable massive participation (18, 59). Therefore, with the WHO making the recommendation to compare the health outcomes of PA interventions in high and LMIC, it is the perfect timing for Brazil to launch its national guidelines (187).

Additionally, since the new evidence shows that policies to prevent chronic diseases should not be limited to improving individual's health behaviors but also focusing on reducing several inequalities, there is a need for the training of different professionals to put such policies into action (55). According to Lambert et al. (55), this includes transport engineers and urban planners, as well as PA providers in the health sector, such as qualified exercise professionals, who should be well prepared to deliver socially contextualized PA interventions. However, health agents in charge of promoting PA in the Brazilian Unified Health System reported a lack of knowledge and protocols to properly do so (188), which emphasizes the importance of the newly released PA guidelines in the country.

CONCLUSION

Canada followed the pioneer work of Brazil, in launching innovative dietary guidelines. Besides targeting chronic disease prevention, both documents also apply a wholistic approach, addressing economic, biological, sociodemographic, ecological, and cultural dimensions. As well, Brazil and Canada are developing and implementing policies to help support the uptake of their respective dietary guides. Similarly, broader and more inclusive initiatives are needed to allow proper PA access in both countries. Although some PA disparities still persist in Canada, the newest evidence shows that Brazil's population would greatly benefit if the country could follow the Canadian lead in prioritizing investments in PA policies. The launch of the brand new PA Guidelines for the Brazilian Population is a significant step in this respect. In addition to individuals in both countries having a clear guidance to help them to decide what to eat and how, they should also have appropriate guidance to support their entitlement to be physically active and thereby enjoy the numerous advantages linked to this human right.

AUTHOR CONTRIBUTIONS

JS, PO, RER, and DERW conceived and designed the study. JS searched and read the literature, and drafted the manuscript. PO, MBP, RER, WF, SSDB, AG-G, and DERW critically revised and provided insightful edits to the manuscript. All authors reviewed and approved the submitted version.

FUNDING

This work was supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES 2185-15-6 to JS).

REFERENCES

1. WHO. *World Health Statistics 2020: Monitoring Health for the SDGs, Sustainable Development Goals*. World Health Organization (2020).
2. Precoma DB, Oliveira GMMd, Simao AF, Dutra OP, Coelho OR, Izar MCO, et al. Updated cardiovascular prevention guideline of the Brazilian society of cardiology-2019. *Arq Bras Cardiol.* (2019) 113:787–891. doi: 10.5935/abc.20190204
3. Teo KK, Rafiq T. Cardiovascular risk factors and prevention: a perspective from developing countries. *Can J Cardiol.* (2021) 37:733–43. doi: 10.1016/j.cjca.2021.02.009
4. Varin M, Baker M, Palladino E, Lary T. Canadian chronic disease indicators, 2019 - updating the data and taking into account mental health. *Health Promot Chronic Dis Prev Can.* (2019) 39:281. doi: 10.24095/hpcdp.39.10.02
5. Ranasinghe PD, Pokhrel S, Anokye NK. Economics of physical activity in low-income and middle-income countries: a systematic review. *BMJ Open.* (2021) 11:e037784. doi: 10.1136/bmjopen-2020-037784
6. Brasil. *Vigitel Brasil 2019: Vigilância de Fatores de Risco e Proteção Para Doenças Crônicas por Inquérito Telefônico: Estimativas Sobre Frequência e Distribuição Sociodemográfica de Fatores de Risco e Proteção Para Doenças Crônicas nas Capitais dos 26 Estados Brasileiros e no Distrito Federal em 2019*. Brasilia: Ministerio da saude (2020).
7. WHO. *Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013-2020*. Geneva: World Health Organization (2013).
8. WHO. *Assessing National Capacity for the Prevention and Control of Noncommunicable Diseases: Report of the 2019 Global Survey*. Geneva: World Health Organization (2020).
9. IBGE. *Pesquisa Nacional de Saúde 2019*. Instituto Brasileiro de Geografia e Estatística (2020). p. 1–105.
10. Branchard B, Deb-Rinker P, Dubois A, Lapointe P, O'Donnell S, Pelletier L, et al. At a glance: how healthy are Canadians? A brief update. *Health Promot Chronic Dis Prev Can.* (2018) 38:385–7. doi: 10.24095/hpcdp.38.10.05
11. Brasil. *Vigitel Brasil 2010: Vigilância de Fatores de Risco e Proteção Para Doenças Crônicas por Inquérito Telefônico*. Brasilia: Ministerio da Saúde (2011).
12. Statistics Canada. *Table 13-10-0096-11 Heavy Drinking, by Age Group* (2019).

13. Statistics Canada. *Table 13-10-0373-01 Overweight and Obesity Based on Measured Body Mass Index, by Age Group and Sex* (2021).
14. WHO. *Obesity and Overweight: Key Facts*. World Health Organization (2020).
15. Steene-Johannessen J, Anderssen SA, van der Ploeg HP, Hendriksen IJ, Donnelly AE, Brage S, et al. Are self-report measures able to define individuals as physically active or inactive? *Med Sci Sports Exerc.* (2016) 48:235–44. doi: 10.1249/mss.0000000000000760
16. Colley RC, Butler G, Garriguet D, Prince SA, Roberts KC. Comparison of self-reported and accelerometer-measured physical activity in Canadian adults. *Health Rep.* (2018) 29:3–15.
17. Dai Z, Kroeger CM, Lawrence M, Scrinis G, Bero L. Comparison of methodological quality between the 2007 and 2019 Canadian dietary guidelines. *Public Health Nutr.* (2020) 23:2879–85. doi: 10.1017/S1368980020000956
18. Ferrari CKB. Implementation of public health policies for healthy lifestyles promotion: what Brazil should tell us? *Health Promot Perspect.* (2018) 8:243. doi: 10.15171/hpp.2018.33
19. Truelove S, Vanderloo LM, Tucker P, Di Sebastiano KM, Faulkner G. The use of the behaviour change wheel in the development of ParticipACTION's physical activity app. *Prev Med Rep.* (2020) 20:101224. doi: 10.1016/j.pmedr.2020.101224
20. Oliveira M, Santos L. Dietary guidelines for Brazilian population: an analysis from the cultural and social dimensions of food. *Cien Saude Colet.* (2020) 25:2519–28. doi: 10.1590/1413-81232020257.22322018
21. Monteiro CA, Cannon G, Moubarac J-C, Martins APB, Martins CA, Garzillo J, et al. Dietary guidelines to nourish humanity and the planet in the twenty-first century. A blueprint from Brazil. *Public Health Nutr.* (2015) 18:2311–22. doi: 10.1017/S1368980015002165
22. Vandevijvere S, Jaacks LM, Monteiro CA, Moubarac J-C, Girling-Butcher M, Lee AC, et al. Global trends in ultraprocessed food and drink product sales and their association with adult body mass index trajectories. *Obes Rev.* (2019) 20:10–19. doi: 10.1111/obr.12860
23. Bédard A, Lamarche P-O, Grégoire L-M, Trudel-Guy C, Provencher V, Desroches S, et al. Can eating pleasure be a lever for healthy eating? A systematic scoping review of eating pleasure and its links with dietary behaviors and health. *PLoS ONE.* (2020) 15:e0244292. doi: 10.1371/journal.pone.0244292
24. Kirkpatrick SI, Vanderlee L, Dias GM, Hanning RM. *Can Dietary Guidelines Support the Transformation of Food Systems to Foster Human and Planetary Health*. UNSCN News (2019). p. 122–8.
25. Brazilian Ministry of Health. *Dietary Guidelines for the Brazilian Population,* 2nd edition. Brasilia: Ministry of Health (2014).
26. Health Canada. *Canada's Dietary Guidelines For Health Professionals and Policy Makers* (2019).
27. Gardner CD. Preventing weight gain more important than weight loss and more realistic to study in cohorts than in randomized controlled trials. *Am J Clin Nutr.* (2019) 110:544–5. doi: 10.1093/ajcn/nqz101
28. WHO. *A Guide for Population-Based Approaches to Increasing Levels of Physical Activity: Implementation of the WHO Global Strategy on Diet, Physical Activity and Health*. Geneva: World Health Organization (2007).
29. Malta DC, Reis AACd, Jaime PC, Morais Neto OLd, Silva MMAd, Akerman M. Brazil's Unified Health System and the National Health Promotion Policy: prospects, results, progress and challenges in times of crisis. *Ciencia Saude Coletiva.* (2018) 23:1799–809. doi: 10.1590/1413-81232018236.04782018
30. Monteiro CA, Jaime PC. Brazilian Food Guide attacked. Now, overwhelming support for the Guide in Brazil and worldwide. *World Nutr.* (2020) 11:94–9. doi: 10.26596/wn.202011494-99
31. Sebastião E, Schwingel A, Chodzko-Zajko W. Brazilian physical activity guidelines as a strategy for health promotion. *Rev Saude Publica.* (2014) 48:709–12. doi: 10.1590/s0034-8910.2014048005338
32. Craig CL. Evolution and devolution of national physical activity policy in Canada. *J Phys Act Health.* (2011) 8:1044–56. doi: 10.1123/jpah.8.8.1044
33. Public Health Agency of Canada. *A Common Vision for Increasing Physical Activity and Reducing Sedentary Living in Canada: Let's Get Moving*. Ottawa, ON (2018).
34. Warburton DER, Bredin SSD. Health benefits of physical activity: a strengths-based approach. *J Clin Med.* (2019) 8:2044. doi: 10.3390/jcm8122044
35. Bouchard C, Shephard RJ. Physical activity fitness and health: the model and key concepts. In: Bouchard C, Shephard RJ, Stephens T, editors. *Physical Activity Fitness and Health: International Proceedings and Consensus Statement*. Champaign, IL: Human Kinetics (1994). p. 77–88.
36. Gledhill N, Jamnik R. Acknowledging the immense contribution of Dr. Roy Shephard in promoting the health benefits of physical activity. *Health Fitness J Can.* (2011) 4:4–8. doi: 10.14288/hfjc.v4i1.78
37. Giacomantonio NB, Bredin SS, Foulds HJ, Warburton DE. A systematic review of the health benefits of exercise rehabilitation in persons living with atrial fibrillation. *Can J Cardiol.* (2013) 29:483–91. doi: 10.1016/j.cjca.2012.07.003
38. Global Advocacy Council for Physical Activity International Society for Physical Activity and Health. The Toronto charter for physical activity: a global call for action. *J Phys Act Health.* (2010) 7(Suppl. 3):S370–85. doi: 10.1123/jpah.7.s3.s370
39. Warburton DER, Nicol CW, Bredin SSD. Health benefits of physical activity: the evidence. *Can Med Assoc J.* (2006) 174:801–9. doi: 10.1503/cmaj.051351
40. Ashamalla M, Ho A, Magdangal B, Ogunyannwo T, Panesar G, Sandhu S. Promoting the 8th International Society for physical activity and health congress: engaging indigenous ways of understanding. *Health Fitness J Can.* (2021) 14:25–30. doi: 10.14288/hfjc.v14i1.298
41. Bouchard C. Physical activity and health: introduction to the dose-response symposium. *Med Sci Sports Exerc.* (2001) 33:S347–50. doi: 10.1097/00005768-200106001-00002
42. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med.* (2020) 54:1451–62. doi: 10.1136/bjsports-2020-102955
43. WHO. *Guidelines on Physical Activity and Sedentary Behaviour*. Geneva: World Health Organization (2020).
44. Geidl W, Abu-Omar K, Weege M, Messing S, Pfeifer K. German recommendations for physical activity and physical activity promotion in adults with noncommunicable diseases. *Int J Behav Nutr Phys Act.* (2020) 17:12. doi: 10.1186/s12966-020-0919-x
45. Wen CP, Wai JPM, Tsai MK, Yang YC, Cheng TYD, Lee M-C, et al. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. *Lancet.* (2011) 378:1244–53. doi: 10.1016/S0140-6736(11)60749-6
46. Warburton DE, Bredin SS. Reflections on physical activity and health: what should we recommend? *Can J Cardiol.* (2016) 32:495–504. doi: 10.1016/j.cjca.2016.01.024
47. Basky G. Fitness advice ignores realities of life on the margins. *Can Med Assoc J.* (2020) 192:E103–4. doi: 10.1503/cmaj.1095843
48. Manta SW, da Silva KS, Del Duca GF, Malheiros LEA, Knebel MTG, da Silva AF, et al. Physical activity clusters and income inequality in Brazilian adults. *J Phys Act Health.* (2020) 17:859–66. doi: 10.1123/jpah.2019-0355
49. Segar ML, Marques MM, Palmeira AL, Okely AD. Everything counts in sending the right message: science-based messaging implications from the 2020 WHO guidelines on physical activity and sedentary behaviour. *Int J Behav Nutr Phys Act.* (2020) 17:1–5. doi: 10.1186/s12966-020-01048-w
50. Lehne G, Bolte G. Impact of universal interventions on social inequalities in physical activity among older adults: an equity-focused systematic review. *Int J Behav Nutr Phys Act.* (2017) 14:20. doi: 10.1186/s12966-017-0472-4
51. Sfm C, Van Cauwenberg J, Maenhout L, Cardon G, Lambert EV, Van Dyck D. Inequality in physical activity, global trends by income inequality and gender in adults. *Int J Behav Nutr Phys Act.* (2020) 17:142. doi: 10.1186/s12966-020-01039-x
52. Althoff T, Hicks JL, King AC, Delp SL, Leskovec J. Large-scale physical activity data reveal worldwide activity inequality. *Nature.* (2017) 547:336–9. doi: 10.1038/nature23018
53. Warburton DE, Bredin SS. Cardiovascular health benefits of physical activity: time to focus on strengths. *Cahiers Nutr Diét.* (2021) 56:40–50. doi: 10.1016/j.cnd.2020.12.001

54. Knox EC, Webb OJ, Esliger DW, Biddle SJ, Sherar LB. Using threshold messages to promote physical activity: implications for public perceptions of health effects. *Eur J Public Health.* (2014) 24:195–9. doi: 10.1093/eurpub/ckt060
55. Lambert EV, Kolbe-Alexander T, Adlakha D, Oyeyemi A, Anokye NK, Goenka S, et al. Making the case for 'physical activity security': the 2020 WHO guidelines on physical activity and sedentary behaviour from a Global South perspective. *Br J Sports Med.* (2020) 54:1447–8. doi: 10.1136/bjsports-2020-103524
56. Steinmetz-Wood M, Kestens Y. Does the effect of walkable built environments vary by neighborhood socioeconomic status? *Prev Med.* (2015) 81:262–7. doi: 10.1016/j.ypmed.2015.09.008
57. Battista GA, Manaugh K. Examining social inclusion among pedestrian plans in Canada. *Can Geogr.* (2019) 63:663–75. doi: 10.1111/cag.12549
58. Sá THd, Pereira RHM, Duran AC, Monteiro CA. Socioeconomic and regional differences in active transportation in Brazil. *Rev Saude Publica.* (2016) 50:37. doi: 10.1590/S1518-8787.2016050006126
59. Crochemore-Silva I, Knuth AG, Mielke GI, Loch MR. Promotion of physical activity and public policies to tackle inequalities: considerarions based on the Inverse Care Law and Inverse Equity Hypothesis. *Cad Saude Publica.* (2020) 36:e00155119. doi: 10.1590/0102-311X00155119
60. Nykiforuk C, Kayla A, Sara B, Wayne C, Tracey G, Jason G, et al. Promotion of physical activity in rural, remote and northern settings: a Canadian call to action. *Health Promot Chronic Dis Prev Can.* (2018) 38:419. doi: 10.24095/hpcdp.38.11.03
61. Loprinzi PD, Walker JF. Association of longitudinal changes of physical activity on smoking cessation among young daily smokers. *J Phys Act Health.* (2016) 13:1–5. doi: 10.1123/jpah.2014-0605
62. Nigg C, Nigg CR. It's more than climate change and active transport-physical activity's role in sustainable behavior. *Transl Behav Med.* (2021) 11:945–53. doi: 10.1093/tbm/ibaa129
63. Dwyer MJ, Pasini M, De Dominicis S, Righi E. Physical activity: benefits and challenges during the COVID-19 pandemic. *Scand J Med Sci Sports.* (2020) 30:1291. doi: 10.1111/sms.13710
64. Stamatakis E, Bull FC. Putting physical activity in the 'must-do' list of the global agenda. *Br J Sports Med.* (2020) 54:1445–6. doi: 10.1136/bjsports-2020-103509
65. Sallis JF, Saelens BE. Assessment of physical activity by self-report: status, limitations, and future directions. *Res Q Exerc Sport.* (2000) 71:1–14. doi: 10.1080/02701367.2000.11082780
66. Thompson D, Peacock O, Western M, Batterham AM. Multidimensional physical activity: an opportunity not a problem. *Exerc Sport Sci Rev.* (2015) 43:67. doi: 10.1249/JES.0000000000000039
67. Moreno-Murcia JA, Belando N, Huéscar E, Torres MD. Social support, physical exercise and life satisfaction in women. *Rev Latinoamericana Psicol.* (2017) 49:194–202. doi: 10.1016/j.rlp.2016.08.002
68. Clarke J, Colley R, Janssen I, Tremblay MS. Accelerometer-measured moderate-to-vigorous physical activity of Canadian adults, 2007 to 2017. *Health Rep.* (2019) 30:3–10. doi: 10.25318/82-003-x201900800001-eng
69. Scatigna M, D'Eugenio S, Cesarini V, Coppola L, Lemma P, Fabiani L, et al. Physical activity as a key issue for promoting human health on a local and global scale: evidences and perspectives. *Ann Ig.* (2019) 31:595–613. doi: 10.7416/ai.2019.2320
70. Ball K, Carver A, Downing K, Jackson M, O'Rourke K. Addressing the social determinants of inequities in physical activity and sedentary behaviours. *Health Promot Int.* (2015) 30(Suppl. 2):ii18–9. doi: 10.1093/heapro/dav022
71. Swinburn B, Egger G, Raza F. Dissecting obesogenic environments: the development and application of a framework for identifying and prioritizing environmental interventions for obesity. *Prev Med.* (1999) 29(Pt. 1):563–70. doi: 10.1006/pmed.1999.0585
72. Cardinal BJ, Tuominen KJ, Rintala P. Cross-cultural comparison of American and Finnish college students' exercise behavior using transtheoretical model constructs. *Res Q Exerc Sport.* (2004) 75:92–101. doi: 10.1080/02701367.2004.10609137
73. El Masri A, Kolt GS, George ES. Physical activity interventions among culturally and linguistically diverse populations: a systematic review. *Ethn Health.* (2019) 26:1–21. doi: 10.1080/13557858.2019.1658183
74. Mahmood B, Bhatti JA, Leon A, Gotay C. Leisure time physical activity levels in immigrants by ethnicity and time since immigration to Canada: findings from the 2011–2012 Canadian Community Health Survey. *J Immigr Minor Health.* (2019) 21:801–10. doi: 10.1007/s10903-018-0789-3
75. Tharmaratnam T, Iskandar MA, Doherty S, D'Urzo KA, Kopalakrishnan S, Tabobondung TC, et al. The role of physical activity prescription in cardiovascular disease prevention amongst South Asian Canadians. *Front Cardiovasc Med.* (2018) 5:165. doi: 10.3389/fcvm.2018.00165
76. Williamson TM, Moran C, McLennan A, Seidel S, Ma PP, Koerner M-L, et al. Promoting adherence to physical activity among individuals with cardiovascular disease using behavioral counseling: a theory and research-based primer for health care professionals. *Prog Cardiovasc Dis.* (2021) 64:41–54. doi: 10.1016/j.pcad.2020.12.007
77. Mikell M, Snethen J, Kelber ST. Exploring factors associated with physical activity in Latino immigrants. *West J Nurs Res.* (2020) 42:680–9. doi: 10.1177/0193945919897547
78. Perrin AJ, Caren N, Skinner AC, Odulana A, Perrin EM. The unbuilt environment: culture moderates the built environment for physical activity. *BMC Public Health.* (2016) 16:1–8. doi: 10.1186/s12889-016-3866-3
79. Guthold R, Stevens GA, Riley LM, Bull FC. Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1· 9 million participants. *Lancet Glob Health.* (2018) 6:e1077–86. doi: 10.1016/S2214-109X(18)30357-7
80. Chor D, Pereira A, Pacheco AG, Santos RV, Fonseca MJM, Schmidt MI, et al. Context-dependence of race self-classification: results from a highly mixed and unequal middle-income country. *PLoS ONE.* (2019) 14:e0216653. doi: 10.1371/journal.pone.0216653
81. Pitanga FJG, Lessa I, Barbosa PJB, Barbosa SJO, Costa MC, da Silva Lopes A. Factors associated with leisure time physical inactivity in black individuals: hierarchical model. *PeerJ.* (2014) 2:e577. doi: 10.7717/peerj.577
82. Matsudo S, Matsudo V, Araujo TL, Andrade DR, Andrade EL, Oliveira LCd, et al. The Agita São Paulo Program as a model for using physical activity to promote health. *Rev Panam Salud Publica.* (2003) 14:265–72. doi: 10.1590/s1020-49892003000900007
83. Paez DC, Reis RS, Parra DC, Hoehner CM, Sarmiento OL, Barros M, et al. Bridging the gap between research and practice: an assessment of external validity of community-based physical activity programs in Bogotá, Colombia, and Recife, Brazil. *Transl Behav Med.* (2015) 5:1–11. doi: 10.1007/s13142-014-0275-y
84. Baldoni NR, Aquino JA, Alves GCS, Sartorelli DS, Franco LJ, Madeira SP, et al. Prevalence of overweight and obesity in the adult indigenous population in Brazil: a systematic review with meta-analysis. *Diabetes Metab Syndr.* (2019) 13:1705–15. doi: 10.1016/j.dsx.2019.03.024
85. Schwingel A, Nakata Y, Ito LS, Chodzko-Zajko WJ, Erb CT, Shigematsu R, et al. Central obesity and health-related factors among middle-aged men: a comparison among native Japanese and Japanese-Brazilians residing in Brazil and Japan. *J Physiol Anthropol.* (2007) 26:339–47. doi: 10.2114/jpa2.26.339
86. Statistics Canada. *Immigration and Ethnocultural Diversity Highlight Tables* (2016).
87. Forde SD, Lee DS, Mills C, Frisby W. Moving towards social inclusion: manager and staff perspectives on an award winning community sport and recreation program for immigrants. *Sport Manag Rev.* (2015) 18:126–38. doi: 10.1016/j.smr.2014.02.002
88. Mead EL, Gittelsohn J, Roache C, Corriveau A, Sharma S. A community-based, environmental chronic disease prevention intervention to improve healthy eating psychosocial factors and behaviors in indigenous populations in the Canadian Arctic. *Health Educ Behav.* (2013) 40:592–602. doi: 10.1177/1090198112467793
89. Sharma S. Assessing diet and lifestyle in the Canadian Arctic Inuit and Inuvialuit to inform a nutrition and physical activity intervention programme. *J Hum Nutr Diet.* (2010) 23:5–17. doi: 10.1111/j.1365-277X.2010.01093.x
90. Teufel-Shone NI, Fitzgerald C, Teufel-Shone L, Gamber M. Systematic review of physical activity interventions implemented with American Indian and Alaska Native populations in the United States and Canada. *Am J Health Promot.* (2009) 23:S8–32. doi: 10.4278/ajhp.07053151

91. Giles AR, Darroch FE. The need for culturally safe physical activity promotion and programs. *Can J Public Health.* (2014) 105:e317–9. doi: 10.17269/cjph.105.4439
92. Mansfield ED, Ducharme N, Koski KG. Individual, social and environmental factors influencing physical activity levels and behaviours of multiethnic socio-economically disadvantaged urban mothers in Canada: a mixed methods approach. *Int J Behav Nutr Phys Act.* (2012) 9:1–15. doi: 10.1186/1479-5868-9-42
93. Culp B. Eliminating barriers to physical activity: using cultural negotiation and competence. *Strategies.* (2013) 26:35–40. doi: 10.1080/08924562.2013.784135
94. Brooks-Cleator LA, Giles AR. Culturally relevant physical activity through Elders in Motion: physical activity programming for older Aboriginal adults in the Northwest Territories, Canada. *J Cross Cult Gerontol.* (2016) 31:449–70. doi: 10.1007/s10823-016-9307-z
95. Sanz-Remacha M, García-González L, Sevil Serrano J, Generelo Lanaspa E, Aibar Solana A. Barriers to physical activity in disadvantaged population: a qualitative comparison between Roma and Non-Roma women. *Res Q Exerc Sport.* (2019) 90:567–77. doi: 10.1080/02701367.2019.1635245
96. Galvim AL, Oliveira IM, Martins TV, Vieira LM, Cerri NC, de Castro Cezar NO, et al. Adherence, adhesion, and dropout reasons of a physical activity program in a high social vulnerability context. *J Phys Act Health.* (2019) 16:149–56. doi: 10.1123/jpah.2017-0606
97. Hafner M, Yerushalmi E, Stepanek M, Phillips W, Pollard J, Deshpande A, et al. Estimating the global economic benefits of physically active populations over 30 years (2020–2050). *Br J Sports Med.* (2020) 54:1482–7. doi: 10.1136/bjsports-2020-102590
98. Venn D, Strazdins L. Your money or your time? How both types of scarcity matter to physical activity and healthy eating. *Soc Sci Med.* (2017) 172:98–106. doi: 10.1016/j.socscimed.2016.10.023
99. Silva KS, Del Duca GF, Garcia LMT, da Silva JA, Bertuol C, de Oliveira ESA, et al. Barriers associated with frequency of leisure-time physical activity among Brazilian adults of different income strata. *Scand J Med Sci Sports.* (2016) 26:206–13. doi: 10.1111/sms.12419
100. Peixoto SV, Mambrini JVdM, Firmo JOA, Loyola Filho AId, Souza Junior PRBd, Andrade FBd, et al. Physical activity practice among older adults: results of the ELSI-Brazil. *Rev Saude Publica.* (2018) 52(Suppl. 2):5s. doi: 10.11606/S1518-8787.2018052000605
101. Lima AM, Werneck AO, Cyrino E, Farinatti P. Supervised training in primary care units but not self-directed physical activity lowered cardiovascular risk in Brazilian low-income patients: a controlled trial. *BMC Public Health.* (2019) 19:1738. doi: 10.1186/s12889-019-7716-y
102. Moreno-Llamas A, García-Mayor J, De la Cruz-Sánchez E. Physical activity barriers according to social stratification in Europe. *Int J Public Health.* (2020) 65:1477–84. doi: 10.1007/s00038-020-01488-y
103. Tepperman J. Brazil's antipoverty breakthrough: the surprising success of Bolsa Familia. *Foreign Aff.* (2016) 95:34.
104. IBGE. *Síntese de Indicadores Sociais: Uma Análise das Condições de Vida da População Brasileira*. Rio de Janeiro: Instituto Brasileiro de Geografia e Estatística (2016).
105. IBGE. *Síntese de Indicadores Sociais: Uma Análise das Condições de Vida da População Brasileira*. Rio de Janeiro: Instituto Brasileiro de Geografia e Estatística (2020).
106. Hallal PC. SOS Brazil: science under attack. *Lancet.* (2021) 397:373–4. doi: 10.1016/S0140-6736(21)00141-0
107. Silva DAS. Physical inactivity as a risk factor to mortality by ischemic heart disease during economic and political crisis in Brazil. *PeerJ.* (2020) 8:e10192. doi: 10.7717/peerj.10192
108. Werneck AO, Fernandes RA, Silva DR. Economic crises, behavioral changes and hospitalization due to affective disorders in Brazil between 2003 and 2017: a nationwide cross-sectional study. *São Paulo Med J.* (2020) 138:167–70. doi: 10.1590/1516-3180.2019.0127.R2.19112019
109. Alberico CO, Hipp JA, Reis RS. Association between neighborhood income, patterns of use, and physical activity levels in fitness zones of Curitiba, Brazil. *J Phys Act Health.* (2019) 16:447–54. doi: 10.1123/jpah.2018-0234
110. Araujo MYC, Sarti FM, Fernandes RA, Monteiro HL, Turi BC, Anokye N, et al. Association between costs related to productivity loss and modified risk factors among users of the Brazilian National Health System. *J Occup Environ Med.* (2017) 59:313–9. doi: 10.1097/JOM.0000000000000951
111. Bueno DR, Marucci MdFN, Gobbo LA, de Almeida-Roediger M, de Oliveira Duarte YA, Lebrão ML. Expenditures of medicine use in hypertensive/diabetic elderly and physical activity and engagement in walking: cross secctional analysis of SABE Survey. *BMC Geriatr.* (2017) 17:1–8. doi: 10.1186/s12877-017-0437-0
112. Barnett TA, Gauvin L, Craig CL, Katzmarzyk PT. Distinct trajectories of leisure time physical activity and predictors of trajectory class membership: a 22 year cohort study. *Int J Behav Nutr Phys Act.* (2008) 5:1–8. doi: 10.1186/1479-5868-5-57
113. McGavock J, Brunton N, Klaprat N, Swanson A, Pancoe D, Manley E, et al. Walking on water—a natural experiment of a population health intervention to promote physical activity after the winter holidays. *Int J Environ Res Public Health.* (2019) 16:3627. doi: 10.3390/ijerph16193627
114. Luan H, Ramsay D, Fuller D. Household income, active travel, and their interacting impact on body mass index in a sample of urban Canadians: a Bayesian spatial analysis. *Int J Health Geogr.* (2019) 18:1–10. doi: 10.1186/s12942-019-0168-x
115. Mondor L, Watson T, Kornas K, Bornbaum C, Wodchis WP, Rosella LC. Direct and indirect pathways between low income status and becoming a high-cost health care user in Ontario, Canada: a mediation analysis of health risk behaviors. *Ann Epidemiol.* (2020) 51:28–34. doi: 10.1016/j.annepidem.2020.07.006
116. Alberga A, Holder L, Kornas K, Bornbaum C, Rosella L. Effects of behavioural risk factors on high-cost users of healthcare: a population-based study. *Can J Public Health.* (2018) 109:441–50. doi: 10.17269/s41997-018-0127-5
117. Lee Y, Park S. Understanding of physical activity in social ecological perspective: application of multilevel model. *Front Psychol.* (2021) 12:622929. doi: 10.3389/fpsyg.2021.622929
118. Mielke GI, da Silva ICM, Kolbe-Alexander TL, Brown WJ. Shifting the physical inactivity curve worldwide by closing the gender gap. *Sports Med.* (2018) 48:481–9. doi: 10.1007/s40279-017-0754-7
119. Dai S, Wang F, Morrison H. Predictors of decreased physical activity level over time among adults: a longitudinal study. *Am J Prev Med.* (2014) 47:123–30. doi: 10.1016/j.amepre.2014.04.003
120. Dohrn M, Gardiner PA, Winkler E, Welmer A-K. Device-measured sedentary behavior and physical activity in older adults differ by demographic and health-related factors. *Eur Rev Aging Phys Act.* (2020) 17:1–11. doi: 10.1186/s11556-020-00241-x
121. Eime RM, Harvey JT, Charity MJ, Nelson R. Demographic characteristics and type/frequency of physical activity participation in a large sample of 21,603 Australian people. *BMC Public Health.* (2018) 18:1–10. doi: 10.1186/s12889-018-5608-1
122. Mäkinen TE, Sippola R, Borodulin K, Rahkonen O, Kunst A, Klumbiene J, et al. Explaining educational differences in leisure-time physical activity in Europe: the contribution of work-related factors. *Scand J Med Sci Sports.* (2012) 22:439–47. doi: 10.1111/j.1600-0838.2010.01234.x
123. Fan M, Su M, Tan Y, Liu Q, Ren Y, Li L, et al. Gender, age, and education level modify the association between body mass index and physical activity: a cross-sectional study in Hangzhou, China. *PLoS ONE.* (2015) 10:e0125534. doi: 10.1371/journal.pone.0125534 eCollection 2015
124. Sánchez Castillo S, Smith L, Díaz Suárez A, López Sánchez GF. Physical activity behavior in people with asthma and COPD overlap residing in Spain: a cross-sectional analysis. *J Asthma.* (2021). doi: 10.1080/02770903.2021.1888977. [Epub ahead of print].
125. Sánchez Castillo S, Smith L, Díaz Suárez A, López Sánchez GF. Levels of physical activity in Spanish asthmatics: a cross-sectional study. *Medicina.* (2020) 56:643. doi: 10.3390/medicina56120643
126. Sánchez Castillo S, Smith L, Suárez AD, Sánchez GFL. Physical activity behaviour in people with COPD Residing in Spain: a cross-sectional analysis. *Lung.* (2019) 197:769–75. doi: 10.1007/s00408-019-00287-4
127. Akande VO, Ruiter RAC, Kremers SPJ. Environmental and motivational determinants of physical activity among Canadian Inuit in the Arctic. *Int J Environ Res Public Health.* (2019) 16:2437. doi: 10.3390/ijerph16132437
128. Chad KE, Reeder BA, Harrison EL, Ashworth NL, Sheppard SM, Schultz SL, et al. Profile of physical activity levels in

community-dwelling older adults. *Med Sci Sports Exerc.* (2005) 37:1774–84. doi: 10.1249/01.mss.0000181303.51937.9c
129. Lipscombe C, Smith KJ, Gariépy G, Schmitz N. Gender differences in the relationship between anxiety symptoms and physical inactivity in a community-based sample of adults with type 2 diabetes. *Can J Diabetes.* (2014) 38:444–50. doi: 10.1016/j.jcjd.2013.12.002
130. Aparicio-Ting FE, Friedenreich CM, Kopciuk KA, Plotnikoff RC, Bryant HE. Intrapersonal and social environment correlates of leisure-time physical activity for cancer prevention: a cross-sectional study among Canadian adults. *J Phys Act Health.* (2014) 11:790–800. doi: 10.1123/jpah.2012-0110
131. Bicalho PG, Hallal PC, Gazzinelli A, Knuth AG, Velásquez-Meléndez G. Adult physical activity levels and associated factors in rural communities of Minas Gerais State, Brazil. *Rev Saude Publica.* (2010) 44:884–93. doi: 10.1590/s0034-89102010005000023
132. Dumith SC, Gigante DP, Domingues MR. Stages of change for physical activity in adults from Southern Brazil: a population-based survey. *Int J Behav Nutr Phys Act.* (2007) 4:1–10. doi: 10.1186/1479-5868-4-25
133. Marcellino C, Henn RL, Olinto MTA, Bressan AW, Paniz VMV, Pattussi MP. Physical inactivity and associated factors among women from a municipality in southern Brazil. *J Phys Act Health.* (2014) 11:777–83. doi: 10.1123/jpah.2011-0448
134. Boclin KLS, Faerstein E, Leon ACMP. Neighborhood contextual characteristics and leisure-time physical activity: Pró-Saúde study. *Rev Saude Publica.* (2014) 48:249–57. doi: 10.1590/s0034-8910.2014048004935
135. Vagetti GC, Barbosa Filho VC, Moreira NB, de Oliveira V, Mazzardo O, de Campos W. The prevalence and correlates of meeting the current physical activity for health guidelines in older people: a cross-sectional study in Brazilian women. *Arch Gerontol Geriatr.* (2013) 56:492–500. doi: 10.1016/j.archger.2012.12.003
136. Warburton DE, Gledhill N, Jamnik VK, Bredin SS, McKenzie DC, Stone J, et al. Evidence-based risk assessment and recommendations for physical activity clearance: consensus Document 2011. *Appl Physiol Nutr Metab.* (2011) 36:S266–98. doi: 10.1139/h11-062
137. WHO. *Global Recommendations on Physical Activity for Health*. Geneva: World Health Organization (2010).
138. Shephard RJ. For debate: medical clearance: a possible inhibitor of physical activity in the elderly? Trends in Canadian thought. *Sci Sports.* (2000) 15:207–11.
139. Myers AM, Gonda G. Research on physical activity in the elderly: practical implications for program planning. *Can J Aging.* (1986) 5:175–88.
140. Boulton ER, Horne M, Todd C. Involving older adults in developing physical activity interventions to promote engagement: a literature review. *J Popul Ageing.* (2020) 13:325–45. doi: 10.1007/s12062-019-09247-5
141. Son JS, Nimrod G, West ST, Janke MC, Liechty T, Naar JJ. Promoting older adults' physical activity and social well-being during COVID-19. *Leis Sci.* (2020) 43:287–94. doi: 10.1080/01490400.2020.1774015
142. Schwartz J, Mas-Alòs S, Takito MY, Martinez J, Cueto MEÁ, Mibelli MSR, et al. Cross-cultural translation, adaptation, and reliability of the Spanish version of the Physical Activity Readiness Questionnaire for Everyone (PAR-Q+). *Health Fitness J Can.* (2019) 12:3–14. doi: 10.14288/hfjc.v12i4.291
143. Warburton DE, Jamnik VK, Bredin SS, Gledhill N. The physical activity readiness questionnaire for everyone (PAR-Q+) and electronic physical activity readiness medical examination (ePARmed-X+). *Health Fitness J Can.* (2011) 4:3–17. doi: 10.14288/hfjc.v4i2.103
144. Schwartz J, Oh P, Takito MY, Saunders B, Dolan E, Franchini E, et al. Translation, cultural adaptation, and reproducibility of the physical activity readiness questionnaire for everyone (PAR-Q+): the Brazilian Portuguese version. *Front Cardiovasc Med.* (2021) 8:e712696. doi: 10.3389/fcvm.2021.712696
145. WHO. *Global Action Plan on Physical Activity 2018-2030: More Active People for a Healthier World*. Geneva: World Health Organization (2018).
146. Oliveira F, Nery D, Costa DG, Silva I, Lima L. A survey of technologies and recent developments for sustainable smart cycling. *Sustainability.* (2021) 13:3422. doi: 10.3390/su13063422
147. Willett W, Rockström J, Loken B, Springmann M, Lang T, Vermeulen S, et al. Food in the anthropocene: the EAT-Lancet Commission on healthy diets from sustainable food systems. *Lancet.* (2019) 393:447–92. doi: 10.1016/s0140-6736(18)31788-4
148. Bernard P, Chevance G, Kingsbury C, Baillot A, Romain A-J, Molinier V, et al. Climate change, physical activity and sport: a systematic review. *Sports Med.* (2021) 51:1041–59. doi: 10.1007/s40279-021-01439-4
149. Galway LP, Deck E, Carastathis J, Sanderson R. Exploring social-ecological influences on commuter cycling in a midsize northern city: a qualitative study in Thunder Bay, Canada. *J Transp Geogr.* (2021) 92:102995. doi: 10.1016/j.jtrangeo.2021.102995
150. Jahanshahi D, Chowdhury S, Costello SB, van Wee B. Review of key findings and future directions for assessing equitable cycling usage. *Transp Res Rec.* (2021) 2675:453–64. doi: 10.1177/0361198121995193
151. Benedini DJ, Lavieri PS, Strambi O. Understanding the use of private and shared bicycles in large emerging cities: the case of São Paulo, Brazil. *Case Stud Transp Policy.* (2020) 8:564–75. doi: 10.1016/j.cstp.2019.11.009
152. Memon AR, Stanton R, To Q, Schoeppe S, Urooj A, Alley S, et al. Sedentary behaviour research in adults: a scoping review of systematic reviews and meta-analyses. *J Sports Sci.* (2021). doi: 10.1080/02640414.2021.1928382. [Epub ahead of print].
153. Owen N, Healy GN, Matthews CE, Dunstan DW. Too much sitting: the population-health science of sedentary behavior. *Exerc Sport Sci Rev.* (2010) 38:105. doi: 10.1097/JES.0b013e3181e373a2
154. Hämäläinen R-M, Breda J, da Silva Gomes F, Gongal G, Khan W, Mendes R, et al. New global physical activity guidelines for a more active and healthier world: the WHO Regional Offices perspective. *Br J Sports Med.* (2020) 54:1449–50. doi: 10.1136/bjsports-2020-103531
155. LeBlanc AG, Gunnell KE, Prince SA, Saunders TJ, Barnes JD, Chaput J-P. The ubiquity of the screen: an overview of the risks and benefits of screen time in our modern world. *Transl J Am Coll Sports Med.* (2017) 2:39. doi: 10.1249/TJX.0000000000000039
156. Pierce J, Legg S, Godfrey JR, Kawabata E. The effects of introducing electric adjustable height desks in an office setting on workplace physical activity levels: a randomised control field trial. *Work.* (2019) 62:139–50. doi: 10.3233/wor-182849
157. Larson MJ, LeCheminant JD, Hill K, Carbine K, Masterson T, Christenson E. Cognitive and typing outcomes measured simultaneously with slow treadmill walking or sitting: implications for treadmill desks. *PLoS ONE.* (2015) 10:e0121309. doi: 10.1371/journal.pone.0121309
158. Torbeyns T, de Geus B, Bailey S, Decroix L, Meeusen R. The potential of bike desks to reduce sedentary time in the office: a mixed-method study. *Public Health.* (2017) 144:16–22. doi: 10.1016/j.puhe.2016.11.006
159. Hadgraft NT, Brakenridge CL, LaMontagne AD, Fjeldsoe BS, Lynch BM, Dunstan DW, et al. Feasibility and acceptability of reducing workplace sitting time: a qualitative study with Australian office workers. *BMC Public Health.* (2016) 16:933. doi: 10.1186/s12889-016-3611-y
160. Rovniak LS, Sciamanna CN, George DR, Bopp M, Kong L, Ding D. Interest in using workplace energy expenditure devices among primary care patients. *J Prim Care Community Health.* (2016) 7:96–101. doi: 10.1177/2150131915624892
161. Niven A, Hu D. Office workers' beliefs about reducing sitting time at work: a belief elicitation study. *Health Psychol Behav Med.* (2018) 6:15–29. doi: 10.1080/21642850.2018.1428103
162. McCarthy M, Edwardson CL, Davies MJ, Henson J, Rowlands A, King JA, et al. Breaking up sedentary time with seated upper body activity can regulate metabolic health in obese high-risk adults: a randomized crossover trial. *Diabetes Obes Metab.* (2017) 19:1732–9. doi: 10.1111/dom.13016
163. Lin L, Yang J, Ni S, Wang X, Bian H, Dai H. Resource utilization and ionization modification of waste starch from the recycling process of old corrugated cardboard paper. *J Environ Manage.* (2020) 271:111031. doi: 10.1016/j.jenvman.2020.111031
164. Rudecki J, Weatherson K, Faulkner G. Evaluating the acceptability of low-cost standing desks in the home environment: an exploratory study. *J Phys Act Health.* (2019) 16:375–9. doi: 10.1123/jpah.2018-0575
165. Sones M, Fuller D, Kestens Y, Winters M. If we build it, who will come? The case for attention to equity in healthy community design. *Br J Sports Med.* (2019) 53:467–8. doi: 10.1136/bjsports-2018-099667
166. Macridis S, Cameron C, Chaput JP, Chulak-Bozzer T, Clark P, Davenport MH, et al. Results from the 2019 participaction report card on physical activity for adults. *J Phys Act Health.* (2020) 17:995–1002. doi: 10.1123/jpah.2019-0646

167. Craig CL, Cameron CA, Bauman A. Utility of surveillance research to inform physical activity policy: an exemplar from Canada. *J Phys Act Health.* (2017) 14:229–39. doi: 10.1123/jpah.2015-0698
168. Corbin CB. Implications of physical literacy for research and practice: a commentary. *Res Q Exerc Sport.* (2016) 87:14–27. doi: 10.1080/02701367.2016.1124722
169. Jones G, Stathokostas L. Letter to the editor: can older adults "walk" their way to successful aging? The case for physical activity literacy for an aging population. *J Aging Phys Act.* (2016) 24:341. doi: 10.1123/japa.2016-0005
170. Cornish K, Fox G, Fyfe T, Koopmans E, Pousette A, Pelletier CA. Understanding physical literacy in the context of health: a rapid scoping review. *BMC Public Health.* (2020) 20:1569. doi: 10.1186/s12889-020-09583-8
171. Porter D. *Health Citizenship: Essays in Social Medicine and Biomedical Politics*. San Francisco, CA: University of California Medical Humanities Press (2011).
172. Bredin SSD, Warburton DER. Physical activity line: effective knowledge translation of evidence-based best practice in the real-world setting. *Can Fam Phys.* (2013) 59:967–8.
173. Clark RE, Milligan J, Ashe MC, Faulkner G, Canfield C, Funnell L, et al. A patient-oriented approach to the development of a primary care physical activity screen for embedding into electronic medical records. *Appl Physiol Nutr Metab.* (2021) 46:589–96. doi: 10.1139/apnm-2020-0356
174. Warburton D, Bredin S. The legacy of cheryl and jack taunton in sports and exercise medicine: pioneers, mentors, and friends. *Health Fitness J Can.* (2020) 13:3–7. doi: 10.14288/hfjc.v13i4.314
175. Miles RM, Yang TY, Hanna SB. The 7th annual national indigenous physical activity & wellness conference proceedings. *Health Fitness J Can.* (2019) 12:3–12. doi: 10.14288/hfjc.v12i2.288
176. Fioravanti CH. Brazilian fitness programme registers health benefits. *Lancet.* (2012) 380:206. doi: 10.1016/s0140-6736(12)61201-x
177. Lane R. Pedro Hallal: putting physical activity at the heart of better health. *Lancet.* (2016) 388:1271. doi: 10.1016/S0140-6736(16)31148-5
178. Florindo AA, Nakamura PM, Farias JCd, Siqueira FV, Reis RS, Cruz DKA, et al. Promotion of physical activity, healthy eating and family health in municipalities with health gym. *Rev Bras Educ Fís Esporte.* (2016) 30:913–24. doi: 10.1590/1807-55092016000400913
179. Seus T, Freitas M, Siqueira F. Publications scenario about Family Health Support Centers. *Rev Bras Ativ Fis Saúde.* (2018) 22:429–38. doi: 10.12820/rbafs.v.22n5p429-438
180. Malta DC, Oliveira TP, Santos MA, Andrade SS, Silva MM. Progress with the strategic action plan for tackling chronic non-communicable diseases in Brazil, 2011-2015. *Epidemiol Serv Saude.* (2016) 25:373–90. doi: 10.5123/s1679-49742016000200016
181. Kirakosyan L. Sport for all and social inclusion of individuals with impairments: a case study from Brazil. *Societies.* (2019) 9:44. doi: 10.3390/soc9020044
182. Souza Neto JM, Florindo AA, Costa FFD. Associated factors with physical activity counseling among Brazilian family health strategy workers. *Cien Saude Colet.* (2021) 26:369–78. doi: 10.1590/1413-81232020261.10082019
183. Paiva FTd, Mazo GZ, Sandreschi PF, Petreça DR, Rech CR. Barriers to implementation of academia da saúde program in Santa Catarina. *J Phys Educ.* (2019) 30:e3406. doi: 10.4025/jphyseduc.v30i1.3046
184. Tristão FI, Gomes IM. Brazilian's Health Policy and its misalignment with international guidelines for Health Promotion. *Eur J Public Health.* (2020) 30(Suppl. 5):ckaa166.535. doi: 10.1093/eurpub/ckaa166.535
185. Starepravo FA, Souza Jd, Bernabe AP, Marchi Júnior W. Program sport and leisure in the city: where is the intersection between political/bureaucratic and scientific/academic? *Movimento.* (2018) 24:23–34. doi: 10.22456/1982-8918.63125
186. Brasil. *Guia de Atividade Física Para a População Brasileira*. Brasilia: Ministério da Saúde, Secretaria de Atenção Primária à Saúde, Departamento de Promoção da Saúde (2021).
187. DiPietro L, Al-Ansari SS, Biddle SJH, Borodulin K, Bull FC, Buman MP, et al. Advancing the global physical activity agenda: recommendations for future research by the 2020 WHO physical activity and sedentary behavior guidelines development group. *Int J Behav Nutr Phys Act.* (2020) 17:1–11. doi: 10.1186/s12966-020-01042-2
188. Becker L, Gonçalves P, Reis R. Primary health care programs for physical activity promotion in the Brazil: a systematic review. *Rev Bras Ativ Fis Saúde.* (2016) 21:110–22. doi: 10.12820/rbafs.v.21n2p110-122

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Cardiovascular Medicine

REVIEW
published: 03 September 2021
doi: 10.3389/fcvm.2021.734278

Optimizing Outcomes in Cardiac Rehabilitation: The Importance of Exercise Intensity

Jenna L. Taylor, Amanda R. Bonikowske and Thomas P. Olson*

Division of Preventative Cardiology, Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, United States

Exercise based cardiac rehabilitation (CR) is recognized internationally as a class 1 clinical practice recommendation for patients with select cardiovascular diseases and heart failure with reduced ejection fraction. Over the past decade, several meta-analyses have generated debate regarding the effectiveness of exercise-based CR for reducing all-cause and cardiovascular mortality. A common theme highlighted in these meta-analyses is the heterogeneity and/or lack of detail regarding exercise prescription methodology within CR programs. Currently there is no international consensus on exercise prescription for CR, and exercise intensity recommendations vary considerably between countries from light-moderate intensity to moderate intensity to moderate-vigorous intensity. As cardiorespiratory fitness [peak oxygen uptake (VO_2peak)] is a strong predictor of mortality in patients with coronary heart disease and heart failure, exercise prescription that optimizes improvement in cardiorespiratory fitness and exercise capacity is a critical consideration for the efficacy of CR programming. This review will examine the evidence for prescribing higher-intensity aerobic exercise in CR, including the role of high-intensity interval training. This discussion will highlight the beneficial physiological adaptations to pulmonary, cardiac, vascular, and skeletal muscle systems associated with moderate-vigorous exercise training in patients with coronary heart disease and heart failure. Moreover, this review will propose how varying interval exercise protocols (such as short-duration or long-duration interval training) and exercise progression models may influence central and peripheral physiological adaptations. Importantly, a key focus of this review is to provide clinically-relevant recommendations and strategies to optimize prescription of exercise intensity while maximizing safety in patients attending CR programs.

Keywords: interval training, coronary artery disease, cardiovascular disease, heart failure, cardiorespiratory fitness, peak oxygen consumption, exercise prescription, progression

OPEN ACCESS

Edited by:
Jian Yang,
Zhongshan Hospital, Fudan University, China

Reviewed by:
Paulo M. Dourado,
University of São Paulo, Brazil
Ferdinando Iellamo,
University of Rome Tor Vergata, Italy

****Correspondence:***
Jenna L. Taylor
taylor.jenna-lee@mayo.edu

Specialty section:
This article was submitted to General Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

Received: *30 June 2021*
Accepted: *31 July 2021*
Published: *03 September 2021*

Citation:
Taylor JL, Bonikowske AR and Olson TP (2021) Optimizing Outcomes in Cardiac Rehabilitation: The Importance of Exercise Intensity. Front. Cardiovasc. Med. 8:734278. doi: 10.3389/fcvm.2021.734278

INTRODUCTION

Exercise-based cardiac rehabilitation (CR) is a class 1A recommendation for patients with select cardiovascular diseases (CVD) and heart failure with reduced ejection fraction (HFrEF), as it leads to significant improvements in exercise capacity, CVD risk profile, and reductions in hospital readmissions, cardiovascular (CV) events, and mortality (1–6). Compared with standard

medical care, systematic reviews from 2004 (5) to 2011 (4) in coronary heart disease, showed that exercise-based CR reduced hospitalizations, CV mortality, and all-cause mortality by 31, 26, and 20 %, respectively (4, 5). However, over the past decade, results from RAMIT (Rehabilitation after Myocardial Infarction Trial) (7) and subsequent systematic reviews (8, 9) questioned the effectiveness of exercise-based CR for reducing recurrent CV events (7, 9), CV mortality (9), and all-cause mortality (7–9).

This generated substantial debate within the scientific community (10–12), with speculation that low exercise training intensity and dose may be responsible (13). Moreover, meta-analyses have shown significant heterogeneity and lack of detail regarding exercise prescription methodology within CR programs (2, 3). Currently there is no international consensus on exercise prescription or program duration for CR, and exercise intensity recommendations vary considerably between countries from light-moderate intensity (Australia, Japan), moderate intensity (United Kingdom, France), and moderate-vigorous intensity (Canada, United States, South America, and other European countries) (14). Furthermore, studies from the United Kingdom have highlighted that in CR practice the actual exercise training intensities performed by patients, may not progress to the upper range of exercise intensity recommendations (13). Despite numerous publications outlining international CR practices and program characteristics from national registries or surveys, relatively few include data on exercise intensity prescription or implementation (15–18). This data is important to determine whether exercise training during CR is being prescribed and implemented effectively across international programs. There is a need to define internationally accepted standards in CR delivery and scientific evaluation (2, 3).

This review will examine the evidence for prescribing moderate-vigorous intensity aerobic exercise and high intensity interval training (HIIT) in CR programs, including beneficial physiological adaptations to the pulmonary, cardiac, vascular, and skeletal muscle systems in patients with CVD and heart failure (HF). Moreover, this review will discuss how increasing the duration of intervals and training volume may improve physiological adaptations; and will discuss practical applications and progression models to optimize exercise prescription in CR programs.

Exercise Prescription in Cardiac Rehabilitation

Methods for prescribing exercise intensity in CR vary internationally but can also be program-specific depending on the resources available. Objective methods for determining exercise intensity can include indices of peak exercise capacity, ventilatory thresholds, anaerobic threshold, or the myocardial ischemia threshold. These require availability of maximal exercise testing, preferably with cardiopulmonary gas analysis for intensities based on peak oxygen uptake (VO_2peak), and/or ventilatory thresholds. In programs where maximal exercise testing is not available, subjective measures of exercise intensity including rating of perceived exertion (RPE) (19) or the talk test (TT) (20), are predominately used to guide exercise intensity.

Indices of Peak Exercise Capacity

The majority of guidelines on exercise training in CR recommend aerobic exercise prescription based on relative indices of peak exercise capacity. These include percentage of peak workload (Wpeak), percentage of peak heart rate (%HRpeak), percentage of VO_2peak (%VO_2peak), percentage of HR reserve (%HRR), or percentage of VO_2 reserve (%VO_2R) (1, 21). Reserve calculations are generally preferred for precise exercise intensity prescription given they also take into account the patient's resting values (22) and may be more appropriate for patients with chronotropic incompetence (23). In addition to issues with practicality of maximal exercise testing (due to cost, lack of expertise, technological resources, and/or medical supervision) (24, 25), limitations with using relative indices of peak exercise capacity can include patient failure to reach a near-maximal effort, subsequent dose adjustment and timing of rate-control medications, and the fact that VO_2peak or Wpeak are highly influenced by the ramp rate during the test (1, 26). Furthermore, a disadvantage with a workload-based approach is that progression is based on arbitrary increments, rather than a physiological change with improvements in exercise capacity (as HR does) (1).

Ventilatory Thresholds

An alternative approach to using indices of peak exercise capacity, is to relate exercise intensity to ventilatory thresholds. This approach requires cardiopulmonary gas analysis and is more commonly used for exercise prescription in European CR programs. Nomenclature of these thresholds remains controversial and methodologies to assess them are not universally accepted. The first ventilatory threshold (VT1) (*also termed anaerobic threshold*) is most widely known and represents the transition from a predominately aerobic metabolism to a point where blood lactate begins to accumulate and a greater reliance on anaerobic metabolism is needed for continued energy production (1, 27). At this point, ventilation (VE) accelerates to counterbalance and eliminate the excess carbon dioxide (CO_2) in the blood produced during the conversion of lactic acid to lactate (27). The second ventilatory threshold (VT2) (*also termed respiratory compensation point, critical power, or lactate threshold*) represents the exercise intensity at which blood lactate accumulates rapidly, excess CO_2 can no longer be eliminated, and there is a disproportionate increase in VE relative to CO_2 production (VCO2) (1, 28). The VT1 is commonly assessed using the V-slope method (i.e., the departure of VO_2 from a line of identity drawn through a plot of VCO_2 vs. VO_2) or the nadir (lowest point) of the VE/VO_2 to work rate relationship (1, 27). The VT2 is assessed as the nadir of VE/VCO_2 to work rate relationship (1, 28). Exercise training zones can then be extrapolated from these thresholds using a corresponding HR or workload, with light intensity below VT1, moderate intensity between VT1 and VT2, and high intensity above VT2 (1). There are several disadvantages with using threshold-based exercise prescription. There can be substantial within-subject variability from two consecutive tests (29), a high variation between observers and sites (30), and the reproducibility of VT2 is not well established in patients with CVD (1). Furthermore, VT thresholds cannot be directly translated to constant-load exercise

due to slowed VO_2 kinetics and delay in VO_2 response to the imposed work (1, 31), which is exaggerated in patients with CVD and HF (32–34).

Subjective Measures

Regardless of whether objective measures of effort (such as HR or VO_2) are available, subjective measures of effort (e.g., RPE or TT) should be used as an adjunct in CR settings, particularly for patients who have difficulty obtaining a reliable or meaningful exercise-related HR (e.g., patients with atrial fibrillation, pacemakers, chronotropic incompetence, heart transplant, or patients receiving beta blockade therapy) (23, 28). Subjective measures can also be useful for comparing the perceived effort across exercise modalities (28). The Borg 6–20 RPE scale is a widely used instrument to measure exercise intensity, by asking patients to self-report their perceived effort of exercise on a scale of 6 (no exertion at all) to 20 (very, very hard) (19). It is a practical, validated, and effective method for prescribing and monitoring exercise intensity in patients with CVD (35, 36) and HF (37, 38), and is not influenced by beta-blocker medication (38). Limitations of using the RPE scale may include the influence of psychological factors or environmental conditions (28), difficulties in patients with impaired vision (23), or use during outdoor exercise (24). Lack of familiarity with exercise training, fitness level, age, gender, education level, and use of diuretics have also been reported to influence RPE (39–41). It is imperative that patients are educated on correct use of the RPE scale, anchored to sensations of *extremely hard/maximal* and *no exertion at all*, and representing an integrated rating of muscular and cardiovascular sensations (19, 26). The TT is another practical tool for prescribing exercise intensity, that has shown to be valid and reliable in patients with CVD (20). Physiologically, it is based on the swift increase in breathing above VT2 (or lactate threshold) that causes difficultly in comfortable talking during exercise (1), and can therefore help to identify the boundary between moderate and vigorous intensity exercise (24). The TT is not a practical tool for customizing interval training protocols with short durations (<1 min) or at very high intensity (>95 %HRpeak) (20), however further research into its use for longer duration HIIT protocols of 85–95 %HRpeak [e.g., 4 × 4 min protocol (26, 42)] would be of interest. For home-based HIIT, Wisløff et al. instructed patients with HF to complete a 4 min interval at an intensity where "they are breathing heavily and talking becomes uncomfortable" (43), which corresponded to an RPE of 17 ± 1 and 93 ± 3 % of HRpeak (44).

Summary

Recent guidelines have suggested that while subjective measures can be a practical method to prescribe exercise intensity, they should be used as an adjunct rather than alternative to objective methods (1). Furthermore, concerns have been raised that exercise training intensity based on results of indirect, submaximal exercise testing (e.g., 6 min walk test, incremental shuttle walk test), which do not rigorously evaluate the cardiorespiratory system, may result in under-prescription of exercise intensity and reduced effectiveness of CR programs (12). Where available, VO_2peak and HRpeak should be determined from a maximal cardiopulmonary exercise test, during which the patient has taken prescribed HR-modulating medications. If a maximal exercise test is not feasible, a new predictive equation combining age and HR measured during a 200 m fast walk test (45), has shown good correlation with HRpeak measured during a maximal exercise test. In this case, accounting for age and HR response to a submaximal test may be more predictive of an accurate HRpeak than relying on age-predicted equations for patients with (46) and without beta-blockade (47, 48). However, the equation for patients with beta-blockade (46) accounts for resting HR and test mode in addition to age (46).

Is There a Benefit for Prescribing Higher Intensity Exercise?

Definition of Exercise Intensity Ranges and Protocols

Classifications of exercise intensity by the American College of Sports Medicine (ACSM) (49) and European Association of Preventative Cardiology (EAPC) (1) are outlined in **Table 1**. As exercise performed at a vigorous to high intensity cannot be sustained for long periods, HIIT can be a more feasible method by alternating bouts of high intensity exercise with recovery bouts of lower intensity exercise or no exercise. There has been a large amount of scientific interest regarding HIIT in patients with CVD and HF, mostly comparing its effectiveness to moderate intensity continuous training (MICT). Sprint interval training (SIT) involves intense "all-out" or supramaximal efforts (i.e., workloads greater than VO_2peak or peak power output) with typically shorter bouts (<45 s) (50). Although HIIT involves near-maximal intensities, efforts are still submaximal (i.e., workloads below VO_2peak or peak power output), and therefore HIIT has been considered more appropriate for use in clinical populations than SIT (51). The terminology of HIIT and MICT are preferred given they provide a description of intensity (51). However, aerobic interval training (AIT) and aerobic continuous training (ACT), respectively are alternative terminology frequently used within with the literature. Common intensity prescription of HIIT and MICT used in patients with coronary artery disease (CAD) and HF are outlined in **Table 2**, devised from studies included in reviews by Pattyn et al. (52) and Taylor et al. (53). While these ranges outline the HIIT and MICT prescriptions for the majority of studies in cardiac patients, two studies have prescribed notably higher intensities for MICT in CAD including 60–80 %VO_2peak (54, 55) and 65–85 %HRpeak (56). There are also three studies that prescribed notably lower intensity for HIIT, with one in CAD (50 % peak workload from a steep ramp test) (57), and two in HF with 50–80 % maximal power (58) and 50–75 % of VO_2peak (59).

Influence of Exercise Intensity on CVD and Mortality

Numerous studies investigating all-cause mortality in healthy populations, have demonstrated that higher intensity exercise may induce larger health benefits than low or moderate intensity exercise. Furthermore, benefits with high intensity exercise can be achieved in substantially less time than MICT. The Hunt Study (60) demonstrated that one single bout of high intensity exercise reduced all-cause and CV mortality to a similar or

TABLE 1 | Classification of aerobic exercise intensity.

ACSM Guidelines (49)			EAPC and ESC Guidelines (1)			
Intensity	**VO_2 and HR**	**RPE**	**Intensity**	**VO_2 and HR**	**RPE**	**Training zone**
Light	37–45 %VO_2max 57–63 %HRmax 30–39 %HRR	9–11	Low	<40 %VO_2max <55 %HRmax <40 %HRR	10–11	Aerobic
Moderate	46–63 %VO_2max 64–76 %HRmax 40–59 %HRR	12–13	Moderate	40–69 %VO_2max 55–74 %HRmax 40–69 %HRR	12–13	Aerobic
Vigorous	64–90 %VO_2max 77–95 %HRmax 60–89 %HRR	14–17	High	70–85 %VO_2max 75–90 %HRmax 70–85 %HRR	14–16	Aerobic + lactate
Near-maximal to maximal	>90 %VO_2max >95 %HRmax >89 %HRR	>17	Very high	>85 %VO_2max >90 %HRmax >85 %HRR	17–19	Aerobic + lactate + anerobic

Adapted from guidelines from the American College of Sports Medicine (ACSM) (49) and European Association of Preventative Cardiology (EAPC) (1). HR, heart rate; HRR, heart rate reserve; RPE, rating of perceived exertion on 6–20 Borg scale (19); VO_2, oxygen uptake.

TABLE 2 | Common intensity prescriptions for HIIT and MICT.

	Patients with CAD		Patients with HF	
Training protocol	**HR or VO_2**	**Other measures**	**HR or VO_2**	**Other measures**
MICT	60–75 %HRpeak	RPE 11–14	60–75 %HRpeak	50–75 %PPO
	60–85 %HRR	50–65 %PPO	45–60 %HRR	90–100 %VT1
	50–60 %VO_2peak	100–110 %VT1	60–70 %VO_2peak	
HIIT	80–100 %HRpeak	RPE 15–18	80–95 %HRpeak	90–100 %PPO
	80–95 %HRR	90–110 %PPO	75–80 %HRR	
	80–90 %VO_2peak	100 %VT2 or %RCP	70–80 %VO_2peak	

MICT, moderate intensity continuous training; HIIT, high intensity interval training; HR, heart rate; HRR, heart rate reserve; RPE, rating of perceived exertion on 6-20 Borg scale (19); VO_2, oxygen uptake; VT1, first ventilatory threshold; VT2, second ventilatory threshold; PPO, peak power output; RCP, respiratory compensation point.

greater degree than several hours of MICT. Similarly, Wen et al. (61), demonstrated the superior or time-efficient advantages of vigorous intensity exercise, with similar health benefit to MICT in half the weekly exercise time, or double the health benefit to MICT with the same weekly exercise time. Furthermore, studies have shown the proportion of vigorous activity has an inverse dose-response relationship with all-cause mortality in people with and without CVD, calling for physical activity (PA) guidelines to endorse participation in vigorous activity (62, 63). Finally, several studies have also shown an inverse association between exercise intensity and incidence of coronary heart disease in men independent of total exercise volume (64, 65), however the association of exercise intensity is less clear in women (66, 67).

Influence of Exercise Intensity on Cardiorespiratory Fitness

Cardiorespiratory fitness (assessed as VO_2peak) reflects an integrated ability to transport oxygen (O_2) around the body, encompassing pulmonary function, cardiac function (systolic and diastolic), ventricular-arterial coupling, vascular function, and the ability of muscle cells to receive and use O_2 (68). There is extensive evidence that VO_2peak is a strong predictor of future CV events and mortality, and even modest increments in VO_2peak can be clinically meaningful in patients with CAD and HF (69–71). A landmark study by Kavanagh et al. in 12,169 CAD patients referred for CR, found that each 1.0 mL/kg/min increment in VO_2peak was associated with a 9 % increase in survival. Moreover, Keteyian et al. (72) found an increased survival of 15 % per 1.0 mL/kg/min increment of VO_2peak in patients with CAD. A study by Mikkelsen et al. (69) including 1,561 cardiac patients (predominately with CAD; 84 %), found that for every 1.0 mL/kg/min improvement in VO_2peak during CR, there was a 21 % reduction in CV events and a 13 % reduction in all-cause mortality. In patients with HF, the HF-ACTION trial (71) showed that every 6 % improvement in VO_2peak (adjusted for other factors) was associated with an 8 % lower risk of CV mortality and HF hospitalization, and a 7 % lower risk of all-cause mortality. In a large meta-regression analysis examining 55 trials of either HIIT or MICT compared with control in patients with CAD and HF, Uddin et al. (73) demonstrated that exercise intervention intensity was the greatest predictor of VO_2peak

post CR, even when including age, sex, and baseline fitness level in the multivariable regression model. Furthermore, each 10 % increase in exercise intensity (as %VO_2peak or %HRpeak) was associated with a 1.0 mL/kg/min increase in VO_2peak post CR. This is supported by Mitchell et al. (74) in patients attending CR for any indication, finding the greatest improvements in VO_2peak with vigorous intensity exercise (5.5 mL/kg/min), followed by moderate-vigorous intensity (4.9 mL/kg/min), and then moderate intensity exercise (4.1 mL/kg/min). In contrast, a meta-analysis in patients with HF that adjusted for total exercise expenditure (75) found duration and frequency of exercise sessions to be greater predictors of VO_2peak improvement than exercise intensity, however this review excluded interval training studies (including HIIT). Another meta-analysis in patients with HF that included HIIT studies (76), found high intensity (≥90 %HRpeak or ≥85 %HRR) but not vigorous intensity exercise (70–90 %HRpeak; 60–85 %HRR) produced larger improvements in VO_2peak compared with moderate intensity exercise (55–80 %HRpeak; 50–60 %HRR) with gains of 3.3, 2.3, and 2.2 mL/kg/min, respectively. Low intensity exercise (40–55 %HRpeak; 20–40 %HRR) produced the smallest improvement (1.0 mL/kg/min) (76).

Studies based in the United Kingdom (UK) have found smaller improvements in cardiorespiratory fitness [∼0.7–0.8 metabolic equivalents (METs)] compared with international programs (∼1.5 METs) (77). The UK guidelines for CR programs typically recommend exercise of a moderate intensity (40–70 %HRR), compared with moderate-high intensity exercise recommendations in Canada (40–85 %HRR), United States (40–80 %VO_2peak) and other European countries (40–80 %VO_2peak; up to 90 %HRpeak) (14). Furthermore, a UK study by Nichols et al. (13) reported that the peak exercise training intensities achieved (46–54 %HRR) did not progress to the upper range of the UK exercise prescription targets (40–70 %HRR), and that after 8 weeks the exercise duration achieved (23 min) only marginally exceeded the minimum recommended duration of 20 min. Therefore, lower exercise intensity and volume have been reported as contributors to the smaller VO_2peak improvements in CR programs within the UK (13, 78). This may also be typical of CR programs in other countries with low-moderate intensity guidelines, with potential to reduce the overall effectiveness of CR.

There have been several meta-analyses comparing HIIT with MICT on cardiorespiratory fitness as VO_2peak. Weston et al. (51) examined 10 studies in patients with cardiometabolic disease and found that HIIT improved VO_2peak by 19 % compared to 10 % with MICT (mean difference = 3.0 mL/kg/min). In patients with CAD, several meta-analyses have shown a superior effect of HIIT compared with MICT on VO_2peak improvement, with a mean difference 1.3–1.8 mL/kg/min (52, 79–82). Pattyn et al. found HIIT protocols that were isocaloric with MICT were more likely to show superiority over MICT (+2.1 mL/kg/min) compared with HIIT protocols that were a lower energy expenditure to MICT (+0.2 mL/kg/min) (52). Furthermore, Way et al. (83) demonstrated that although women tend to experience lower absolute improvements in VO_2peak with HIIT than men, they have similar relative improvements in VO_2peak (83). The FITR Heart Study, a recently published pragmatic trial in 93 CAD patients using RPE as the primary method of exercise prescription (36), also demonstrated a superior effect of HIIT compared with MICT during a 4-week CR program, with a mean difference in VO_2peak improvement of 1.7 mL/kg/min. In contrast to this trial and previous meta-analyses, the SAINTEX-CAD multicenter trial in 200 patients with CAD, found both HIIT and MICT produced equally substantial improvements in VO_2peak (23 and 20 %, respectively) during a 12-week CR program (84). A noteworthy consideration with this trial, was the higher training intensity of the MICT group (average training intensity of 80 %HRpeak), compared with previous trials that prescribed training intensity at 65–75 %HRpeak (42, 85). Although the SAINTEX-CAD had designed MICT to be prescribed at 70–75 %HRpeak, patients were not restrained from exercising at higher intensities. Therefore, results of the SAINTEX-CAD study suggest that continuous training may be equally effective to HIIT for improving VO_2peak, when performed at a vigorous intensity. In patients with HF, meta-analyses have also found a superior effect of HIIT compared with MICT on VO_2peak improvement, with a mean difference 1.0–2.4 mL/kg/min (52, 82, 86, 87). However, the large multicenter SMARTEX HF study (88) in 261 patients with HFrEF, found similar improvements in VO_2peak with HIIT (1.4 mL/kg/min) and MICT (0.8 mL/kg/min) compared with an exercise guidelines group that showed a decrease in VO_2peak (−1.0 mL/kg/min). While median training intensity for HIIT was 90 %HRpeak (interquartile range 88–92 %) and 77 %HRpeak (interquartile range 74–82 %) for MICT, 51 % of HIIT patients exercised at a lower intensity than prescribed and 80 % of MICT participants trained at a higher intensity than the protocol prescribed (88). In 180 patients with preserved ejection (HFpEF), the multicenter OptimEX-Clin study (89) found neither HIIT or MICT met the prespecified minimal clinically important improvement in VO_2peak (2.5 mL/kg/min) compared with a PA guidelines control group. However, HIIT and MICT showed similar increases in VO_2peak of 1.1 and 1.6 mL/kg/min, respectively, over the 3-month supervised training (89). The meta-analysis by Pattyn et al. (52), also found no differences between HIIT and MICT for improvement of VO_2peak in the HFpEF sub-analysis.

Influence of Exercise Intensity on Other Cardiometabolic Parameters

Exercise intensity appears to have a significant influence on increasing exercise capacity at VT1. An early study by Jensen et al. in patients with CAD (90), found high intensity continuous training was superior to low intensity training for improving VO_2 at VT1. Furthermore, the meta-analysis by Pattyn et al. (52) in both CAD and HF patients, found greater improvements in VO_2 at VTI after HIIT compared with MICT (mean difference of 0.9 mL/kg/min). This is important as the improved ability to use O_2 aerobically may translate into improved performance of daily living activities (52). Pattyn et al. (52) also found a greater improvement in HRpeak with HIIT compared with MICT, and a trend for greater improvement in peak O_2 pulse and O_2 uptake efficiency slope (OUES) favoring HIIT. Other

cardiorespiratory parameters (e.g., HR recovery, VE/VCO_2 slope) and CVD risk factors (e.g., body weight, resting HR, blood pressure, cholesterol, triglycerides, and fasting glucose) do not appear to be influenced by exercise intensity (52, 82, 91). Studies investigating 24-hr blood pressure, have found a superior effect of HIIT compared with MICT in patients with hypertension (92) but similar improvement to MICT in patients with HF (93). Pattyn et al. (52) found a trend ($p = 0.09$) toward greater improvements in vascular function [via flow-mediated dilation (FMD)] with HIIT compared with MICT. In a meta-analysis with a more diverse cohort of cardiometabolic diseases, Ramos et al. (94) found HIIT was superior to MICT with a 2-fold greater improvement in flow-mediated dilation (4.31 vs. 2.15 %, respectively). For changes in body composition, HIIT provides similar benefit compared with MICT, but not when total energy expenditure is less (95). Therefore, exercise volume appears to play a greater role in body composition than exercise intensity (95). A retrospective study by Dun et al. (96) in 120 CR patients with myocardial infarction, found greater reductions in total fat mass and abdominal fat percentage with HIIT compared to MICT using dual-energy x-ray absorptiometry (DEXA). In contrast, Taylor et al. (97) found similar reductions for visceral adipose tissue and subcutaneous fat quantified by magnetic resonance imaging and total fat mass with DEXA, when comparing isocaloric HIIT and MICT in patients with CAD. The influence of exercise intensity on resting left ventricular ejection fraction (LVEF) and left ventricular end-diastolic diameter (LVEDD) remain inconclusive. Meta-analyses by Cornelis et al. (98) and Pattyn et al. (52) both found HIIT significantly improved both LVEF compared with MICT in patients with HF, however Haykowsky et al. (86) found only a trend toward greater improvements in LVEF. Cornelis et al. (98) also found HIIT significantly improved LVEDD compared with MICT. While the multi-center SMARTEX HF study (88) found only HIIT significantly improved LVEDD after 12-weeks compared with the control group, there was no difference between HIIT and MICT.

Influence of Exercise Intensity on Long-Term Outcomes and Adherence

Only three studies have investigated long-term outcomes of HIIT compared with MICT in patients with CAD at 6-months (85) and 12-months (36, 99). Moholdt et al. (85) found a superior effect of HIIT compared with MICT on improvement of VO_2peak and HR recovery at 6-months in patients with CABG, but similar improvements in quality of life and adiponectin. At 12-months, the SAINTEX-CAD and FITR Heart studies found similar improvements between HIIT and MICT in patients with CAD for VO_2peak and other exercise variables (36, 99), CVD risk factors (36, 99), quality of life (36, 99), FMD (99, 100), body composition (97, 101), moderate-vigorous PA (36, 99), and no changes in dietary intake (101). Although for The FITR Heart Study, the improvement in VO_2peak was numerically higher for HIIT (2.9 mL/kg/min) than MICT (1.8 mL/kg/min) (36) which may be related to greater long-term survival as noted above. In contrast, the SMARTEX HF (88) and OptimEX-Clin (89) studies in patients with HFrEF and HFpEF, respectively, showed a regression of supervised training improvements at 12-months regardless of exercise intensity. A difference with The FITR Heart Study (36) and OptimEx-Clin study (89) was after the supervised training period, participants were instructed to continue home-based HIIT or MICT (as randomized) until the 12-month follow-up, and therefore long-term adherence to the HIIT and MICT protocols were assessed. At 12-months, The FITR Heart Study reported 38 % of MICT participants had starting exercising at a higher intensity than prescribed and 24 % of HIIT participants exercised at a lower intensity than prescribed, although overall adherence (>70 % of sessions at prescribed intensity) was similar between groups (53 % for HIIT and 41 % for MICT) (36). When non-adherent participants were excluded from the analysis, HIIT showed a considerably greater improvement in VO_2peak (5.2 mL/kg/min) compared with MICT (2.2 mL/kg/min) (36), however improvements in other cardiometabolic outcomes remained similar between groups. This demonstrates that adherence to the intensity of exercise protocols over the long-term can significantly influence improvements in VO_2peak. In contrast, Moholdt et al. (85) found after 5 months of home-based training that a higher proportion of participants stopped HIIT in favor of MICT (35 %), compared to only 4 % of MICT participants starting higher intensity exercise. Although adherence to the randomized training (≥3 times/week) at 6-months was slightly lower for HIIT (52 %) than MICT (64 %), the proportion of participants performing 3 sessions/week of at least moderate intensity exercise was similar for HIIT (74 %) and MICT (68 %), and improvements in VO_2peak were superior with HIIT at 6-months. In patients with HFpEF, the Optimex-Clin study (89) reported that adherence (>70 % of sessions) did not influence improvements in VO_2peak. The authors found similar adherence between HIIT and MICT (56 and 60 %, respectively) but did not report on adherence to the intensity of the exercise protocols. A recent review in CR patients with CAD, found short-term adherence (as number of sessions) to supervised or home-based HIIT was similar to MICT (53). However, the review highlighted that adherence to intensity and duration of the training protocols was under-reported, and the authors provided recommendations for how future studies can collect and report this important data (53). This is particularly important given the findings from larger pragmatic trials such as the SAINTEX-CAD, SMARTEX-HF, and FITR Heart studies on non-adherence to training intensity, which can provide insight into feasibility and effectiveness of exercise prescription. The review by Taylor et al. (53) in patients with CAD, found the majority of studies reporting on feasibility (8/11 studies) reported HIIT to be equally feasible to MICT in patients attending CR, while the other three studies reported HIIT was less feasible than MICT. Factors that appeared to improve feasibility of HIIT included: setting realistic expectations for training intensities; including a variety of exercise modalities (for enjoyment and reducing musculoskeletal impact); and using progressive models of HIIT (53).

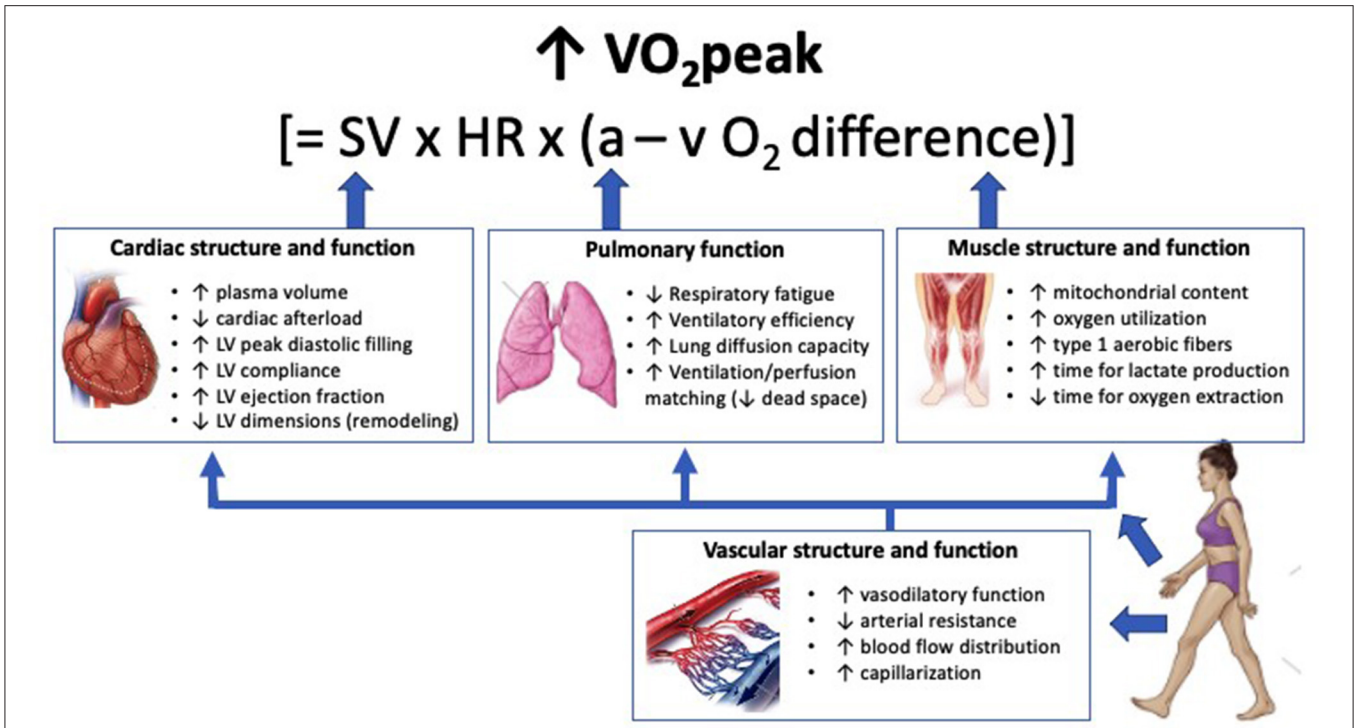


FIGURE 1 | Physiological adaptations from exercise training that may contribute to improvement in VO_2peak in patients with cardiovascular disease or heart failure. Cardiac adaptations contribute to VO_2peak improvements primarily through increases in stroke volume. Pulmonary adaptations contribute to VO_2peak by optimizing arterial oxygen content and therefore oxygen delivery. Muscle adaptations contribute to VO_2peak improvements through increased exercise tolerance and enhanced oxygen extraction. Vascular adaptations contribute to oxygen delivery by reducing arterial resistance, increasing capillary density, and enhancing blood flow distribution, which in turn enhances function of the cardiac, pulmonary, and muscle systems. Increases in plasma volume can occur within days of commencing exercise training. Adaptations within skeletal muscle and to the vasculature can occur within weeks of training. Current evidence supports greater adaptations in mitochondrial content, vascular vasodilatory function, and stroke volume following HIIT compared with MICT, although the precise cardiac mechanisms that lead to increased stroke volume remain unclear. VO_2peak, peak oxygen uptake; SV, stroke volume; HR, heart rate; a–vO_2 difference, oxygen content difference between arterial and venous blood; LV, left ventricle.

Physiological Adaptations With Exercise Training for Improving VO_2peak

There are numerous integrative physiological adaptations that may improve VO_2peak in patients with CVD or HF (**Figure 1**). Based on the Fick equation, VO_2 is the product of cardiac output and arterial-venous O_2 content difference (a-vO_2 difference), where cardiac output is the product of stroke volume and HR (68). This equation can also be summarized as "central" and "peripheral" determinants of VO_2, respectively (50).

Pulmonary Adaptations

The pulmonary system is responsible for the transport of O_2 from the atmosphere to the bloodstream, with alveolar ventilation (O_2 exchange with the atmosphere) and diffusion (O_2 exchange with the bloodstream) contributing to arterial O_2 content, O_2 delivery, and VO_2peak (68). Reduced alveolar exchange can be a significant contributor to exercise intolerance in patients with HF, which can occur due to impaired pulmonary vasodilation, ventilation/perfusion mismatch, impaired diffusion, abnormal ventilatory reserve (i.e., respiratory muscle dysfunction), or abnormal ventilatory regulation (i.e., oscillatory patterns) (102–105). Furthermore, respiratory muscle fatigue has also been shown to affect O_2 delivery by causing peripheral vasoconstriction and reduced blood flow to skeletal muscles, further exacerbating exercise intolerance (106). There are limited studies comparing the effect of exercise training intensity on pulmonary adaptations. In patients with HF, Tasoulis et al. (107) demonstrated that HIIT improved ventilatory regulation, with an improvement in ventilatory drive (as $P_{0.1}/PI_{max}$) and ventilatory patterns during rest and exercise, although there was no control group. In healthy adults, Dunham and Harms (108), demonstrated significant improvements in respiratory muscle function with HIIT and MICT (43 vs. 25 %) over 4-weeks, however there was a greater increase with HIIT. Finally, Guazzi et al. (109) studied patients with HF, and found that compared with a control group, 8-weeks of moderate-vigorous intensity training improved lung diffusion, alveolar-capillary conductance, and pulmonary capillary blood volume with concomitant improvements in VO_2peak. Whether HIIT is superior to MICT for pulmonary adaptations remains unclear.

Cardiac Adaptations

One of the proposed mechanisms for greater improvement in VO_2peak with higher intensity exercise is greater central

adaptations in left ventricular structure and function (110), by challenging the cardiac muscle to provide increased cardiac output and O_2 to the working muscles (52). In athletes, exercise training is associated with expansion of red blood cell volume and augmented plasma volume (111), reduced total peripheral resistance, and increased LV end-diastolic volumes (i.e., LVEDV), leading to increased stroke volume, cardiac output, and VO_2peak (112). Increased LV diastolic volumes in the short-term can be attributed to increased plasma volume and venous return via the Frank-Starling mechanism (111), while long-term adaptation involves structural changes from exercise training that enhance LV compliance (112). However, in cardiac patients, who may have pathological LV dilation (cardiomegaly), exercise training has been associated with reversal of LV remodeling (i.e., reduction in LVEDD), increases in peak diastolic filling, and reduced peripheral resistance, with concomitant increases in stroke volume, cardiac output, and VO_2peak (44, 113, 114). Several studies in healthy subjects (115, 116) and patients with HFrEF (44, 58, 117) have shown greater improvements in maximal stroke volume alongside VO_2peak with HIIT compared with MICT. In contrast, Iellamo et al. (118) found no improvement in central hemodynamics (cardiac output or stroke volume) for HIIT or MICT in patients with HFrEF despite large increases in VO_2peak for both groups. A proposed reason for differences in central adaptation outcomes between studies, is that some patients with a high degree of peripheral limitation (e.g., muscle atrophy or overt cachexia) may have a limited ability to exercise at a high intensity for a sufficient amount of time (110). Peripheral limitations are known to be a significant contributor to exercise intolerance in patients with HF (102). Inability to achieve the target training intensity of HIIT (51 % participants) was a significant limitation of the SMART-EX HF study in patients with HFrEF (88), which showed no change in LVEDD or peak O_2 pulse (a surrogate for stroke volume). In contrast, the SAINTEX-CAD study in patients without HF (84) showed significant improvements in peak O_2 pulse for both HIIT and MICT, although the average intensity of the MICT group was 80 %HRpeak and therefore higher than a moderate intensity. In summary, majority of studies investigating central hemodynamics have found greater improvements in stroke volume with HIIT compared with MICT. However, the effect of exercise training intensity on structural adaptations remains unclear.

Vascular Adaptations

Another potential mechanism for the greater improvement in VO_2peak with higher intensity exercise is the superior effect on vascular function for HIIT compared with MICT (52, 94). Greater elasticity and function of the central and peripheral vasculature allows for greater accommodation and more efficient transport of blood and O_2 to the heart and skeletal muscles (68). A common method for measuring vascular function adaptations is brachial artery FMD (119), a non-invasive test shown to correlate well with invasively measured coronary artery vasodilatory function (120). There is extensive evidence that aerobic exercise training improves vascular function in large conduit arteries, with repeated hemodynamic stimuli and laminar shear stress playing a central role in vascular adaptation (119). A proposed mechanism for the superior effect of HIIT on vascular function, when compared with MICT, is that higher intensity exercise provokes greater blood flow and shear stress stimulus, that allows for greater vascular adaptation through upregulation of vasodilatory prostaglandins (119, 121) and nitric oxide (119, 122). Thijssen et al. (123) demonstrated that with incremental increases in exercise intensity for various modalities (walking, cycling, leg kicking), there was a parallel increase in mean blood flow and shear rate within the brachial artery.

Skeletal Muscle Adaptations

In addition to O_2 delivery, peripheral adaptations with training that increase O_2 extraction and utilization may also lead to increases in VO_2peak by increasing a-vO_2 difference. In healthy populations, skeletal muscle capacity for oxidation usually exceeds the capacity for systemic O_2 transport (50), and therefore peripheral adaptations may not contribute to large increases in VO_2peak. However, in deconditioned patients, particularly those with HFrEF and HFpEF, peripheral adaptations within skeletal muscle can have a significant effect on exercise tolerance and capacity (102, 124). The major training-induced adaptations that increase O_2 extraction and utilization within skeletal muscle, include increased capillary density and mitochondrial volume density (111). The former may enhance local blood perfusion and distribution with or without improvements in vascular function (111), while the latter increases capacity for substrate oxidation at a given workload (50, 125). Increased mitochondrial content with exercise training "promotes greater reliance on fat oxidation with a proportional decrease in carbohydrate oxidation," which in turn "reduces glycogen degradation and lactate production at a given workload" (126, 127). As a result, lactate threshold is increased and patients can exercise for longer durations at a greater percentage of VO_2peak (128). This is particularly important for cardiac patients, as reduced oxidative capacity can significantly contribute to exercise intolerance (102). There is strong evidence from studies in healthy populations that exercise intensity mediates mitochondrial adaptations to exercise and improvements in VO_2peak (126). During higher intensity exercise, there is greater accumulation of metabolites and free radicals from calcium release, ATP turnover, and carbohydrate utilization (1, 126). This accumulation leads to activation of several mitochondrial enzymes, which stimulate expression of peroxisome proliferator-activated receptor γ coactivator-1*a* (PGC-1*a*), an important regulator of mitochondrial biogenesis (50, 126). Studies involving patients with HF (44), metabolic syndrome (43), and obesity (129) have shown greater increases in PGC-1*a* with HIIT compared with MICT, with concomitant increases in the maximal rate of calcium reuptake into the sarcoplasmic reticulum. Enhanced calcium cycling, may also help to reduce muscle fatigue and exercise capacity (51). In addition to exercise intensity, this greater activation of signaling pathways for mitochondrial adaptations is thought to be triggered by the metabolic fluctuations with intermittent exercise bouts, that occurs during interval training (50). In contrast, short bursts of high intensity exercise do not appear to improve vascular endothelial growth factor (VEGF) secretion and skeletal

muscle capillarization, which may require longer durations of constant work exercise (130). Studies that have found superior improvements in VEGF and skeletal muscle capillarization with MICT compared with HIIT, have used short duration HIIT intervals of ≤1 min (131, 132). There is limited research comparing training of different intensities on muscle fiber type. However, studies comparing exercise to a control group, have found an increased proportion of type 1 fibers with decreased type IIb fibers after either 15-weeks of SIT (133) or 6-months of MICT (134). On the other hand, Tan et al. (135), found 6-weeks of HIIT improved oxidative capacity of both type 1 and type 2 muscle fibers to a similar degree. Based on the current evidence, it appears that high intensity exercise provides a potent stimulus for mitochondrial adaptations compared with MICT, however the effect of training intensity on other peripheral adaptations such as capillarization, blood flow distribution, and muscle fiber shift, remain unclear.

Influence of Interval Duration and Protocol Volume on Physiological Adaptations

Currently, there is no consensus on the optimal HIIT protocol. Moreover, the effectiveness of HIIT protocols may vary according to the physiological adaptation of interest. HIIT protocols have previously been classified by interval duration as short-duration (≤1 min), medium-duration (1–3 min), or long-duration (≥3 min) (136, 137). Furthermore, high-volume HIIT has been defined as protocols that accumulate ≥15 min of high intensity effort per session (138). The Norwegian model (110) involving 4 × 4 min high intensity intervals (85–95 %HRpeak) separated by 3 min active recovery intervals, is an example of a long-duration, high-volume HIIT protocol, that has been studied extensively in populations with CAD and HF. Two meta-analyses in healthy populations suggest that longer interval durations increase VO_2peak to a greater extent than short duration intervals (139, 140). This may be related to greater improvements in central adaptations with longer duration intervals. This is supported by Matsuo et al. (116), who compared SIT (7 × 30 s intervals; 100 kcal), HIIT (3 × 3 min intervals; 180 kcal) and MICT (40 min; 360 kcal), and found the greatest increases in stroke volume, LV mass, and VO_2peak in the HIIT group, followed by the SIT group. Therefore, exercise intensity is important, but also time to reach and maintain an elevated cardiac filling (which can take 1–4 min in athletes) is believed to be necessary for improving maximal cardiac function (41). However, in the meta-analysis by Pattyn et al. in patients with CAD and HF (52), subgroup analyses revealed no differences in VO_2peak improvement based on the duration of the HIIT intervals. Instead, intensity of the HIIT intervals appeared more important, with numerically larger increases in VO_2peak with HIIT intervals at a very hard near-maximal effort (+1.5 mL/kg/min) compared with HIIT intervals at a vigorous effort (+1.1 mL/kg/min) (52). Moreover, HIIT protocols with greater total energy expenditure also produced greater gains in VO_2peak (52). This is supported by others, in that high-volume HIIT protocols appear to elicit the greatest increases in VO_2peak (138, 140) and vascular function (94).

Practical Application and Progression Models for HIIT in CR Programs

Safety Considerations

While HIIT provides greater improvements in VO_2peak, there remains a concern regarding its safety in cardiac populations (91). A scientific report from the American Heart Association (AHA) (141), outlined that vigorous exercise can acutely and transiently increase risk of sudden cardiac death and acute myocardial infarction in patients with atherosclerotic disease. However, this report and others have highlighted that incidence of these events is greatest in adults who are the least active (141, 142). For deconditioned patients, many of their daily living activities can fall into the category of vigorous intensity (143). Concerns around safety should take this into account, as including HIIT with appropriate progression may expose patients to vigorous efforts in a safer and more controlled manner. The most recent systematic review and meta-analysis on safety of HIIT in patients with CVD, found that HIIT showed a low rate of major adverse events for patients with CAD and HF when applied in CR settings (144). As all studies within the review had included baseline exercise testing, this was a recommendation from the authors prior to HIIT (144). However, maximal exercise testing is not routinely conducted in many CR settings, although guidelines in North America and Europe do recommend electrocardiographic exercise testing as standard procedure (14). The FITR Heart Study medically excluded 3 % of participants following baseline exercise testing, however the need for further coronary intervention was very low (1 %) (36). The AHA report (141), also outlines that appropriate screening and exclusion of high-risk patients from vigorous activities, can help to minimize the incidence of CV events. To assist clinicians in safely implementing HIIT without maximal exercise testing, guidelines have been published on screening and monitoring for HIIT in clinical populations (26). For example, three studies have reported a hypotensive event during HIIT (36, 88, 145). Therefore, in patients taking anti-hypertensive medication, a gradual and extended cool-down is recommended, particularly if medications have been recently modified (26). Given the higher risk of CV events with vigorous activity in adults who are less physically fit and active (141, 142), starting patients with a lead-in period of MICT is a sensible approach to ensure proper education on exercise training, assess exercise response, improve exercise tolerance, and minimize musculoskeletal injuries, particularly for patients who are unaccustomed to vigorous exercise (144). Furthermore, progressively increasing interval duration and time spent at a vigorous intensity (see practical applications section), may improve safety and exercise tolerance. Recent guidelines from the European Society of Cardiology (146) outline that high intensity exercise is appropriate for low risk revascularized patients with CAD, if they are asymptomatic and stable, and without residual high risk CAD lesions or exercise-induced arrhythmias. For patients with HF (reduced and preserved ejection fraction), high intensity exercise can also be prescribed for patients who are stable and without exercise-induced arrhythmias (146). Further studies are required to determine whether high intensity exercise is safe in higher risk patients with CAD or HF.

Intensity Prescription of HIIT

As outlined earlier in this review, all methods of exercise prescription have their advantages and limitations in patients with CVD and HF. For this reason, we recommend using both objective and subjective measures to prescribe exercise intensity for HIIT. The multicenter SAINTEX-CAD study relied only on objective measures of intensity for HIIT prescription, and subsequently found and acknowledged that when prescribing HIIT "it is necessary to adjust the objectively defined target HR zones and workloads according to the patient's subjective feelings." Furthermore, the SAINTEX-CAD study (84) and Pattyn et al. (52) have found significant increases in HRpeak over 12-weeks of training. This suggests that target HR zones may need to be adapted over the training period, either by repeating a maximal exercise test, or using subjective measures of intensity to titrate the workload accordingly. Patients may experience the same external training load (e.g., %HRpeak) differently depending on their individual "internal" metabolic responses to changes in exercise intensity (e.g., lactate accumulation) (147). Therefore, subjective measures are important to consider, and RPE has been shown to be a good indicator of internal training load (37). Currently the most common methods for prescribing HIIT that are also practical for clinical settings, are %HRpeak and RPE. For shorter duration intervals (<2 min), %HRpeak may underestimate the training stimulus due to insufficient time for HR to rise and HR lag compared with VO_2 response (41, 53), particularly in patients with HF or chronotropic incompetence. For long-duration HIIT, a framework for clinicians on using a combination of %HRpeak and RPE for HIIT prescription has previously been outlined by Taylor et al. (26). This framework involves using a maximally-derived or estimated HRpeak to determine a training target of 85–95 %HRpeak, in combination with a validation session with RPE of 15–18 by the patient, or observer (clinician supervising the exercise) if a patient has difficulty reporting an accurate RPE. Although it is practically attractive for clinicians to solely use RPE for HIIT prescription, Aamot et al. (148) found that using an RPE of 17 (very hard) alone for HIIT prescription, results in a lower mean training intensity (82 %HRpeak) than a target range of 85–95 %HRpeak. Therefore, HR monitoring in combination with RPE during HIIT may result in greater adherence to exercise intensity targets that are optimal for HIIT (85–95 %HRpeak).

Incorporating HIIT Into the Optimal Exercise Dose

Exercise volume, or "dose" encompasses both exercise intensity and duration of exercise (21). According to current PA guidelines from the World Health Organization (149) and US Department of Health (150), it is recommended that adults (even those with chronic health conditions) should accumulate 150–300 min/week of moderate intensity exercise, or 75–150 min/week of vigorous intensity exercise, or an equivalent combination of moderate and vigorous exercise. In the context of high-volume HIIT protocols that typically involve ∼16 min/session of high intensity effort and 10–15 min/session of moderate intensity effort, three sessions/week of high-volume HIIT would provide ∼48 min/week of vigorous exercise and ∼45 min/week of moderate exercise. While this may approach the minimum level of the PA recommendations, guidelines advocate for achieving more than the minimum level of PA to sustain optimal health (149, 150). Moreover, it is recommended that patients undergoing CR, progress to an optimal weekly exercise dose equivalent to 1,500 kcal/week (151, 152). For example, a high-volume HIIT protocol in patients with CAD measured energy expenditure to be ∼50L O_2/session (42) [equating to ∼250 kcal/session with ACSM estimation of 1L VO_2 = 5 kcal (21)]. Therefore, three sessions/week would equate to half the weekly exercise dose that patients undergoing CR should progress to (1,500 kcal/week) (151, 152). To extend the volume of training beyond the minimum level of PA recommendations and progress to 1,500 kcal/week, while also allowing for variety of exercise training, HIIT can be prescribed as an adjunct rather than alternative to MICT. For example, HIIT could be prescribed as 3 sessions/week in combination with 2–3 sessions/week of MICT and/or resistance training. Alternating days of HIIT and MICT training may also aid in recovery from HIIT sessions while reducing the potential for musculoskeletal discomfort.

Exercise volume can also be quantified as MET-min per week, which is calculated as intensity (in METs) multiplied by the number of minutes at that intensity, accumulated over a week. Current PA guidelines recommend 500–1,000 MET-min per week from moderate-vigorous activities (153). According to ACSM (49), average METs for moderate intensity exercise ranges from 3.0 to 5.9 METs, vigorous intensity exercise ranges from 6.0 to 8.7 METs, and near-maximal intensity exercise is ≥ 8.8 METs, although these MET ranges can vary according to age. For use in clinical practice, METs can be estimated from treadmill and cycle workload equations (21, 154, 155), a list of PA intensities (156), and/or some commercial exercise equipment can provide an estimate of METs.

In addition to energy expenditure, methods have been explored that consider individual "internal" training responses to quantify and monitor training dose (147). For example, the training impulse (TRIMP) is calculated by multiplication of (1) the duration of a specific training session, (2) the average change in HR (i.e., HRexercise–HRrest/HRmax–HRrest) during the training session, and (3) an individual weighting factor to reflect metabolic effort (157). This weighting factor is calculated from a maximal exercise test as the best-fitting exponential line from a plot of blood lactate concentration against fractional elevation in HR (157). Given the potential complexities of this method in a clinical setting (i.e., availability of maximal exercise testing, blood lactate measurement, and limitations with HRmax), a session-RPE method (i.e., RPE representative of the overall session multiplied by session duration), has been validated in patients with HF as an alternative to TRIMP for monitoring training dose (37). However, further research is needed to determine the optimal weekly session-RPE for CR programs.

Interval Duration and Progression of HIIT

Although high-volume HIIT with longer-duration intervals may increase exercise dose and provide superior improvements in central adaptations, vascular adaptations, and VO_2peak, sustaining high intensity of exercise for longer than 1–2 min may be challenging for some patients commencing a CR program. In particular, patients who are exercise naïve (137) and/or have a high degree of exercise intolerance (from skeletal muscle

dysfunction, respiratory limitations, reduced cardiac reserve, or a combination of these factors) (102), would benefit from a more gradual introduction to HIIT. Primary components of exercise prescription defined by ACSM include frequency, intensity, time, type, volume, and progression (FITT-VP) (21). Progression can often be a difficult component of exercise prescription for clinicians to master, but essential to optimize gains in VO_2peak and minimize adverse complications (151). In athletic and healthy populations progression has traditionally involved the training principles of progressive overload, specificity, and periodization (136). It seems appropriate that throughout a CR program, patients may undergo progression from short-duration intervals, to medium-duration intervals, and finally to long-duration intervals as training-induced physiological adaptations occur and exercise tolerance improves (137, 158). Overload is defined as "an exercise dose which is above and beyond the accustomed amount of exercise for a given individual" (151). For aerobic training, it is generally recommended to just increase one

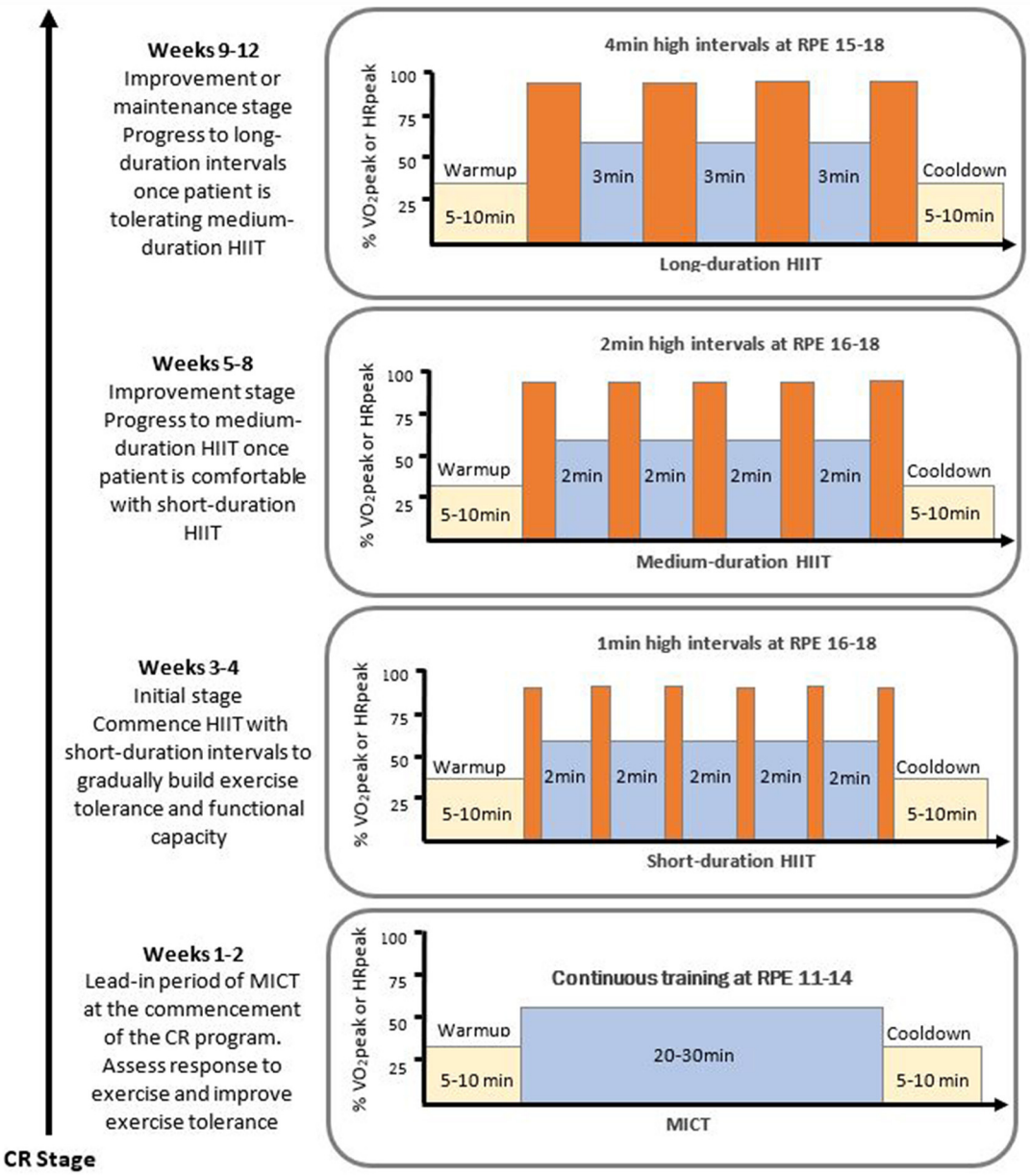


FIGURE 2 | Example of a HIIT progression model within a cardiac rehabilitation program. Exercise intensity remains constant for each HIIT protocol with high intensity intervals eliciting 85-95 %HRpeak and RPE 15-18, and the low intensity intervals involving recovery at 50-75 %HRpeak or RPE 11-14. CR, cardiac rehabilitation; HIIT, high intensity interval training; HRpeak, peak heart rate; MICT, moderate intensity continuous training; RPE, rating of perceived exertion on 6-20 Borg scale; VO_2peak, peak oxygen consumption. This figure has been adapted from the previously published work of (158); with permission of Mayo Foundation for Medical Education and Research, all rights reserved.

component of frequency, intensity, or duration at a time (151). As suggested by Wewege et al. (144), commencing a CR program with a "lead-in period" of MICT seems appropriate before commencing HIIT. This may allow for a graduated approach to evaluate a patient's exercise response, improve exercise tolerance, and aid in minimizing adverse events and musculoskeletal injuries (144). Furthermore, in terms of progression, it is generally recommended in cardiac patients that "duration and frequency of exercise should be up-titrated before intensity is increased" (to ≥30 min/session, 4 days/week) (159, 160). Once patients are tolerating 30 min of MICT, intensity could then be progressed to include short-duration HIIT, which may provide a greater stimulus than MICT for improving mitochondrial volume and oxidative capacity (50). Adaptations to mitochondrial content have been shown to occur at a rapid rate, with as little as 6 sessions of HIIT in healthy populations (126). Further progressions in interval duration from medium-duration to long-duration could then be made throughout the CR program, to further improvements in central adaptations (116), vascular function (94), and VO_2peak (138, 140). Another option for progression is to introduce HIIT once/week initially and then progress to 2–3 sessions/week.

HIIT Progression Model Example

In **Figure 2** we provide an example of how HIIT commencement and progression could occur during a CR program. Following a 2-week lead-in period of MICT, patients with low functional capacity [<5 metabolic equivalent (METs)] (161) or in the initial stage of HIIT, can commence a short-duration HIIT protocol (e.g., 1 min HIIT interval every 3–4 min of MICT), with progression to reduce the recovery interval timing to 2 min. As patients understanding of exercise training and comfort level with the available training modalities increases to an acceptable level, further progressions in interval duration to medium-duration intervals could be prescribed (e.g., 2–3 min HIIT with 2 min recovery). Initially, clinicians may want to keep the total time at high intensity constant (e.g., from 6 × 1 min HIIT to 3 × 2 min HIIT), and then gradually progress the number of intervals to 5 × 2 min or 4 × 3 min over a number of weeks by just changing one prescription factor (interval frequency or duration) at a time. Once patients are comfortable with 4 × 3 min intervals, patients could be progressed to 4-min intervals with 3 min recovery for a high-volume HIIT protocol (e.g., 4 × 4 min) to further improvements in central adaptations (116), vascular function (94), and VO_2peak (138, 140). Once again, clinicians may want to initially keep the total time at high intensity constant (e.g., from 4 × 3 min HIIT to 3 × 4 min HIIT) and then progress the number of intervals to 4 × 4 min HIIT.

CONCLUSION

There is extensive evidence that higher intensity exercise contributes to greater improvements in VO_2peak than MICT or low intensity exercise, by increments that are known to be clinically meaningful. Higher intensity exercise also produces greater improvements in VO_2 at submaximal exercise, which is important for exercise tolerance and carrying out daily living activities. While short-duration HIIT protocols can be a potent stimulus for improving peripheral mitochondrial adaptations and providing similar VO_2peak improvements to MICT, longer-duration and higher-volume HIIT protocols seem to be superior for eliciting stroke volume and vascular adaptations, and greater VO_2peak improvements compared with MICT. Finally, rather than adopting a one-size fits all model for HIIT, gradual introduction and progression of HIIT in accordance with individual exercise experience and tolerance, may be optimal for reducing musculoskeletal discomfort, as well as maximizing safety, adherence, enjoyment, and physiological outcomes.

AUTHOR CONTRIBUTIONS

JLT, ARB, and TPO all contributed to the conception of the manuscript idea and design. JLT was responsible for composing the manuscript. ARB and TPO provided critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

Open access fees were funded by Department of Cardiovascular Medicine, Mayo Clinic.

REFERENCES

1. Hansen D, Abreu A, Ambrosetti M, Cornelissen V, Gevaert A, Kemps H, et al. Exercise intensity assessment and prescription in cardiovascular rehabilitation and beyond: why and how: a position statement from the secondary prevention and rehabilitation section of the european association of preventive cardiology. *Eur J Prev Cardiol.* (2021). 2:zwab007. doi: 10.1093/eurjpc/zwab007
2. Rauch B, Davos CH, Doherty P, Saure D, Metzendorf M-I, Salzwedel A, et al. The prognostic effect of cardiac rehabilitation in the era of acute revascularisation and statin therapy: a systematic review and meta-analysis of randomized and non-randomized studies - The Cardiac Rehabilitation Outcome Study (CROS). *Eur J Prev Cardiol.* (2016) 23:1914–39. doi: 10.1177/2047487316671181
3. Salzwedel A, Jensen K, Rauch B, Doherty P, Metzendorf MI, Hackbusch M, et al. Effectiveness of comprehensive cardiac rehabilitation in coronary artery disease patients treated according to contemporary evidence based medicine: update of the cardiac rehabilitation outcome study (CROS-II). *Eur J Prev Cardiol.* (2020) 27:1756–74. doi: 10.1177/2047487320905719
4. Heran BS, Chen JM, Ebrahim S, Moxham T, Oldridge N, Rees K, et al. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev.* (2011). 6:CD001800. doi: 10.1002/14651858.CD001800.pub2
5. Taylor RS, Brown A, Ebrahim S, Jolliffe J, Noorani H, Rees K, et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *Am J Med.* (2004) 116:682–92. doi: 10.1016/j.amjmed.2004.01.009
6. Long L, Mordi IR, Bridges C, Sagar VA, Davies EJ, Coats AJ, et al. Exercise-based cardiac rehabilitation for adults with heart failure. *Cochrane Database Syst Rev.* (2019) 1:Cd003331. doi: 10.1002/14651858.CD003331.pub5
7. West RR, Jones DA, Henderson AH. Rehabilitation after myocardial infarction trial (RAMIT): multi-centre randomised controlled trial of

comprehensive cardiac rehabilitation in patients following acute myocardial infarction. *Heart.* (2012) 98:637–44. doi: 10.1136/heartjnl-2011-300302
8. Anderson L, Oldridge N, Thompson DR, Zwisler A-D, Rees K, Martin N, et al. Exercise-based cardiac rehabilitation for coronary heart disease: cochrane systematic review and meta-analysis. *J Am Coll Cardiol.* (2016) 67:1–12. doi: 10.1016/j.jacc.2015.10.044
9. Powell R, McGregor G, Ennis S, Kimani PK, Underwood M. Is exercise-based cardiac rehabilitation effective? A systematic review and meta-analysis to re-examine the evidence. *BMJ Open.* (2018) 8:e019656. doi: 10.1136/bmjopen-2017-019656
10. Conraads VM, Denollet J, De Maeyer C, Van Craenenbroeck E, Verheyen J, Beckers P. Exercise training as an essential component of cardiac rehabilitation. *Heart.* (2012) 98:674. doi: 10.1136/heartjnl-2012-301912
11. Franklin BA. Multifactorial cardiac rehabilitation did not reduce mortality or morbidity after acute myocardial infarction. *Ann. Internal Med.* (2012) 157:JC1-11. doi: 10.7326/0003-4819-157-2-201207170-02011
12. Ingle L, Carroll S. Cardiac rehabilitation and exercise training. *Heart.* (2013) 99:1298. doi: 10.1136/heartjnl-2013-304015
13. Nichols S, Taylor C, Goodman T, Page R, Kallvikbacka-Bennett A, Nation F, et al. Routine exercise-based cardiac rehabilitation does not increase aerobic fitness: a CARE CR study. *Int J Cardiol.* (2020) 305:25–34. doi: 10.1016/j.ijcard.2020.01.044
14. Price KJ, Gordon BA, Bird SR, Benson AC. A review of guidelines for cardiac rehabilitation exercise programmes: is there an international consensus? *Eur J Prev Cardiol.* (2016) 23:1715–33.
15. Vromen T, Spee RF, Kraal JJ, Peek N, van Engen-Verheul MM, Kraaijenhagen RA, et al. Exercise training programs in Dutch cardiac rehabilitation centres. *Neth Heart J.* (2013) 21:138–43. doi: 10.1007/s12471-013-0374-2
16. Korenfeld Y, Mendoza-Bastidas C, Saavedra L, Montero-Gómez A, Perez-Terzic C, Thomas RJ, et al. Current status of cardiac rehabilitation in Latin America and the Caribbean. *Am Heart J.* (2009) 158:480–7. doi: 10.1016/j.ahj.2009.06.020
17. Hannan AL, Hing W, Climstein M, Coombes JS, Furness J, Jayasinghe R, et al. Australian cardiac rehabilitation exercise parameter characteristics and perceptions of high-intensity interval training: a cross-sectional survey. *Open Access J Sports Med.* (2018) 9:79–89. doi: 10.2147/OAJSM.S160306
18. Borghi-Silva A, Mendes RG, Trimer R, Cipriano G. Current trends in reducing cardiovascular disease risk factors from around the world: focus on cardiac rehabilitation in Brazil. *Prog Cardiovasc Dis.* (2014) 56:536–42. doi: 10.1016/j.pcad.2013.09.008
19. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc.* (1982) 14:377–81.
20. Reed JL, Pipe AL. The talk test: a useful tool for prescribing and monitoring exercise intensity. *Curr Opin Cardiol.* (2014) 29:475–80. doi: 10.1097/HCO.0000000000000097
21. American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription, 10th Edn*. Philadelphia, PA: Lippincott Williams & Wilkins (2018).
22. Carvalho VO, Mezzani A. Aerobic exercise training intensity in patients with chronic heart failure: principles of assessment and prescription. *Eur J Cardiovasc Prev Rehabil.* (2011) 18:5–14. doi: 10.1097/HJR.0b013e32833a9c63
23. Casillas J-M, Gudjoncik A, Gremeaux V, Aulagne J, Besson D, Laroche D. Assessment tools for personalizing training intensity during cardiac rehabilitation: Literature review and practical proposals. *Ann Phys Rehabil Med.* (2017) 60:43–9. doi: 10.1016/j.rehab.2016.01.011
24. Reed JL, Pipe AL. Practical approaches to prescribing physical activity and monitoring exercise intensity. *Can J Cardiol.* (2016) 32:514–22. doi: 10.1016/j.cjca.2015.12.024
25. Reeves RG, Gupta ES, Forman ED. Evolving role of exercise testing in contemporary cardiac rehabilitation. *J Cardiopulm Rehabil Prev.* (2016) 36:309–19. doi: 10.1097/HCR.0000000000000176
26. Taylor JL, Holland DJ, Spathis JG, Beetham KS, Wisløff U, Keating SE, et al. Guidelines for the delivery and monitoring of high intensity interval training in clinical populations. *Prog Cardiovasc Dis.* (2019) 62:140–6. doi: 10.1016/j.pcad.2019.01.004
27. Balady Gary J, Arena R, Sietsema K, Myers J, Coke L, Fletcher Gerald F, et al. Clinician's guide to cardiopulmonary exercise testing in adults. *Circulation.* (2010) 122:191–225. doi: 10.1161/CIR.0b013e3181e52e69
28. Mezzani A, Hamm LF, Jones AM, McBride PE, Moholdt T, Stone JA, et al. Aerobic exercise intensity assessment and prescription in cardiac rehabilitation: a joint position statement of the European Association for Cardiovascular Prevention and Rehabilitation, the American Association of Cardiovascular and Pulmonary Rehabilitation and the Canadian Association of Cardiac Rehabilitation. *Eur J Prev Cardiol.* (2013) 20:442–67. doi: 10.1177/2047487312460484
29. Bensimhon DR, Leifer ES, Ellis SJ, Fleg JL, Keteyian SJ, Piña IL, et al. Reproducibility of peak oxygen uptake and other cardiopulmonary exercise testing parameters in patients with heart failure (from the Heart Failure and A Controlled Trial Investigating Outcomes of exercise traiNing). *Am J Cardiol.* (2008) 102:712–7. doi: 10.1016/j.amjcard.2008.04.047
30. Myers J, Goldsmith RL, Keteyian SJ, Brawner CA, Brazil DA, Aldred H, et al. The ventilatory anaerobic threshold in heart failure: a multicenter evaluation of reliability. *J Card Fail.* (2010) 16:76–83. doi: 10.1016/j.cardfail.2009.08.009
31. Whipp BJ. Dynamics of pulmonary gas exchange. *Circulation.* (1987) 76(6 Pt 2):Vi18–28.
32. Chatterjee NA, Murphy RM, Malhotra R, Dhakal BP, Baggish AL, Pappagianopoulos PP, et al. Prolonged mean VO_2 response time in systolic heart failure. *Circ Heart Fail.* (2013) 6:499–507. doi: 10.1161/CIRCHEARTFAILURE.112.000157
33. Hearon Jr CM, Sarma S, Dias KA, Hieda M, Levine BD. Impaired oxygen uptake kinetics in heart failure with preserved ejection fraction. *Heart.* (2019) 105:1552. doi: 10.1136/heartjnl-2019-314797
34. Koike A, Yajima T, Adachi H, Shimizu N, Kano H, Sugimoto K, et al. Evaluation of exercise capacity using submaximal exercise at a constant work rate in patients with cardiovascular disease. *Circulation.* (1995) 91:1719–24. doi: 10.1161/01.CIR.91.6.1719
35. Ilarraza H, Myers J, Kottman W, Rickli H, Dubach P. An evaluation of training responses using self-regulation in a residential rehabilitation program. *J Cardiopulm Rehabil.* (2004) 24:27–33. doi: 10.1097/00008483-200401000-00006
36. Taylor JL, Holland DJ, Keating SE, Leveritt MD, Gomersall SR, Rowlands AV, et al. Short-term and long-term feasibility, safety, and efficacy of high-intensity interval training in cardiac rehabilitation: the FITR heart study randomized controlled trial. *JAMA Cardiol.* (2020) 5:1–9. doi: 10.1001/jamacardio.2020.3511
37. Iellamo F, Manzi V, Caminiti G, Vitale C, Massaro M, Cerrito A, et al. Validation of rate of perceived exertion-based exercise training in patients with heart failure: insights from autonomic nervous system adaptations. *Int J Cardiol.* (2014) 176:394–8. doi: 10.1016/j.ijcard.2014.07.076
38. Levinger I, Bronks R, Cody DV, Linton I, Davie A. Perceived exertion as an exercise intensity indicator in chronic heart failure patients on Beta-blockers. *J Sports Sci Med.* (2004) 3(YISI 1):23–27.
39. Buckley JP, Sim J, Eston RG. Reproducibility of ratings of perceived exertion soon after myocardial infarction: responses in the stress-testing clinic and the rehabilitation gymnasium. *Ergonomics.* (2009) 52:421–7. doi: 10.1080/00140130802707691
40. Gondoni LA, Nibbio F, Caetani G, Augello G, Titon AM. What are we measuring? Considerations on subjective ratings of perceived exertion in obese patients for exercise prescription in cardiac rehabilitation programs. *Int J Cardiol.* (2010) 140:236–8. doi: 10.1016/j.ijcard.2008.11.068
41. Buchheit M, Laursen PB. High-intensity interval training, solutions to the programming puzzle: Part I: cardiopulmonary emphasis. *Sports medicine (Auckland, NZ).* (2013) 43:313–38. doi: 10.1007/s40279-013-0029-x
42. Rognmo O, Hetland E, Helgerud J, Hoff J, Slordahl SA. High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease. *Eur J Cardiovasc Prev Rehabil.* (2004) 11:216–22. doi: 10.1097/01.hjr.0000131677.96762.0c
43. Tjønna AE, Lee SJ, Rognmo Ø, Stølen TO, Bye A, Haram PM, et al. Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study. *Circulation.* (2008) 118:346–54. doi: 10.1161/CIRCULATIONAHA.108.772822
44. Wisløff U, Støylen A, Loennechen JP, Bruvold M, Rognmo Ø, Haram PM, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure

patients: a randomized study. *Circulation.* (2007) 115:3086–94. doi: 10.1161/CIRCULATIONAHA.106.675041
45. Casillas JM, Joussain C, Gremeaux V, Hannequin A, Rapin A, Laurent Y, et al. A study of the 200-metre fast walk test as a possible new assessment tool to predict maximal heart rate and define target heart rate for exercise training of coronary heart disease patients. *Clin Rehabil.* (2015) 29:175–83. doi: 10.1177/0269215514540922
46. Keteyian SJ, Kitzman D, Zannad F, Landzberg J, Arnold JM, Brubaker P, et al. Predicting maximal HR in heart failure patients on β-blockade therapy. *Med Sci Sports Exerc.* (2012) 44:371–76. doi: 10.1249/MSS.0b013e318234316f
47. Nes BM, Janszky I, Wisloff U, Stoylen A, Karlsen T. Age-predicted maximal heart rate in healthy subjects: the HUNT fitness study. *Scand J Med Sci Sports.* (2013) 23:697–704. doi: 10.1111/j.1600-0838.2012.01445.x
48. Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. *J Am Coll Cardiol.* (2001) 37:153–6. doi: 10.1016/S0735-1097(00)01054-8
49. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc.* (2011) 43:1334–59. doi: 10.1249/MSS.0b013e318213fefb
50. Gibala MJ. Physiological basis of interval training for performance enhancement. *Exp Physiol.* (2020) 1–4. doi: 10.1113/ep088190
51. Weston KS, Wisløff U, Coombes JS. High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis. *Br J Sports Med.* (2014) 48:1227. doi: 10.1136/bjsports-2013-092576
52. Pattyn N, Beulque R, Cornelissen V. Aerobic Interval vs. Continuous training in patients with coronary artery disease or heart failure: an updated systematic review and meta-analysis with a focus on secondary outcomes. *Sports Med.* (2018) 48:1189–205. doi: 10.1007/s40279-018-0885-5
53. Taylor JL, Holland DJ, Keating SE, Bonikowske AR, Coombes JS. Adherence to high-intensity interval training in cardiac rehabilitation: a REVIEW AND RECOMMENDATIONS. *J Cardiopulm Rehabil Prev.* (2021) 41:61–77. doi: 10.1097/HCR.0000000000000565
54. Lee LS, Tsai M-C, Brooks D, Oh PI. Randomised controlled trial in women with coronary artery disease investigating the effects of aerobic interval training versus moderate intensity continuous exercise in cardiac rehabilitation: CAT versus MICE study. *BMJ Open Sport Exerc Med.* (2019) 5:e000589. doi: 10.1136/bmjsem-2019-000589
55. Lee LS, Tsai M-C, Oh PI, Brooks D. The Effectiveness of Progressive Aerobic Interval Training in Cardiac Rehabilitation. *Med Sci Sports Exerc.* (2018) 50:881–8. doi: 10.1249/MSS.0000000000001526
56. Tschentscher M, Eichinger J, Egger A, Droese S, Schonfelder M, Niebauer J. High-intensity interval training is not superior to other forms of endurance training during cardiac rehabilitation. *Eur J Prev Cardiol.* (2016) 23:14–20. doi: 10.1177/2047487314560100
57. Jaureguizar KV, Vicente-Campos D, Bautista LR, de la Pena CH, Gomez MJ, Rueda MJ, et al. Effect of high-intensity interval versus continuous exercise training on functional capacity and quality of life in patients with coronary artery disease: a RANDOMIZED CLINICAL TRIAL. *J Cardiopulm Rehabil Prev.* (2016) 36:96–105. doi: 10.1097/HCR.0000000000000156
58. Freyssin C, Verkindt C, Prieur F, Benaich P, Maunier S, Blanc P. Cardiac rehabilitation in chronic heart failure: effect of an 8-week, high-intensity interval training versus continuous training. *Arch Phys Med Rehabil.* (2012) 93:1359–64. doi: 10.1016/j.apmr.2012.03.007
59. Aksoy S, Findikoglu G, Ardic F, Rota S, Dursunoglu D. Effect of 10-week supervised moderate-intensity intermittent vs. Continuous aerobic exercise programs on vascular adhesion molecules in patients with heart failure. *Am J Phys Med Rehabil.* (2015) 94(10 Suppl. 1):898–911. doi: 10.1097/PHM.0000000000000306
60. Wisløff U, Nilsen TI, Drøyvold WB, Mørkved S, Slørdahl SA, Vatten LJ. A single weekly bout of exercise may reduce cardiovascular mortality: how little pain for cardiac gain? 'The HUNT study, Norway'. *Eur J Cardiovasc Prev Rehabil.* (2006). 13:798–804. doi: 10.1097/01.hjr.0000216548.84560.ac
61. Wen CP, Wai JP, Tsai MK, Yang YC, Cheng TY, Lee MC, et al. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. *Lancet.* (2011) 378:1244–53. doi: 10.1016/S0140-6736(11)60749-6
62. Gebel K, Ding D, Chey T, Stamatakis E, Brown WJ, Bauman AE. Effect of moderate to vigorous physical activity on all-cause mortality in middle-aged and older australians. *JAMA Intern Med.* (2015) 175:970–7. doi: 10.1001/jamainternmed.2015.0541
63. Wang Y, Nie J, Ferrari G, Rey-Lopez JP, Rezende LFM. Association of physical activity intensity with mortality: a national cohort study of 403 681 US adults. *JAMA Internal Med.* (2021) 181:203–11. doi: 10.1001/jamainternmed.2020.6331
64. Tanasescu M, Leitzmann MF, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Exercise type and intensity in relation to coronary heart disease in men. *JAMA.* (2002) 288:1994–2000. doi: 10.1001/jama.288.16.1994
65. Lee IM, Sesso HD, Oguma Y, Paffenbarger RS, Jr. Relative intensity of physical activity and risk of coronary heart disease. *Circulation.* (2003). 107:1110–6. doi: 10.1161/01.cir.0000052626.63602.58
66. Manson JE, Hu FB, Rich-Edwards JW, Colditz GA, Stampfer MJ, Willett WC, et al. A prospective study of walking as compared with vigorous exercise in the prevention of coronary heart disease in women. *N Engl J Med.* (1999) 341:650–8. doi: 10.1056/NEJM199908263410904
67. Lee IM, Rexrode KM, Cook NR, Manson JE, Buring JE. Physical activity and coronary heart disease in womenis "no pain, no gain" passé? *JAMA.* (2001) 285:1447–54. doi: 10.1001/jama.285.11.1447
68. Ross R, Blair SN, Arena R, Church TS, Despres JP, Franklin BA, et al. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the american heart association. *Circulation.* (2016) 134:e653–99. doi: 10.1161/CIR.0000000000000461
69. Mikkelsen N, Cadarso-Suarez C, Lado-Baleato O, Diaz-Louzao C, Gil CP, Reeh J, et al. Improvement in VO_2peak predicts readmissions for cardiovascular disease and mortality in patients undergoing cardiac rehabilitation. *Eur J Prev Cardiol.* (2020) 27:811–9. doi: 10.1177/2047487319887835
70. Kavanagh T, Mertens DJ, Hamm LF, Beyene J, Kennedy J, Corey P, et al. Prediction of long-term prognosis in 12 169 men referred for cardiac rehabilitation. *Circulation.* (2002) 106:666. doi: 10.1161/01.CIR.0000024413.15949.ED
71. Swank AM, Horton J, Fleg JL, Fonarow GC, Keteyian S, Goldberg L, et al. Modest increase in peak VO_2 is related to better clinical outcomes in chronic heart failure patients: results from heart failure and a controlled trial to investigate outcomes of exercise training. *Circ Heart Fail.* (2012) 5:579–85. doi: 10.1161/CIRCHEARTFAILURE.111.965186
72. Keteyian SJ. Peak aerobic capacity predicts prognosis in patients with coronary heart disease. *Am Heart J.* (2008) 156:292–300. doi: 10.1016/j.ahj.2008.03.017
73. Uddin J, Zwisler AD, Lewinter C, Moniruzzaman M, Lund K, Tang LH, et al. Predictors of exercise capacity following exercise-based rehabilitation in patients with coronary heart disease and heart failure: a meta-regression analysis. *Eur J Prev Cardiol.* (2016) 23:683–93. doi: 10.1177/2047487315604311
74. Mitchell BL, Lock MJ, Davison K, Parfitt G, Buckley JP, Eston RG. What is the effect of aerobic exercise intensity on cardiorespiratory fitness in those undergoing cardiac rehabilitation? A systematic review with meta-analysis. *Br J Sports Med.* (2019) 53:1341. doi: 10.1136/bjsports-2018-099153
75. Vromen T, Kraal JJ, Kuiper J, Spee RF, Peek N, Kemps HM. The influence of training characteristics on the effect of aerobic exercise training in patients with chronic heart failure: a meta-regression analysis. *Int J Cardiol.* (2016) 208:120–7. doi: 10.1016/j.ijcard.2016.01.207
76. Ismail H, McFarlane JR, Dieberg G, Smart NA. Exercise training program characteristics and magnitude of change in functional capacity of heart failure patients. *Int J Cardiol.* (2014) 171:62–5. doi: 10.1016/j.ijcard.2013.11.045
77. Sandercock G, Hurtado V, Cardoso F. Changes in cardiorespiratory fitness in cardiac rehabilitation patients: a meta-analysis. *Int J Cardiol.* (2013) 167:894–902. doi: 10.1016/j.ijcard.2011.11.068
78. Almody M, Ingle L, Sandercock GR. Effects of exercise-based cardiac rehabilitation on cardiorespiratory fitness: a meta-analysis of UK studies. *Int J Cardiol.* (2016) 221:644–51. doi: 10.1016/j.ijcard.2016.06.101

79. Liou K, Ho S, Fildes J, Ooi S-Y. High intensity interval versus moderate intensity continuous training in patients with coronary artery disease: a meta-analysis of physiological and clinical parameters. *Heart Lung Circ.* (2016) 25:166. doi: 10.1016/j.hlc.2015.06.828
80. Elliott AD, Rajopadhyaya K, Bentley DJ, Beltrame JF, Aromataris EC. Interval training versus continuous exercise in patients with coronary artery disease: a meta-analysis. *Heart Lung Circ.* (2015) 24:149–57. doi: 10.1016/j.hlc.2014.09.001
81. Pattyn N, Coeckelberghs E, Buys R, Cornelissen V, Vanhees L. Aerobic interval training vs. Moderate continuous training in coronary artery disease patients: a systematic review and meta-analysis. *Sports Med.* (2014) 44:687–700. doi: 10.1007/s40279-014-0158-x
82. Xie B, Yan X, Cai X, Li J. Effects of high-intensity interval training on aerobic capacity in cardiac patients: a systematic review with meta-analysis. *Biomed Res Int.* (2017) 2017:5420840. doi: 10.1155/2017/5420840
83. Way KL, Vidal-Almela S, Moholdt T, Currie KD, Aksetøy IA, Boidin M, et al. Sex differences in cardiometabolic health indicators after HIIT in patients with coronary artery disease. *Med Sci Sports Exerc.* (2021) 53:1345–1355. doi: 10.1249/MSS.0000000000002596
84. Conraads VM, Pattyn N, De Maeyer C, Beckers PJ, Coeckelberghs E, Cornelissen VA, et al. Aerobic interval training and continuous training equally improve aerobic exercise capacity in patients with coronary artery disease: the SAINTEX-CAD study. *Int J Cardiol.* (2015) 179:203–10. doi: 10.1016/j.ijcard.2014.10.155
85. Moholdt TT, Amundsen BH, Rustad LA, Wahba A, Løvø KT, Gullikstad LR, et al. Aerobic interval training versus continuous moderate exercise after coronary artery bypass surgery: a randomized study of cardiovascular effects and quality of life. *Am Heart J.* (2009) 158:1031–7. doi: 10.1016/j.ahj.2009.10.003
86. Haykowsky MJ, Timmons MP, Kruger C, McNeely M, Taylor DA, Clark AM. Meta-analysis of aerobic interval training on exercise capacity and systolic function in patients with heart failure and reduced ejection fractions. *Am J Cardiol.* (2013) 111:1466–9. doi: 10.1016/j.amjcard.2013.01.303
87. Smart NA, Dieberg G, Giallauria F. Intermittent versus continuous exercise training in chronic heart failure: a meta-analysis. *Int J Cardiol.* (2013) 166:352–8. doi: 10.1016/j.ijcard.2011.10.075
88. Ellingsen Ø, Halle M, Conraads VM, Støylen A, Dalen H, Delagardelle C, et al. High intensity interval training in heart failure patients with reduced ejection fraction. *Circulation.* (2017) 135:839–49. doi: 10.1161/CIRCULATIONAHA.116.022924
89. Mueller S, Winzer EB, Duvinage A, Gevaert AB, Edelmann F, Haller B, et al. Effect of high-intensity interval training, moderate continuous training, or guideline-based physical activity advice on peak oxygen consumption in patients with heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA.* (2021) 325:542–51. doi: 10.1001/jama.2020.26812
90. Jensen BE, Fletcher BJ, Rupp JC, Fletcher GF, Lee JY, Oberman A. Training Level Comparison Study: effect of high and low intensity exercise on ventilatory threshold in men with coronary artery disease. *J Cardiopulm Rehabil.* (1996) 16:227–32. doi: 10.1097/00008483-199607000-00003
91. Quindry JC, Franklin BA, Chapman M, Humphrey R, Mathis S. Benefits and risks of high-intensity interval training in patients with coronary artery disease. *Am J Cardiol.* (2019) 123:1370–7. doi: 10.1016/j.amjcard.2019.01.008
92. Molmen-Hansen HE, Stolen T, Tjonna AE, Aamot IL, Ekeberg IS, Tyldum GA, et al. Aerobic interval training reduces blood pressure and improves myocardial function in hypertensive patients. *Eur J Prev Cardiol.* (2012) 19:151–60. doi: 10.1177/1741826711400512
93. Iellamo F, Caminiti G, Sposato B, Vitale C, Massaro M, Rosano G, et al. Effect of High-Intensity interval training versus moderate continuous training on 24-h blood pressure profile and insulin resistance in patients with chronic heart failure. *Intern Emerg Med.* (2014) 9:547–52. doi: 10.1007/s11739-013-0980-4
94. Ramos JS, Dalleck LC, Tjonna AE, Beetham KS, Coombes JS. The impact of high-intensity interval training versus moderate-intensity continuous training on vascular function: a systematic review and meta-analysis. *Sports Med.* (2015) 45:679–92. doi: 10.1007/s40279-015-0321-z
95. Keating S, Johnson N, Mielke G, Coombes J. A systematic review and meta-analysis of interval training versus moderate-intensity continuous training on body adiposity. *Obesity Rev.* (2017) 18 943–64. doi: 10.1111/obr.12536
96. Dun Y, Thomas RJ, Medina-Inojosa JR, Squires RW, Huang H, Smith JR, et al. High-intensity interval training in cardiac rehabilitation: impact on fat mass in patients with myocardial infarction. *Mayo Clin Proc.* (2019) 94:1718–30. doi: 10.1016/j.mayocp.2019.04.033
97. Taylor JL, Holland DJ, Mielke GI, Bailey TG, Johnson NA, Leveritt MD, et al. Effect of high intensity interval training on visceral and liver fat in cardiac rehabilitation: a randomised controlled trial. *Obesity.* (2020) 28:1245–53. doi: 10.1002/oby.22833
98. Cornelis J, Beckers P, Taeymans J, Vrints C, Vissers D. Comparing exercise training modalities in heart failure: a systematic review and meta-analysis. *Int J Cardiol.* (2016) 221:867–76. doi: 10.1016/j.ijcard.2016.07.105
99. Pattyn N, Vanhees L, Cornelissen VA, Coeckelberghs E, De Maeyer C, Goetschalckx K, et al. The long-term effects of a randomized trial comparing aerobic interval versus continuous training in coronary artery disease patients: 1-year data from the SAINTEX-CAD study. *Eur J Prev Cardiol.* (2016) 23:1154–64. doi: 10.1177/2047487316631200
100. Taylor JL, Coombes JS, Holland DJ, Keating SE, Green DJ, Bailey TG. Short and long term effects of exercise intensity on conduit artery function in cardiac rehabilitation patients: (1642). May 30 2:00 PM - 2:15 PM. *Med Sci Sports Exerc.* (2019) 51:449. doi: 10.1249/01.mss.0000561843.86325.1
101. Taylor JL, Keating SE, Holland DJ, Finlayson G, King NA, Gomersall SR, et al. High intensity interval training does not result in short- or long-term dietary compensation in cardiac rehabilitation: results from the FITR heart study. *Appetite.* (2021) 158:105021. doi: 10.1016/j.appet.2020.105021
102. Del Buono MG, Arena R, Borlaug BA, Carbone S, Canada JM, Kirkman DL, et al. Exercise intolerance in patients with heart failure: JACC state-of-the-art review. *J Am Coll Cardiol.* (2019) 73:2209–25. doi: 10.1016/j.jacc.2019.01.072
103. Olson TP, Snyder EM, Johnson BD. Exercise-disordered breathing in chronic heart failure. *Exerc Sport Sci Rev.* (2006) 34:194–201. doi: 10.1249/01.jes.0000240022.30373.a2
104. Smith JR, Berg JD, Curry TB, Joyner MJ, Olson TP. Respiratory muscle work influences locomotor convective and diffusive oxygen transport in human heart failure during exercise. *Physiol Rep.* (2020) 8:e14484. doi: 10.14814/phy2.14484
105. Olson TP, Johnson BD, Borlaug BA. Impaired pulmonary diffusion in heart failure with preserved ejection fraction. *JACC Heart failure.* (2016) 4:490–8. doi: 10.1016/j.jchf.2016.03.001
106. Dempsey JA, Amann M, Romer LM, Miller JD. Respiratory system determinants of peripheral fatigue and endurance performance. *Med Sci Sports Exerc.* (2008) 40:457–61. doi: 10.1249/MSS.0b013e31815f8957
107. Tasoulis A, Papazachou O, Dimopoulos S, Gerovasili V, Karatzanos E, Kyprianou T, et al. Effects of interval exercise training on respiratory drive in patients with chronic heart failure. *Respir Med.* (2010) 104:1557–65. doi: 10.1016/j.rmed.2010.03.009
108. Dunham C, Harms CA. Effects of high-intensity interval training on pulmonary function. *Eur J Appl Physiol.* (2012) 112:3061–8. doi: 10.1007/s00421-011-2285-5
109. Guazzi M, Reina G, Tumminello G, Guazzi MD. Improvement of alveolar-capillary membrane diffusing capacity with exercise training in chronic heart failure. *J Appl Physiol.* (2004) 97:1866–73. doi: 10.1152/japplphysiol.00365.2004
110. Karlsen T, Aamot I-L, Haykowsky M, Rognmo Ø. High intensity interval training for maximizing health outcomes. *Prog Cardiovasc Dis.* (2017) 60:67–77. doi: 10.1016/j.pcad.2017.03.006
111. Lundby C, Montero D, Joyner M. Biology of VO(2) max: looking under the physiology lamp. *Acta Physiol (Oxf).* (2017) 220:218–28. doi: 10.1111/apha.12827
112. Levine BD.VO_2max: what do we know, and what do we still need to know? *J Physiol.* (2008). 586:25–34. doi: 10.1113/jphysiol.2007.147629
113. Hambrecht R, Gielen S, Linke A, Fiehn E, Yu J, Walther C, et al. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure: a randomized trial. *JAMA.* (2000) 283:3095–101. doi: 10.1001/jama.283.23.3095
114. Piña IL, Apstein CS, Balady GJ, Belardinelli R, Chaitman BR, Duscha BD, et al. Exercise and heart failure. *Circulation.* (2003) 107:1210–25. doi: 10.1161/01.CIR.0000055013.92097.40
115. Helgerud JAN, HØYdal K, Wang E, Karlsen T, Berg P, Bjerkaas M, et al. Aerobic high-intensity intervals improve VO_2max more

than moderate training. *Med Sci Sports Exerc.* (2007) 39:665–71. doi: 10.1249/mss.0b013e3180304570
116. Matsuo T, Saotome K, Seino S, Shimojo N, Matsushita A, Iemitsu M, et al. Effects of a low-volume aerobic-type interval exercise on VO_2max and cardiac mass. *Med Sci Sports Exerc.* (2014) 46:42–50. doi: 10.1249/MSS.0b013e3182a38da8
117. Fu TC, Yang NI, Wang CH, Cherng WJ, Chou SL, Pan TL, et al. Aerobic interval training elicits different hemodynamic adaptations between heart failure patients with preserved and reduced ejection fraction. *Am J Phys Med Rehabil.* (2016) 95:15–27. doi: 10.1097/PHM.0000000000000312
118. Iellamo F, Manzi V, Caminiti G, Vitale C, Castagna C, Massaro M, et al. Matched dose interval and continuous exercise training induce similar cardiorespiratory and metabolic adaptations in patients with heart failure. *Int J Cardiol.* (2013) 167:2561–5. doi: 10.1016/j.ijcard.2012.06.057
119. Green DJ, Hopman MT, Padilla J, Laughlin MH, Thijssen DH. Vascular adaptation to exercise in humans: role of hemodynamic stimuli. *Physiol Rev.* (2017) 97:495–528. doi: 10.1152/physrev.00014.2016
120. Anderson TJ, Uehata A, Gerhard MD, Meredith IT, Knab S, Delagrange D, et al. Close relation of endothelial function in the human coronary and peripheral circulations. *J Am Coll Cardiol.* (1995) 26:1235–41. doi: 10.1016/0735-1097(95)00327-4
121. Barnes JN, Schmidt JE, Nicholson WT, Joyner MJ. Cyclooxygenase inhibition abolishes age-related differences in cerebral vasodilator responses to hypercapnia. *J Appl Physiol (1985).* (2012) 112:1884–90. doi: 10.1152/japplphysiol.01270.2011
122. Calverley TA, Ogoh S, Marley CJ, Steggall M, Marchi N, Brassard P, et al. HIITing the brain with exercise; mechanisms, consequences and practical recommendations. *J Physiol.* (2020) 598:2513–30. doi: 10.1113/JP275021
123. Thijssen DHJ, Dawson EA, Black MA, Hopman MTE, Cable NT, Green DJ. Brachial artery blood flow responses to different modalities of lower limb exercise. *Med Sci Sports Exerc.* (2009) 41:1072–9. doi: 10.1249/MSS.0b013e3181923957
124. Haykowsky MJ, Brubaker PH, Stewart KP, Morgan TM, Eggebeen J, Kitzman DW. Effect of endurance training on the determinants of peak exercise oxygen consumption in elderly patients with stable compensated heart failure and preserved ejection fraction. *J Am Coll Cardiol.* (2012) 60:120–8. doi: 10.1016/j.jacc.2012.02.055
125. Lundby C, Jacobs RA. Adaptations of skeletal muscle mitochondria to exercise training. *Exp Physiol.* (2016) 101:17–22. doi: 10.1113/EP085319
126. MacInnis MJ, Gibala MJ. Physiological adaptations to interval training and the role of exercise intensity. *J Physiol.* (2017) 595:2915–30. doi: 10.1113/JP273196
127. Egan B, Zierath JR. Exercise metabolism and the molecular regulation of skeletal muscle adaptation. *Cell Metabolism.* (2013) 17:162–84. doi: 10.1016/j.cmet.2012.12.012
128. Joyner MJ, Coyle EF. Endurance exercise performance: the physiology of champions. *J Physiol.* (2008) 586:35–44. doi: 10.1113/jphysiol.2007.143834
129. Schjerve IE, Tyldum GA, Tjønna AE, Stølen T, Loennechen JP, Hansen HEM, et al. Both aerobic endurance and strength training programmes improve cardiovascular health in obese adults. *Clin Sci.* (2008) 115:283–93. doi: 10.1042/CS20070332
130. Gliemann L. Training for skeletal muscle capillarization: a Janus-faced role of exercise intensity? *Eur J Appl Physiol.* (2016) 116:1443–4. doi: 10.1007/s00421-016-3419-6
131. Daussin FN, Zoll J, Dufour SP, Ponsot E, Lonsdorfer-Wolf E, Doutreleau S, et al. Effect of interval versus continuous training on cardiorespiratory and mitochondrial functions: relationship to aerobic performance improvements in sedentary subjects. *Am J Physiol Regul Integr Compar Physiol.* (2008) 295:R264–72. doi: 10.1152/ajpregu.00875.2007
132. Hoier B, Passos M, Bangsbo J, Hellsten Y. Intense intermittent exercise provides weak stimulus for vascular endothelial growth factor secretion and capillary growth in skeletal muscle. *Exp Physiol.* (2013) 98:585–97. doi: 10.1113/expphysiol.2012.067967
133. Simoneau JA, Lortie G, Boulay MR, Marcotte M, Thibault MC, Bouchard C. Human skeletal muscle fiber type alteration with high-intensity intermittent training. *Eur J Appl Physiol Occup Physiol.* (1985) 54:250–3. doi: 10.1007/BF00426141
134. Hambrecht R, Fiehn E, Yu J, Niebauer J, Weigl C, Hilbrich L, et al. Effects of endurance training on mitochondrial ultrastructure and fiber type distribution in skeletal muscle of patients with stable chronic heart failure. *J Am Coll Cardiol.* (1997) 29:1067–73. doi: 10.1016/S0735-1097(97)00015-6
135. Tan R, Nederveen JP, Gillen JB, Joanisse S, Parise G, Tarnopolsky MA, et al. Skeletal muscle fiber-type-specific changes in markers of capillary and mitochondrial content after low-volume interval training in overweight women. *Physiol Rep.* (2018) 6:e13597. doi: 10.14814/phy2.13597
136. Ribeiro PAB, Boidin M, Juneau M, Nigam A, Gayda M. High-intensity interval training in patients with coronary heart disease: Prescription models and perspectives. *Ann Phys Rehabil Med.* (2016) 60:50–7. doi: 10.1016/j.rehab.2016.04.004
137. Gayda M, Ribeiro PA, Juneau M, Nigam A. Comparison of different forms of exercise training in patients with cardiac disease: where does high-intensity interval training fit? *Can J Cardiol.* (2016) 32: 485–94. doi: 10.1016/j.cjca.2016.01.017
138. Williams CJ, Gurd BJ, Bonafiglia JT, Voisin S, Li Z, Harvey N, et al. A multi-center comparison of VO_2peak trainability between interval training and moderate intensity continuous training. *Front Physiol.* (2019) 10:19. doi: 10.3389/fphys.2019.00019
139. Milanovic Z, Sporis G, Weston M. Effectiveness of high-intensity interval training (HIT) and continuous endurance training for vo2max improvements: a systematic review and meta-analysis of controlled trials. *Sports Med.* (2015) 45:1469–81. doi: 10.1007/s40279-015-0365-0
140. Bacon AP, Carter RE, Ogle EA, Joyner MJ. VO_2max trainability and high intensity interval training in humans: a meta-analysis. *PLoS ONE.* (2013) 8:e73182. doi: 10.1371/journal.pone.0073182
141. Thompson PD, Franklin BA, Balady GJ, Blair SN, Corrado D, Estes NA, et al. Exercise and acute cardiovascular events placing the risks into perspective: a scientific statement from the American Heart Association council on nutrition, physical activity, and metabolism and the council on clinical cardiology. *Circulation.* (2007) 115:2358–68. doi: 10.1161/CIRCULATIONAHA.107.181485
142. Mittleman MA, Maclure M, Tofler GH, Sherwood JB, Goldberg RJ, Muller JE. Triggering of acute myocardial infarction by heavy physical exertion. Protection against triggering by regular exertion. Determinants of myocardial infarction onset study investigators. *N Engl J Med.* (1993) 329:1677–83.
143. Haykowsky MJ, Daniel KM, Bhella PS, Sarma S, Kitzman DW. Heart failure: exercise-based cardiac rehabilitation: who, when, and how intense? *Can J Cardiol.* (2016) 32(10 Suppl 2):S382–7. doi: 10.1016/j.cjca.2016.06.001
144. Wewege Michael A, Ahn D, Yu J, Liou K, Keech A. High-Intensity interval training for patients with cardiovascular disease—is it safe? A systematic review. *J Am Heart Assoc.* (2018) 7:e009305. doi: 10.1161/JAHA.118.009305
145. Koufaki P, Mercer TH, George KP, Nolan J. Low-volume high-intensity interval training vs continuous aerobic cycling in patients with chronic heart failure: a pragmatic randomised clinical trial of feasibility and effectiveness. *J Rehabil Med.* (2014) 46:348–56. doi: 10.2340/16501977-1278
146. Pelliccia A, Sharma S, Gati S, Bäck M, Börjesson M, Caselli S, et al. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease: the task force on sports cardiology and exercise in patients with cardiovascular disease of the European Society of Cardiology (ESC). *Eur Heart J.* (2021) 42:17–96. doi: 10.1093/eurheartj/ehaa605
147. Iellamo F, Volterrani M. Letter by iellamo and volterrani regarding article, "high-intensity interval training in patients with heart failure with reduced ejection fraction". *Circulation.* (2017) 136:605–6. doi: 10.1161/CIRCULATIONAHA.117.028249
148. Aamot IL, Forbord SH, Karlsen T, Stoylen A. Does rating of perceived exertion result in target exercise intensity during interval training in cardiac rehabilitation? A study of the Borg scale versus a heart rate monitor. *J Sci Med Sport.* (2014) 17:541–5. doi: 10.1016/j.jsams.2013.07.019
149. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, et al. World health organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med.* (2020) 54:1451. doi: 10.1136/bjsports-2020-102955

150. Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, et al. The physical activity guidelines for americans. *JAMA*. (2018) 320:2020–8. doi: 10.1001/jama.2018.14854
151. Squires RW, Kaminsky LA, Porcari JP, Ruff JE, Savage PD, Williams MA. Progression of Exercise Training in Early Outpatient Cardiac Rehabilitation: AN OFFICIAL STATEMENT FROM THE AMERICAN ASSOCIATION OF CARDIOVASCULAR AND PULMONARY REHABILITATION. *J Cardiopulm Rehabil Prev*. (2018) 38:139–46. doi: 10.1097/HCR.0000000000000337
152. Hambrecht R, Niebauer J, Marburger C, Grunze M, Kälberer B, Hauer K, et al. Various intensities of leisure time physical activity in patients with coronary artery disease: effects on cardiorespiratory fitness and progression of coronary atherosclerotic lesions. *J Am Coll Cardiol*. (1993) 22:468–47. doi: 10.1016/0735-1097(93)90051-2
153. Physical Activity Guidelines Advisory Committee. *2018 Physical Activity Guidelines Advisory Committee Scientific Report*. Washington, DC: US Department of Health and Human Services (2018).
154. Kokkinos P, Kaminsky LA, Arena R, Zhang J, Myers J. New generalized equation for predicting maximal oxygen uptake (from the fitness registry and the importance of exercise national database). *Am J Cardiol*. (2017) 120:688–92. doi: 10.1016/j.amjcard.2017.05.037
155. Kokkinos P, Kaminsky LA, Arena R, Zhang J, Myers J. A new generalized cycle ergometry equation for predicting maximal oxygen uptake: the fitness registry and the importance of exercise national database (FRIEND). *Eur J Prev Cardiol*. (2018) 25:1077–82. doi: 10.1177/2047487318772667
156. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR Jr, Tudor-Locke C, et al. 2011 Compendium of physical activities: a second update of codes and MET values. *Med Sci Sports Exerc*. (2011). 43:1575–81. doi: 10.1249/MSS.0b013e31821ece12
157. Iellamo F, Manzi V, Caminiti G, Sposato B, Massaro M, Cerrito A, et al. Dose–response relationship of baroreflex sensitivity and heart rate variability to individually-tailored exercise training in patients with heart failure. *Int J Cardiol*. (2013) 166:334–9. doi: 10.1016/j.ijcard.2011.10.082
158. Dun Y, Smith JR, Liu S, Olson TP. High-intensity interval training in cardiac rehabilitation. *Clin Geriatr Med*. (2019) 35:469–87. doi: 10.1016/j.cger.2019.07.011
159. Keteyian SJ, Squires RW, Ades PA, Thomas RJ. Incorporating patients with chronic heart failure into outpatient cardiac rehabilitation: practical recommendations for exercise and self-care counseling-a clinical review. *J Cardiopulm Rehabil Prev*. (2014) 34:223–32. doi: 10.1097/HCR.0000000000000073
160. Ades PA, Keteyian SJ, Balady GJ, Houston-Miller N, Kitzman DW, Mancini DM, et al. Cardiac rehabilitation exercise and self-care for chronic heart failure. *JACC Heart Fail*. (2013) 1:540–7. doi: 10.1016/j.jchf.2013.09.002
161. Arena R, Myers J, Williams MA, Gulati M, Kligfield P, Balady GJ, et al. Assessment of functional capacity in clinical and research settings. *Circulation*. (2007) 116:329–43. doi: 10.1161/CIRCULATIONAHA.106.184461

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Cardiovascular Medicine

SYSTEMATIC REVIEW
published: 22 September 2021
doi: 10.3389/fcvm.2021.739473

Evaluation of the Structure and Health Impacts of Exercise-Based Cardiac and Pulmonary Rehabilitation and Prehabilitation for Individuals With Cancer: A Systematic Review and Meta-Analysis

Julia N. Rickard[1], *Arun Eswaran*[2], *Stephanie D. Small*[1], *Alis Bonsignore*[1], *Maureen Pakosh*[3], *Paul Oh*[4] *and Amy A. Kirkham*[1,4]*

[1] Faculty of Kinesiology & Physical Education, University of Toronto, Toronto, ON, Canada, [2] Lawrence S Bloomberg Faculty of Nursing, University of Toronto, Toronto, ON, Canada, [3] Library & Information Services, Toronto Rehabilitation Institute, Toronto, ON, Canada, [4] Cardiovascular Prevention and Rehabilitation Program, Toronto Rehabilitation Institute, Toronto, ON, Canada

OPEN ACCESS

Edited by:
Richard Yang Cao, Shanghai Xuhui Central Hospital, China

Reviewed by:
Jennifer Baima, University of Massachusetts Medical School, United States
Kyuwan Lee, City of Hope National Medical Center, United States

***Correspondence:**
Amy A. Kirkham
amy.kirkham@utoronto.ca

Specialty section:
This article was submitted to General Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

Received: 11 July 2021
Accepted: 25 August 2021
Published: 22 September 2021

Citation:
Rickard JN, Eswaran A, Small SD, Bonsignore A, Pakosh M, Oh P and Kirkham AA (2021) Evaluation of the Structure and Health Impacts of Exercise-Based Cardiac and Pulmonary Rehabilitation and Prehabilitation for Individuals With Cancer: A Systematic Review and Meta-Analysis. Front. Cardiovasc. Med. 8:739473. doi: 10.3389/fcvm.2021.739473

Exercise-based, multimodal rehabilitation programming similar to that used in the existing models of cardiac or pulmonary rehabilitation or prehabilitation is a holistic potential solution to address the range of physical, psychological, and existential (e.g., as their diagnosis relates to potential death) stressors associated with a cancer diagnosis and subsequent treatment. The purpose of this study was to systematically evaluate the structure and format of any type of exercise-based, multimodal rehabilitation programs used in individuals with cancer and the evidence base for their real-world effectiveness on metrics of physical (e.g., cardiorespiratory fitness, blood pressure) and psychological (e.g., health-related quality of life) health. Very few of the 33 included exercise-based, multimodal rehabilitation programs employed intervention components, education topics, and program support staff that were multi-disciplinary or cancer-specific. In particular, a greater emphasis on nutrition care, and the evaluation and management of psychosocial distress and CVD risk factors, with cancer-specific adaptations, would broaden and maximize the holistic health benefits of exercise-based rehabilitation. Despite these opportunities for improvement, exercise-based, multimodal rehabilitation programs utilized under real-world settings in individuals with cancer produced clinically meaningful and large effect sizes for cardiorespiratory fitness (VO_2peak, ±2.9 mL/kg/min, 95% CI = 2.6 to 3.3) and 6-minute walk distance (+47 meters, 95% CI = 23 to 71), and medium effect sizes for various measures of cancer-specific, health-related quality of life. However, there were no changes to blood pressure, body mass index, or lung function. Overall, these findings suggest that exercise-based, multimodal rehabilitation is a real-world therapy that improves physical and psychological health among individuals with cancer, but the holistic health benefits of this intervention

would likely be enhanced by addressing nutrition, psychosocial concerns, and risk factor management through education and counselling with consideration of the needs of an individual with cancer.

Keywords: cancer, cardiac rehabilitation (CR), Pulmonary rehabilitation (PR), prehabilitation, multi-disciplinary, exercise training

INTRODUCTION

Aerobic and resistance exercise training are widely accepted as safe and effective interventions to improve cardiorespiratory fitness, physical function, quality of life, and acute and long-term cancer treatment-related side effects among individuals diagnosed with cancer (1). While exercise training provides numerous health benefits, a cancer diagnosis and subsequent treatment introduces a wide range of physical, psychological, and existential (e.g., as their diagnosis relates to potential death) stressors (2) that are unlikely to be adequately addressed by exercise alone. Exercise-based, multimodal rehabilitation programming similar to that offered in existing models of cardiac or pulmonary rehabilitation or prehabilitation prior to surgery includes aerobic exercise training as the cornerstone, in addition to education and/or counselling for nutritional and psychosocial concerns, and risk factor evaluation and management with the goal of promoting self-management strategies and fostering the adoption and maintenance of healthy lifestyle behaviors (3–5). A comprehensive, multi-disciplinary approach such as this is a holistic potential solution to address the myriad of sequelae associated with cancer.

One particularly detrimental long-term health consequence of cancer types with high cancer survival rates is a significant elevation in risk of cardiovascular disease (CVD)-related morbidity and mortality (6). The etiology of the increased CVD risk is proposed to arise from several factors including pre-existing CVD, pre-existing CVD risk factors (e.g., obesity, hypertension, and diabetes), cancer treatment-related cardiovascular toxicity, and pre-existing and/or treatment-related lifestyle toxicity (e.g., physical inactivity, unhealthy diet, tobacco use, increased psychosocial stress and weight gain) (7). Among heart disease patients, cardiac rehabilitation is an integral component of care as it improves cardiorespiratory fitness and quality of life and reduces CVD mortality (8). Cardiac rehabilitation is defined as "the provision of comprehensive long-term services involving medical evaluation, prescriptive exercise, cardiac risk factor modification, and education, counseling, and behavioral interventions" (9). In recognition of the potential benefit of a multimodal model of care for individuals with cancer, the American Heart Association (AHA) recently published a scientific statement recommending the use of a delivery model similar to cardiac rehabilitation, but with adaptations to address the needs of individuals with cancer, to mitigate CVD risk (10). The AHA statement also provided guidance for the adaptation of the structure of standard cardiac rehabilitation to encompass cancer-specific considerations and stated the need to establish the science base for cardiac rehabilitation in cancer populations to help establish reimbursement pathways (10).

Pulmonary rehabilitation and prehabilitation (i.e., prior to surgery) are similar multimodal models to cardiac rehabilitation that share the core components of exercise training, education, counselling, and risk factor evaluation and management (3, 4). Specifically, pulmonary rehabilitation can be defined as "a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors." (11). Lung cancer is among the cancer types with the worst prognosis, owing in part to the high rate of surgical resection complications, which then limits treatment options for individuals with high risk factors (12). In this context, both prehabilitation prior to surgery and rehabilitation following surgery to optimize a patient's physical and psychological functioning has emerged as a potential solution.

With the first formal scientific statement from an international health organization advocating for the use of, and providing recommendations for exercise-based, multimodal rehabilitation programming to support individuals with cancer, a systematic evaluation of existing programs relative to these new guidelines and the evidence base for their impact on health outcomes is necessary to inform the optimization and adoption of exercise-based multimodal rehabilitation programs for individuals with cancer. In this context, the purpose of this study was to systematically evaluate exercise-based, multimodal rehabilitation programs such as cardiac or pulmonary rehabilitation or prehabilitation used in individuals with cancer in terms of their structure and health impacts. The first objective was to evaluate the setting, components, referral process, patient eligibility criteria, intake assessment of existing exercise-based multimodal programs in cancer populations relative to the AHA's cancer-specific recommendations to highlight gaps in care and areas for improvement for future programs. The second objective was to evaluate the real-world effectiveness of exercise-based, multimodal rehabilitation programs on physiological (i.e., cardiorespiratory fitness) and psychological (i.e., health-related quality of life) health among individuals with cancer by meta-analyses.

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items Systematic Reviews and Meta-Analyses (PRISMA) guidelines (13).

Data Sources and Search Strategy

Six electronic databases were searched from inception to 16 April 2021: CINAHL Complete (EBSCOhost), Embase (Ovid), Emcare (Ovid), Medline (Ovid), PubMed (non-Medline), and Web of Science Core Collection. The search strategies were developed in collaboration with an Information Specialist [MP] and organized according to the relevant concepts of the PICO(S) framework encompassing Population/Problem, Intervention, Comparisons, Outcomes, and Study Design. Valid subject headings as appropriate for each database were utilized, as were free text terms pertinent to each topical concept.

The Population included adults with current or past cancer diagnosis. The Intervention focused on multimodal, exercise-based rehabilitation programs similar to the model used in cardiac or pulmonary rehabilitation or prehabilitation. A Comparator was not required. In order to keep the results as broad as possible to achieve the first objective of evaluating existing programs within cancer, no Outcomes were stipulated in the search strategy. Both retrospective and prospective (observational, single-arm or randomized) qualitative and quantitative Study Designs were included as this is a new research area. No date limits were applied, but the results were restricted to humans and studies published in English. The full Medline search strategy is shown in **Supplementary Table 1**.

Study Selection

Included studies had to report separate data for adults with a history of any type of cancer diagnosis in English. The studies had to describe a structured, multimodal, exercise-based rehabilitation program that also included education to promote self-management strategies or mitigate CVD risk as the two core components of cardiac or pulmonary rehabilitation programs. Additionally, to capture real-world programs, the study had to include an explicit statement about the program being based on the cardiac or pulmonary rehabilitation model, being embedded in an existing rehabilitation program, or being the initiation of a new rehabilitation program. Studies that were purely based in a research setting were excluded. Original research studies $\geq$10 patients were included and reviews, case studies, editorials, commentaries, and research letters were excluded.

Screening and Data Extraction

Titles/abstracts and full texts were reviewed independently for inclusion by two authors [JR, AE] using Covidence (Veritas Health Innovation, Melbourne, AUS; Available at http://www.covidence.org/). Discrepancies were reviewed and resolved by consensus. Data were extracted by one author and verified by a second [JR, AE, SS]. For each meta-analysis, the mean difference was calculated as the post-intervention outcome value minus the pre-intervention outcome value. Studies not reporting measures of variance (or only range) were not included in the meta-analysis. Study authors were contacted primarily for clarification on potential overlap of data between multiple manuscripts.

Outcomes

The aspects of the programs evaluated were aligned with the AHA cardio-oncology rehabilitation recommendations which generally follow the structure for cardiac rehabilitation with adaptations for cancer-specific considerations. Specifically, the following components of the program structure were evaluated: the program setting, program components, referral process, patient eligibility criteria (including specifically CVD risk level), components of the baseline intake assessment, and patient enrollment and retention. The specific physiological, psychological, or patient-reported cancer-related (e.g., fatigue) outcome measures to be assessed in evaluation of the impact of rehabilitation programming were dictated by available data after the search was completed. The expected outcomes of interest were cardiorespiratory fitness (peak volume of oxygen consumption, VO_2peak), exercise capacity (6-minute walk test distance), blood pressure, lipids, muscular strength, body weight, body mass index, quality of life, anxiety, and depression. Variables that were assessed at both time points (pre and post intervention) in at least three unique programs were analyzed via meta-analysis.

Analyses

All evaluation criteria of the program structures are described by frequencies. Meta-analyses of the effect of the programs on available outcomes were performed using random effects models to allow for variation between studies, as the study samples and interventions included in this meta-analysis would be unlikely to have a common variance (14). Effect sizes were expressed as weighted mean difference (WMD) with 95% confidence intervals (CI). The standardized mean difference (SMD) is also provided to enable comparison and interpretation of the magnitude of effect size, where 0.2 = small, 0.5 = medium, and 0.8 = large (15). The risk of bias of an individual study was assessed by the leave-one-out sensitivity analysis approach. When a given study changed the statistical significance of the meta-analysis, results are provided for the analysis with and without that study. Interstudy heterogeneity was assessed using Cochrane Q statistic and quantified by I^2 statistic (16).

Only the immediately post-intervention time point of evaluation was included as very few studies reported follow-up or interim time points. Subgroup analyses were planned a priori to evaluate the potential for differences in effect sizes for: (1) prehabilitation (defined as intervention taking place prior to treatment, often surgical treatment) vs. rehabilitation (defined as taking place after treatment but may overlap with a subsequent treatment); (2) studies that exclusively enrolled patients who were post-treatment (but may be receiving hormonal therapy) versus studies that included some (or all) patients on active treatment (with surgery, chemotherapy, or radiation) due to the potential for cancer treatment to reduce the effect size; (3) retrospective vs. prospective study design; and (4) common cancer types. The availability of studies reporting the same outcome in the same cancer type was too low to perform this subgroup analysis. An additional sub-group analysis was planned *post-hoc* to evaluate the effects of prehabilitation on lung cancer surgical outcomes based on the number of included studies that reported these clinically relevant outcomes. For all other subgroup analyses, only those with two or more programs per group available are reported. Due to the small program number

within subgroups, within-group estimates of tau-squared were pooled for all subgroup analyses and random effects weights were used within subgroups.

RESULTS

Study Selection

A total of 7,130 citations, or 3,749 original studies after removal of duplicates were retrieved with the search strategy. The full text of 203 articles was reviewed to select 35 manuscripts, while one additional manuscript that was published ∼6 weeks after our search was completed was identified by the study team for a total of 36 manuscripts (17–52). **Figure 1** shows the PRISMA diagram with exclusion reasons. In total these 36 manuscripts described 33 unique programs; three programs were described in 2–3 different manuscripts (26, 27, 32, 33, 38, 39, 47, 52), two manuscripts described 2 or 3 unique programs (22, 31).

Evaluation of Programs Relative to Cardio-Oncology Rehabilitation Recommendations

Program Setting

The wide majority ($n = 29$, 88%) of programs were delivered in a clinical or hospital-based setting, while two (6%) were delivered in a community-based setting, and two (6%) were home-based (**Supplementary Table 2**).

Program Components

As per our inclusion criterion, all programs included exercise training and education. Within the exercise prescriptions (described in **Supplementary Table 3**), the majority ($n = 24$, 73%) included both aerobic and resistance exercise, while five (15%) and three (9%) included only aerobic or resistance, respectively, and one did not describe the exercise prescription. For those including aerobic exercise, the majority prescribed frequency as 2–3 times per week, at a moderate-to-vigorous intensity for a wide range of duration from 20 to 120 minutes. For those that specified an aerobic exercise mode, walking and cycle ergometry were the most common. The majority of the studies did not describe the details of the resistance exercise prescriptions beyond frequency, which ranged from once per week to daily. The prescribed resistance exercise intensity was infrequently described, but 8 (24%) programs explicitly stated that n-repetition-maximum testing performed at baseline was used as the basis of the prescription. One-third ($n = 12$, 36%) of programs prescribed unsupervised exercise to be performed at home in addition to supervised exercise. Only 5 (15%) studies explicitly stated the prescription of flexibility exercises.

Education topics included nutrition ($n = 24$, 73%), psychosocial concerns or stress management ($n = 21$, 64%), physical activity ($n = 18$, 55%), cancer-specific topics (e.g., lymphedema, cancer pathology, medications) ($n = 10$, 30%) and weight management ($n = 2$, 6%) (**Supplementary Table 3**). Ten (30%) studies reported performing goal setting within these education sessions.

Beyond exercise training and education, other core components of rehabilitation were not common (**Supplementary Table 3**). Dietary interventions such as cooking classes, supplementation, or a nutrition plan were described in five (15%) programs. Psychosocial interventions such as counselling were described in three (9%) programs. Tobacco cessation was provided in 10 (30%) programs, but half of these were in programs specifically for lung cancer. In terms of CVD factor management, just four (12%) programs reported both assessing and managing hypertension, dyslipidemia, or diabetes. Four (12%) programs reported referrals to other healthcare professionals (e.g., occupational, speech, or massage therapists) as a program component.

Referral Process

The most common referral source was the treating health care provider (n = 26, 79%; **Supplementary Table 2**). Only one study utilized self-referral, and the remainder allowed either self or provider referral ($n = 5$, 15%) or did not report (or imply) the source ($n = 1$, 3%).

Patient Eligibility

Seven (21%) programs allowed enrollment of any type of cancer and the most common type-specific programs were for lung cancer ($n = 8$, 24%) and breast cancer ($n = 8$, 24%; **Supplementary Table 2**). The majority ($n = 23$, 70%) of programs allowed enrollment of individuals diagnosed with any stage of cancer, while 10 (30%) only enrolled individuals with early-stage cancer, and none were specific to advanced cancer. Eligibility with respect to the timing of treatment was specified as during active treatment in 2 (6%), exclusively post-treatment in 9 (27%), at any time of the cancer trajectory in 4 (12%) and not specified in the remainder of programs. Eight (24%) programs were prehabilitation programs, with most being initiated in the pre-operative treatment window. Only one (3%) program described the presence or identification of CVD, cardiotoxicity, cardiac symptoms, or high CVD risk as a program inclusion criterion or requirement for referral. No studies described the requirement for receipt of cardiotoxic treatments such as high-dose anthracyclines or left-sided radiation for inclusion in the program. Five (15%) studies required poor pulmonary function, physical function, or exercise capacity among lung cancer patients for program inclusion (**Supplementary Table 2**).

Baseline Assessment

Cancer-specific, cardiovascular-specific, or general medical history were reported as occurring at the baseline assessment in 22 (67%) programs (**Supplementary Table 3**). Blood work was only explicitly stated as being required or reviewed in two (6%) programs and it was for cardiometabolic markers. The most commonly used subjective psychosocial assessments were quality of life ($n = 17$, 52%) and anxiety or depression ($n = 13$, 39%). Self-reported lifestyle behaviors were infrequently assessed, with 11 (33%) assessing physical activity, 6 (18%) assessing dietary practices, and 17 (52%) assessing tobacco use. Two (6%) programs objectively assessed baseline physical activity using accelerometers. The most commonly assessed cancer-specific condition was cancer-related fatigue ($n = 10$, 30%), while self-reported symptoms, lymphedema, and previous cardiac failure

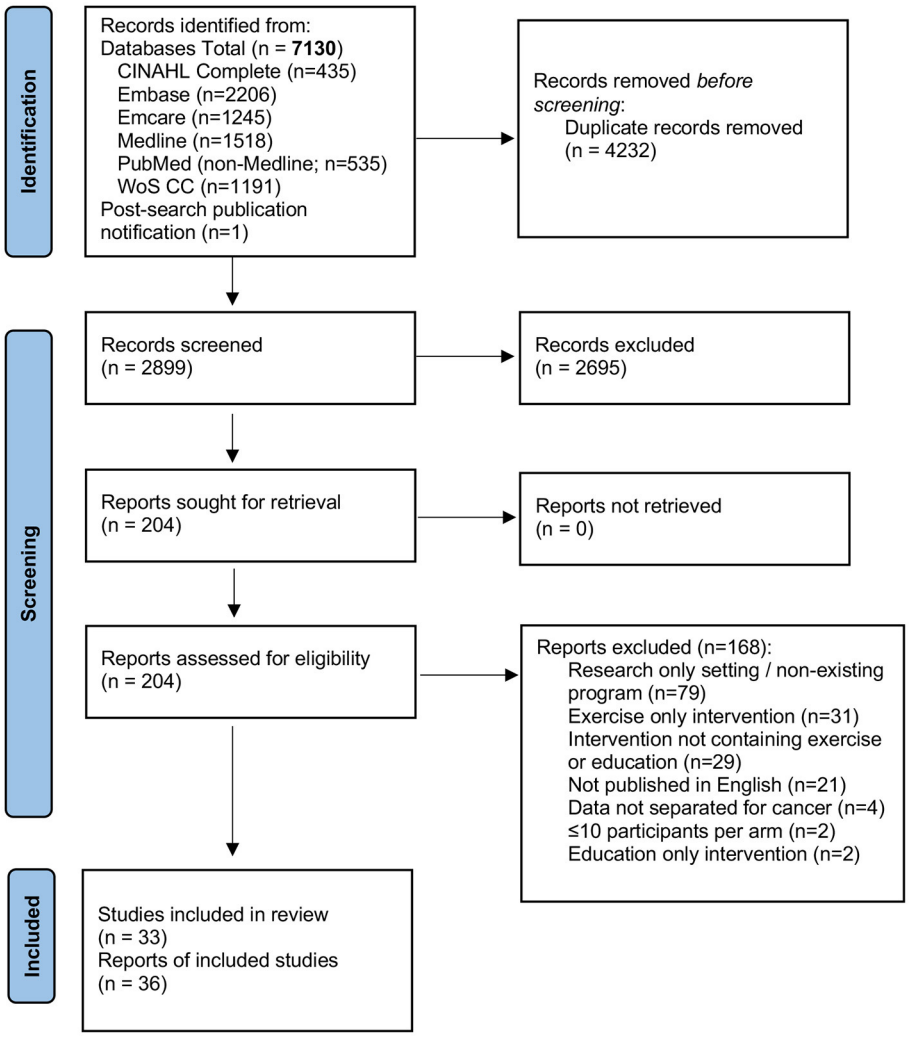


FIGURE 1 | PRISMA flow diagram.

were each assessed in one study. Ten (30%) studies reported assessing basic anthropometrics (height, weight, body mass index), and three (9%) also assessed waist circumference. Blood pressure was reported as being assessed in 3 (9%) programs, while cardiorespiratory fitness (VO_2peak) or exercise capacity (6-min walk test) was assessed in 11 (33%) and 9 (27%), respectively.

Program Staff

Program staff was generally poorly described in most studies (**Supplementary Table 3**), other than inclusion of an exercise professional, which was reported in 24 (73%) studies. Among these studies, 12 (50%) reported that the exercise staff was a physiotherapist, 2 (8%) reported a certified exercise professional, and the remaining did not specify. Nine (27%) studies included a physician, and of these, four (44%) reported that the physician had cancer-specific training or experience. Eleven (33%) studies reported including a registered dietitian or nutritionist, 13 (39%) reported including a mental health professional, and 14 (42%) reported including an oncology care provider. Only one study reported that the exercise, nutrition, or mental health professionals had oncology-specific training.

Meta-Analysis

6-Minute Walk Test Distance

Eight studies with $n = 680$ participants among 10 different programs evaluated change in six-minute walk test distance (22, 24, 29, 30, 37, 42, 45, 46). Including all programs, pre/rehabilitation improved six-minute walk distance by 47 meters (95% CI = 23 to 71, SMD = 0.78, $p < 0.001$, $I^2 = 96\%$; **Figure 2**). When comparing program type, the improvement in six-minute walk distance was only significant for rehab ($n = 7$, WMD = 57 m, 95% CI = 29 to 85, $p < 0.001$, $I^2 = 96\%$) (20, 22, 27, 35, 40, 43, 44) and not for prehab ($n = 3$, WMD = 25 m, 95% CI = −16 to 67, $p = 0.236$, $I^2 = 11\%$) (20, 28)

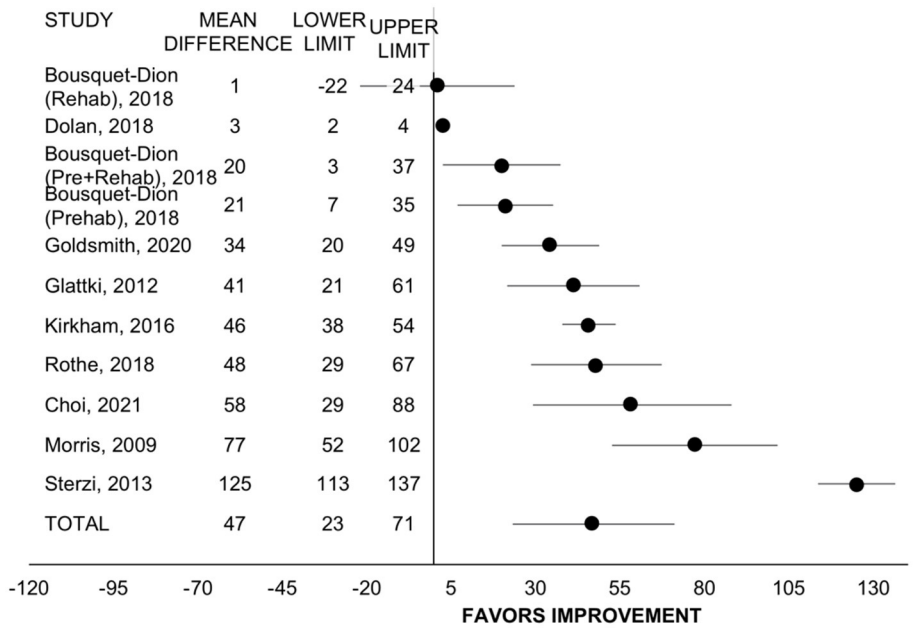


FIGURE 2 | Forest plot displaying mean difference and 95% CIs for the impact of pre/rehabilitation on 6-minute walk test distance (meters).

but was not statistically different between types ($p = 0.211$). For treatment timing, the improvement was significant only among programs with participants exclusively post-treatment ($n = 7$, WMD = 50 m, 95% CI = 18 to 81, $p = 0.002$, $I^{2=}$ 97%) (22, 24, 29, 30, 42, 45) and was only a trend among programs that allowed patients on active treatment with surgery, chemotherapy, or radiation ($n = 3$, WMD = 41 m, 95% CI = −8 to 90, $p = 0.100$, $I^2 = 76\%$) (22, 24, 37) but did not differ between subgroups ($p = 0.765$). Retrospective studies had larger improvements in six-minute walk distance ($n = 5$, WMD = 70 m, 95% CI = 39 to 101, $p < 0.001$, $I^2 = 97\%$) (24, 29, 37, 42, 46) than prospective ($n = 5$, WMD = 25 m, 95% CI = −5 to 56, $p = 0.107$, $I^2 = 66\%$) ($p = 0.042$ between groups).

VO_2peak

Seven studies with $n = 373$ participants evaluated change in VO_2peak via cardiopulmonary gas analysis ($n = 4$) (20, 27, 43, 52) or estimation from workload ($n = 3$) (19, 49, 51). Of these studies, all employed rehabilitation programs. Including all studies, rehabilitation improved VO_2peak by 2.9 mL/kg/min (95% CI = 2.6 to 3.3, SMD = 0.75, $p < 0.001$, $I^2 = 0\%$; **Figure 3**). For treatment timing, the improvement was significant for programs that allowed patients on active treatment ($n = 2$, WMD = 3.1 mL/kg/min, 95% CI = 2.6 to 3.6, $p < 0.001$, $I^2 = 33\%$) (27, 49) and for programs including patients exclusively post-treatment ($n = 5$, WMD= 2.7 mL/kg/min, 95% CI = 2.2 to 3.2, $p < 0.001$, $I^2 = 0\%$) (19, 20, 43, 51, 52) and did not differ between subgroups ($p = 0.257$). The change in VO_2peak did not differ between studies with retrospective vs. prospective design ($p = 0.578$).

Cancer-Specific, Health-Related Quality of Life

Eleven studies reported change in health-related quality of life measures that were cancer-specific among 12 programs and with several studies reporting more than one measure of quality of life (19, 27, 31, 34, 36–39, 43, 44, 47, 51). Of these, $n = 6$ used the European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC-QLQ)-C30 in $n = 2008$ participants, $n = 5$ used the Functional Assessment of Cancer Therapy (FACT)-General in $n = 300$ participants, $n = 4$ used the FACT-Breast total in $n = 206$ participants, $n = 4$ used the FACT-Fatigue in $n = 1410$ participants. All studies employed rehabilitation programming.

All studies utilizing the EORTC-QLQ-C30 included patients who had completed treatment, while all studies utilizing the FACT included patients on active treatment. Rehabilitation improved the EORTC-QLQ-C30 by 9.5 points (95% CI = 7.5 to 11.5, SMD = 0.30, $p < 0.001$, $I^2 = 78\%$; **Figure 4**). Rehabilitation also improved FACT-General by 4.7 points (95% CI = 2.2 to 7.3, SMD = 0.62, $p < 0.001$, $I^2 = 52\%$; **Figure 4**). The effect size of these two general quality of life questionnaires combined was medium (SMD = 0.49, 95% CI = 0.37 to 0.62, $p < 0.001$, $I^2 = 77\%$).

Rehabilitation improved the FACT-Breast total score by 5.1 points (95% CI = 0.1 to 10.1, SMD = 0.26, $p = 0.044$, $I^2 = 98\%$). However, in the leave-one-out sensitivity analyses, with the removal of any of the studies by Dolan et al., Gordon et al.

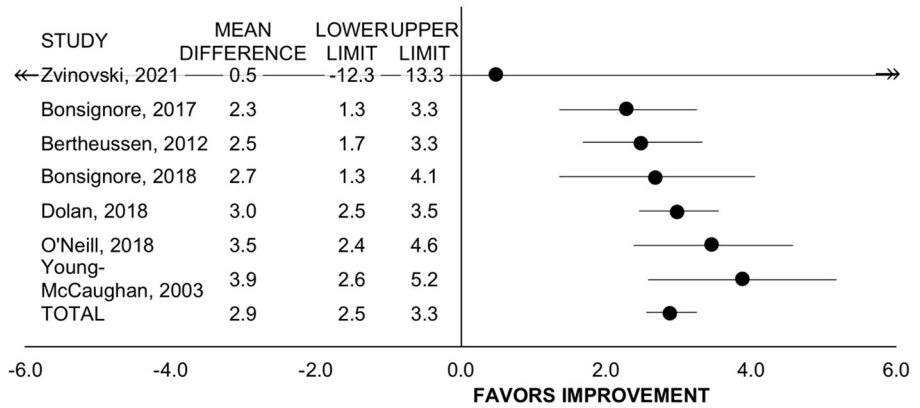


FIGURE 3 | Forest plot displaying mean difference and 95% CIs for the impact of rehabilitation on VO_2peak (mL/kg/min).

(DAART program only), or Rossen et al., the change in FACT-Breast was no longer significant ($p \geq 0.10$). Including all studies, rehabilitation did not change FACT-Fatigue score (WMD = 1.4, 95% CI = −5.0 to 7.8, SMD = 0.11, $p = 0.667$, $I^2 = 68\%$). The FACT-Fatigue effect size did not differ between retrospective and prospective studies ($n = 2$ each, $p = 0.916$).

Anthropometrics

Six studies with $n = 226$ participants reported body mass index (20, 21, 37, 43, 51, 52) and three with $n = 295$ participants reported body mass (27, 37, 43) before and after the program. Prehab/rehab did not change body mass index (WMD = 0 kg/m^2, 95% CI = −0.3 to 0.4, SMD = 0.02, $p = 0.777$, $I^2 = 0\%$) and this did not differ by treatment timing ($p = 0.728$) or study design ($p = 0.576$). Rehabilitation did not change body mass (WMD = −0.2 kg, 95% CI = −0.9 to 0.6, SMD = −0.05, $p = 0.675$, $I^2 = 62\%$).

Spirometry

Four studies with $n = 145$ participants reported forced expiratory volume in one second (FEV_1) (24, 29, 41, 46) and three with $n = 125$ participants reported forced vital capacity (FVC) (24, 29, 46). Pre/rehabilitation did not impact FEV_1 (WMD = 4.6 % predicted, 95% CI = −5.4 to 14.5, SMD = 0.69, $p = 0.369$, $I^2 = 98\%$) or FVC (WMD = 1.0 % predicted, 95% CI = −4.4 to 6.4, SMD = 0.24, $p = 0.719$, $I^2 = 89\%$). However, sensitivity analysis showed that the removal of the study by Sterzi et al. resulted in a significant improvement in FEV_1 (WMD = 9.0% predicted, 95% CI = 2.1 to 15.8, $p = 0.011$, $I^2 = 92\%$) and FVC (WMD = 3.9% predicted, 95% CI = 2.1 to 5.8, $p < 0.001$, $I^2 = 0\%$).

Blood Pressure

Four studies with $n = 183$ participants reported blood pressure (20, 37, 51, 52) and it was not affected by rehabilitation (systolic: WMD = −1.5 mmHg, 95% CI = −3.5 to 0.5, SMD = −0.11, $p = 0.135$, $I^2 = 0\%$; diastolic: WMD = −0.3 mmHg, 95% CI = −1.6 to 1.1, SMD = −0.01, $p = 0.722$, $I^2 = 29\%$).

There were not three or more unique programs that measured fasting glucose, hemoglobin A1c, lipid profile, smoking cessation success rates, nutritional intake, or depression or anxiety (with the same measure) to allow meta-analysis.

Post hoc Analysis of Prehabilitation for Surgical Resection of Lung Cancer

The only programs that reported surgical outcomes were five prehabilitation programs implemented prior to surgical resection for lung cancer (21, 23, 30, 41, 50). Four of these studies compared post-operative outcomes, including complications (e.g., pneumonia, infections), and length of hospital stay between patients who participated in prehabilitation to patients that did not participate (21, 23, 30, 50) but could not be combined by meta-analysis due to variability in outcome reporting formats. All four studies reported a significant reduction or trend to significance for incidence of various post-operative complications and post-operative hospital stay length among participants in the prehabilitation program (21, 23, 30, 50). Two studies reported significant improvements in FEV_1 and exercise capacity following the short prehabilitation program (typically lasting 1–4 weeks) (23, 41). Importantly, these health effects translated to a significant increase in the proportion of participants able to receive surgery (30% vs. 69%) in one program (30) and reduced post-operative health care costs in two programs (21, 23).

DISCUSSION

Through the systematic review, evaluation, and meta-analyses of exercise-based multimodal rehabilitation programs such as cardiac or pulmonary rehabilitation or prehabilitation utilized in individuals diagnosed with cancer, this review summarizes the available evidence base for the effectiveness of these interventions and is a first step towards informing the optimal components, staff, referral process, and setting of future programs. Few of the published exercise-based, multimodal, rehabilitation programs utilized in individuals with cancer have adhered to the AHA's cancer-adapted recommendations for rehabilitation, especially with respect to inclusion of multi-disciplinary and/or cancer-specific interventions and program support staff. However,

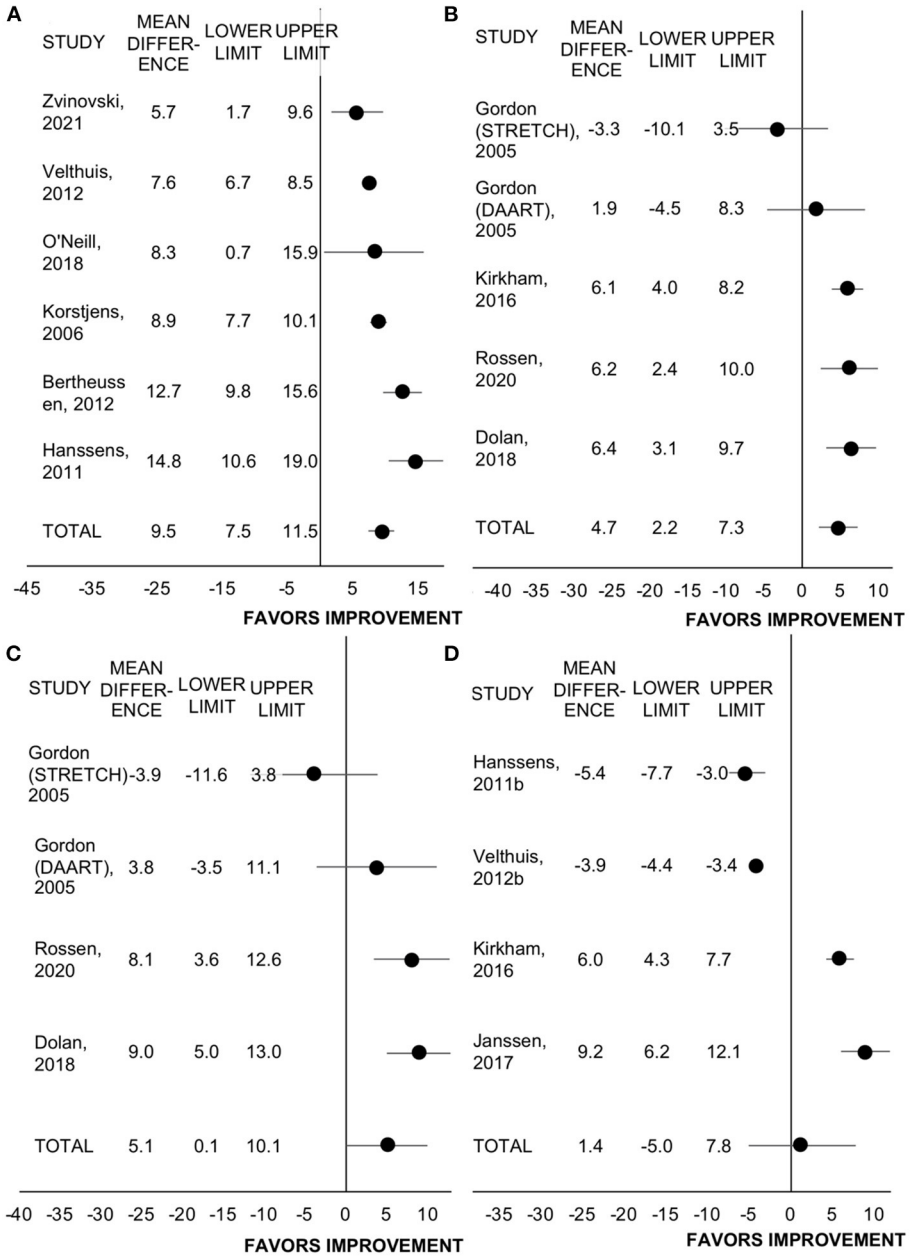


FIGURE 4 | Forest plot displaying mean difference and 95% CIs for the impact of rehabilitation on measures of health-related quality of life: **(A)** EORTC-QLQ-C30; **(B)** FACT-General; **(C)** FACT-Breast; **(D)** FACT-Fatigue.

despite the lack of cancer considerations and holistic approach to rehabilitation employed by the published programs to-date, there were statistically and clinically significant improvements in exercise capacity, cardiorespiratory fitness, and health-related quality of life. Based on these findings, we have identified a number of areas of the program structure with room for improvement to better accommodate the unique needs of individuals with cancer to maximize the size and duration of health benefits of an exercise-based, multimodal rehabilitation approach.

Program Components

Cardiorespiratory fitness is one of the strongest independent predictors of all-cause, cancer-related, and CVD-related mortality in cancer survivors (53). Exercise training is the most effective intervention for improving cardiorespiratory fitness and as such should be a cornerstone of multi-modal programs for individuals diagnosed with cancer, similar to contemporary cardiac and pulmonary rehabilitation (3, 4, 10). An important finding from the current meta-analysis is that real-world, exercise-based, multimodal rehabilitation resulted

in the same effect size of improvement in VO_2peak, the gold standard measure of cardiorespiratory fitness, as compared with rigorously controlled randomized controlled trials of exercise training in individuals with cancer reported in a meta-analysis (2.9 vs. 2.8 mL/kg/min) (54). The six-minute walk test is another reliable measure of exercise capacity that is correlated with cardiorespiratory fitness and also predicts cancer outcomes (55–57). Our meta-analysis also identified a clinically meaningful mean improvement of 47 m in six-minute walk distance with real-world rehabilitation which exceeds the threshold of 42 m identified as a clinically importance change among individuals with lung cancer (58).

While exercise training provides numerous health benefits, a cancer diagnosis and subsequent treatment introduces a wide range of physical, psychological, and existential stressors (2) that are unlikely to be adequately addressed by exercise alone. In particular, nutrition is a core component of traditional cardiac or pulmonary rehabilitation programming that is of high relevance for cancer populations but was inadequately addressed in most programs in this study. While 73% of programs reported providing education on nutritional topics, this may have been limited to a single informational session. Only 14% of programs described any type of nutritional intervention where dietary counselling or planning was provided. Malnutrition is common among individuals diagnosed with cancer due to the combined effects of the tumor itself, anticancer treatments, and poor dietary habits, and its presence contributes to reduced quality of life, increased treatment toxicity, and death independent of cancer (59). The 2021 European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines on nutrition in cancer patients reported that despite the robust evidence base for the crucial role of nutrition as a critical component of multimodal cancer care, it is largely unrecognized, underestimated, and undertreated in practice (59). Among the ESPEN's 43 recommendations for nutritional and metabolic management of patients with cancer, is the recommendation for use of nutritional interventions that provide dietary advice, addressing treatment and nutritional impact symptoms that impair food intake, and offering supplements. These aspects of nutrition support are within the scope of current practice of cardiac rehabilitation program registered dietitians. A greater emphasis on nutrition care as a component of rehabilitation is likely to compound health benefits received from exercise for individuals with cancer. Furthermore, in cancer survivors who are at greater risk for obesity and metabolic impairments (e.g., glucose intolerance) than for malnutrition (e.g., early-stage breast cancer, endometrial cancer), nutritional interventions are needed to normalize glycemic control, induce fat mass loss, and other associated markers of CVD risk. The optimal intervention for inducing these benefits would be one that takes advantage of the synergies in a multimodal diet and exercise intervention.

Psychosocial distress is extremely prevalent among individuals with cancer, especially within the first year after a diagnosis but this may persist long after completion of primary treatment (2). For example, within the first year of a breast cancer diagnosis, ∼50% of women experience depression, anxiety, or both (60). Depression can increase the risk of developing other comorbidities such as CVD, increases CVD mortality risk, and can reduce adherence to rehabilitation if not addressed (61, 62). The psychological health of individuals with cancer is determined by more than simply the absence of distress, but also by the presence of positive psychological responses such as self-esteem, life appreciation and meaning, spirituality, and feelings of peacefulness and purposefulness (2). Screening for and then treating psychosocial distress through education, goal setting, individual or group counselling within the rehabilitation setting can facilitate these positive psychological responses and in turn, reduce the risk of onset of new comorbidities and death. Depression may also reduce adherence and completion rates to multi-modal programming such as cardiac rehabilitation, therefore addressing psychosocial concerns may increase engagement with these potentially life-saving services (63). Only 9% of the included programs in this study reported including psychosocial interventions of any kind, which represents an actionable programmatic change that could significantly enhance the effects of multimodal rehabilitation on the well-being of individuals with cancer.

CVD is a primary competing risk of death for individuals diagnosed with numerous cancer types, especially among those with higher cancer survival rates (6). The risk of CVD-related death is elevated at all points in the survivorship trajectory after a cancer diagnosis when compared to the general population (6). The assessment and management of modifiable CVD risk factors (e.g., blood pressure, glucose, lipids, tobacco use) is an integral component of cardiac rehabilitation but was rarely employed in the programs in the current study. This finding suggests that the majority of rehabilitation programs used in individuals with cancer to-date have not had a focus on mitigation of CVD risk, which represents a missed opportunity to enhance the overall health profile of individuals with cancer by targeting a primary competing risk of death. Furthermore, a shift toward a focus on CVD risk reduction in rehabilitation for cancer types where CVD is a prevalent competing risk may provide a viable avenue for reimbursement from third-party payers based on the precedent set by cardiac rehabilitation. Although offering multi-modal programming including exercise, psychosocial, nutritional, and CVD risk factor modification support is optimal, this might not be viable in all centers, especially in low resource settings. Suggestions for adapting cardiac rehabilitation for low resource settings include a menu-based and flexible implementation of recommendations as possible, use of non-physician-led interventions for low risk patients, or delivery through the community, home, internet/mobile technology, or within primary care settings (64).

Referral Process and Setting

Referral Timing

The AHA cardio-oncology rehabilitation guidelines suggest that referral to rehabilitation should be driven by prior cardiotoxic exposures and current symptoms, rather than considerations of treatment timing (e.g., before, during, or after) relative to treatment (10). Some components of rehabilitation, especially exercise, introduce additional challenges and considerations when performed during active treatment where patients

have time constraints due to appointments and tests, are immunocompromised, and experiencing symptoms such as nausea, emesis, fatigue, and depression. However, exercise training during active treatment has been shown to reduce treatment-related toxicities and potentially impact medical outcomes such as reducing hospitalizations, chemotherapy complications, and reduced dose intensity (66). The results from the current meta-analysis support the implementation of rehabilitation prior to, during, or after primary treatment completion. Our subgroup comparisons of programs that included vs. excluded patients on active treatment and prehabilitation vs. rehabilitation showed that effect size for cardiorespiratory fitness, exercise capacity and quality of life did not differ and was clinically meaningful regardless of timing. This finding suggests that referral timing can be based on individual patient preference or ability. However, our finding that prehabilitation improved surgical outcomes suggests that intervention timing may be important in this context.

Referral Source

The wide majority of programs enrolled patients following referral by a treating health care provider, which was not often an oncologist or cardiologist. A referral by a health care provider may be a requirement for reimbursement of centre-based rehabilitation costs by a third-party payer. Referral rates to cardiac and pulmonary rehabilitation are alarmingly low, with only 28% of patients undergoing cardiac catheterization and less than 35% of eligible patients being referred, respectively (67, 68). Referral of eligible patients with cancer to rehabilitation will likely face similar challenges. The streamlining or automation of referrals from specialists (related to cardiac or pulmonary care), the oncology care team, and primary care providers, and endorsement from the treating physician are a few approaches that could be considered to enhance referrals and uptake of multimodal rehabilitation among individuals with cancer.

Program Setting

Only three (9%) programs in this study took place outside of a clinical setting such as in the community or at home. A recent scoping review of 31 unique programs offering supervised exercise in a community-based setting reported that it was safe and improved health-related quality of life for an individual with cancer (69). Consideration of patient preference, safety, and efficacy is required to determine appropriateness of center-based, home-based or community-based programming for cancer survivors. The AHA cardio-oncology rehabilitation guidelines recommend the use of centre-based rehabilitation for individuals with higher cardiac risk features (e.g., history of CVD, cardiac symptoms, receipt of cardiotoxic treatments, and presence of CVD risk factors), whereas those without these risk factors are appropriate candidates for community-based programming. Despite most of the programs being clinical centre-based in this study, only one study had the requirement for high cardiac risk features for enrollment and in fact, a number of programs excluded patients with these factors. It is not feasible or needed for all individuals with cancer to attend rehabilitation. CVD risk stratification is a viable method to identify and target those in greatest need of intervention.

Program Staff

Oncology-specific certification is available for exercise, nutrition, and mental health professionals (69–72), but only one study reported that their staff had this training. While adequate knowledge of cancer diagnoses and treatments is critical for the safe and effective provision of support for individuals with a history of cancer, the integration of oncology rehabilitation into existing cardiac or pulmonary rehabilitation programs where resources are already limited, may not allow for the additional cost and time associated with additional training of the program staff. It may be more feasible for the cardiac/pulmonary rehabilitation programs to partner with the local cancer treatment centers to share personnel or receive informal training.

Program Funding

A reimbursement strategy is currently unavailable for individuals with cancer participating in cardiac rehabilitation, highlighting the need to demonstrate the effectiveness of these programs in this population (10). In cardiac populations, cardiac rehabilitation has been found to be cost-effective relative to no cardiac rehabilitation, but the most cost-effective delivery model is unclear (65, 73). In cancer survivors, exercise physiologist- or physiotherapist-led physical activity programs have been shown to be more cost-effective compared to home-based self-management programs (74). As such, the cardiac rehabilitation model may be a cost-effective intervention to support cancer survivors. Implementing cancer rehabilitation programs using existing cardiac or pulmonary rehabilitation infrastructure may be a viable solution to reduce costs for utilization of these programs by cancer survivors. However, among the general cardiac rehabilitation landscape in Canada, approximately 200,000 more cardiac spots are needed per year to treat patients with ischemic heart disease alone, not including other patient population such as those living with atrial fibrillation, heart failure, and valvular disease (75). Therefore, funding constraints may limit enrollment of large numbers of cancer survivors directly into existing cardiac/pulmonary rehabilitation programs. Dedicated funding, resources, and staff are likely needed to enhance capacity for individuals with cancer to participate in exercise-based multimodal rehabilitation programming.

Limitations

The results of this meta-analysis are limited by the lack of a control (non-rehabilitation) comparison group, small sample sizes, heterogeneity in results, and inability to perform subgroup analysis by cancer type. Within each evaluated outcome measure, there were too few studies including patients with a given cancer diagnosis type to allow for subgroup comparisons. As such, some analyses had moderate-to-high heterogeneity as indicated by I^2, which indicates genuine differences in results between studies which could be related to grouping various cancer types, stages, and timing relative to treatment together. However, random effects models were used because heterogeneity was expected, and they provide estimates of the average intervention effect.

CONCLUSION

This systematic evaluation of the structure of 33 existing exercise-based multimodal rehabilitation programs utilized in individuals with cancer to-date identified that the program components, education topics, and staff were not often multidisciplinary and/or cancer-specific. In particular, a greater emphasis on nutrition, and evaluation and management of psychosocial distress and CVD risk factors, similar to the program components often offered in traditional cardiac rehabilitation but with cancer-specific adaptations, would provide enhanced holistic health benefits. Further, the wide majority of rehabilitation programs used in individuals with cancer to-date have not required elevated CVD risk (including receipt of cardiotoxic treatments) as an enrollment criterion nor have their program intake assessment or components had a focus on evaluation and mitigation of CVD risk. A shift toward a focus on CVD risk reduction in rehabilitation for cancer types where CVD is a prevalent competing risk will enhance the potential health impact of these programs. This study also found that cardiac rehabilitation, pulmonary rehabilitation, prehabilitation or other exercise-based multimodal rehabilitation programs utilized under real-world settings in individuals with cancer produced clinically meaningful and large effect sizes for cardiorespiratory fitness and 6-minute walk distance, and medium effect sizes for cancer-specific, health-related quality of life. Overall, these findings suggest that a model of exercise-based multimodal rehabilitation that addresses risk factors and nutritional and psychosocial concerns, and risk factors through education and counselling with consideration of the needs of individuals with cancer could be a holistic solution to address the range of physical, psychological, and existential stressors associated with a cancer diagnosis and subsequent treatment.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

MP developed search strategy for the review and assisted with methods description. JR and AE completed article screening. JR, AE, and SS completed data extraction. AE created PRISMA diagram. JR and SS created tables. AK performed meta-analysis. AK, AB, and JR prepared the manuscript. PO is an expert contributor and assisted with manuscript completion. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.739473/full#supplementary-material

REFERENCES

1. Campbell KL, Winters-Stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS, et al. Exercise guidelines for cancer survivors: consensus statement from international multidisciplinary roundtable. *Med Sci Sports Exerc.* (2019) 51:2375–90. doi: 10.1249/MSS.0000000000002116
2. Andrykowski MA, Lykins E, Floyd A. Psychological health in cancer survivors. *Semin Oncol Nurs.* (2008) 24:3. doi: 10.1016/j.soncn.2008.05.007
3. Singh SJ, Danjoux G, Durrand J. Prehabilitation. *Clin Med.* (2019) 19:6. doi: 10.7861/clinmed.2019-0257
4. Holland AE, Singh SJ, Casaburi R, Clini E, Cox NS, Galwicki M, et al. Defining modern pulmonary rehabilitation: an official American thoracic society workshop report. *Ann Am Thorac Soc.* (2021) 18:5. doi: 10.1513/AnnalsATS.202102-146ST
5. Balady GJ, Williams MA, Ades PA, Bittner V, Comoss P, Foody JAM, et al. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update - a scientific statement from the American heart association exercise, cardiac rehabilitation, and prevention committee, the council on clinical cardiology; the councils on cardiovascular nursing, epidemiology and prevention, and nutrition, physical activity, and metabolism; and the American association of cardiovascular and pulmonary rehabilitation. *J Cardiopulm Rehabil Prev.* (2007) 27:3. doi: 10.1097/01.HCR.0000270696.01635.aa
6. Sturgeon KM, Deng L, Bluethmann SM, Zhou S, Trifiletti DM, Jiang C, et al. A population-based study of cardiovascular disease mortality risk in US cancer patients. *Eur Heart J.* (2019) 40:48. doi: 10.1093/eurheartj/ehz766
7. Kirkham AA, Beaudry RI, Paterson DI, Mackey JR, Haykowsky MJ. Curing breast cancer and killing the heart: a novel model to explain elevated cardiovascular disease and mortality risk among women with early stage breast cancer. *Prog Cardiovasc Dis.* (2019) 62:2. doi: 10.1016/j.pcad.2019.02.002
8. American Heart Association (AHA). Cardiac rehabilitation putting more patients on the road to recovery. *Circulation.* (2017) 135:10.
9. Wenger NK, Froelicher ES, Smith LK, Ades PA, Berra K, Blumenthal JA, et al. Cardiac rehabilitation as secondary prevention. Agency for health care policy and research and national heart, lung, and blood institute. *Clin Pract Guidel Quick Reference Guide Clin.* (1995) 17:1–23.
10. Gilchrist SC, Barac A, Ades PA, Alfano CM, Franklin BA, Jones LW, et al. Cardio-oncology rehabilitation to manage cardiovascular outcomes in cancer patients and survivors: a scientific statement from the American heart association. *Circulation.* (2019) 139:21. doi: 10.1161/CIR.0000000000000679
11. Spruit MA, Singh SJ, Garvey C, Zu Wallack R, Nici L, Rochester C, et al. An official American thoracic society/European respiratory society statement: Key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med.* (2013) 188:e13–64. doi: 10.1164/rccm.201309-1634ST
12. Nykamp V. Surgical treatment of non-small cell lung cancer. *South Dakota Med.* (2010) 57–59. doi: 10.7707/hmj.630
13. Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med.* (2009) 151:4. doi: 10.7326/0003-4819-151-4-200908180-00136
14. Higgins J, Green S, editors. *Cochrane handbook for systematic reviews of interventions.* 5 ed. (2011).
15. Faraone SV. Interpreting estimates of treatment effects: Implications for managed care. *P and T.* (2008) 33:12.
16. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Br Med J.* (2003) 327:7414. doi: 10.1136/bmj.327.7414.557
17. Baimas-George M, Watson M, Thompson K, Shastry V, Iannitti D, Martinie JB, et al. Prehabilitation for hepatopancreatobiliary surgical patients: interim analysis demonstrates a protective effect from neoadjuvant chemotherapy

and improvement in the frailty phenotype. *American Surgeon.* (2021) 87:5. doi: 10.1177/0003134820952378
18. Berglund G, Bolund C, Gustafsson UL, Sjödén PO. One-year follow-up of the "Starting Again" Group rehabilitation programme for cancer patients. *Eur J Cancer.* (1994) 30:12. doi: 10.1016/0959-8049(94)00330-8
19. Bertheussen GF, Kaasa S, Hokstad A, Sandmæl JA, Helbostad JL, Salvesen Ø, et al. Feasibility and changes in symptoms and functioning following inpatient cancer rehabilitation. *Acta Oncol.* (2012) 51:8. doi: 10.3109/0284186X.2012.699684
20. Bonsignore A, Field D, Speare R, Dolan L, Oh P, Santa Mina D. The effect of cardiac rehabilitation in men with and without prostate cancer: A retrospective, comparative cohort study. *J Phys Activity Health.* (2018) 15:10. doi: 10.1123/jpah.2017-0362
21. Boujibar F, Bonnevie T, Debeaumont D, Bubenheim M, Cuvellier A, Peillon C, et al. Impact of prehabilitation on morbidity and mortality after pulmonary lobectomy by minimally invasive surgery: A cohort study. *J Thorac Dis.* (2018) 10:4. doi: 10.21037/jtd.2018.03.161
22. Bousquet-Dion G, Awasthi R, Loiselle SÈ, Minnella EM, Agnihotram R, v Bergdahl A, et al. Evaluation of supervised multimodal prehabilitation programme in cancer patients undergoing colorectal resection: a randomized control trial. *Acta Oncologica.* (2018) 57:6. doi: 10.1080/0284186X.2017.1423180
23. Bradley A, Marshall A, Stonehewer L, Reaper L, Parker K, Bevan-Smith E, et al. Pulmonary rehabilitation programme for patients undergoing curative lung cancer surgery. *Eur J Cardio-Thoracic Surger.* (2013) 44:4. doi: 10.1093/ejcts/ezt381
24. Choi MG, Lee HY, Song SY, Kim SS, Lee SH, Kim W, et al. The effects of simultaneous pulmonary rehabilitation during thoracic radiotherapy in the treatment of malignant diseases. *Tuberc Respir Dis.* (2021) 84:2. doi: 10.4046/trd.2020.0135
25. Dennett AM, Peiris CL, Taylor NF, Reed MS, Shields N. 'A good stepping stone to normality': a qualitative study of cancer survivors' experiences of an exercise-based rehabilitation program. *Supportive Care in Cancer.* (2019) 27:5. doi: 10.1007/s00520-018-4429-1
26. Doganay E, Wynter-Blyth V, Halliday L, Mackinnon T, Osborn H, Moorthy K. Study of long-term follow-up of exercise levels following participation in a prehabilitation program in esophagogastric cancer. *Rehabil Oncol.* (2020) 38:3. doi: 10.1097/01.REO.0000000000000205
27. Dolan LB, Barry D, Petrella T, Davey L, Minnes A, Yantzi A, et al. The cardiac rehabilitation model improves fitness, quality of life, and depression in breast cancer survivors. *J Cardiopulm Rehabil Prev.* (2018) 38:4. doi: 10.1097/HCR.0000000000000256
28. Gaskin TA, Lobuglio A, Kelly P, Doss M, Pizitz N. Stretch: a rehabilitative program for patients with breast cancer. *South Med J.* (1989) 82:4. doi: 10.1097/00007611-198904000-00015
29. Glattki GP, Manika K, Sichletidis L, Alexe G, Brenke R, Spyratos D. Pulmonary rehabilitation in non-small cell lung cancer patients after completion of treatment. *Am J Clin Oncol.* (2012) 35:2. doi: 10.1097/COC.0b013e318209ced7
30. Goldsmith I, Chesterfield-Thomas G, Toghill H. Pre-treatment optimization with pulmonary rehabilitation in lung cancer: making the inoperable patients operable. *E Clinic Med.* (2021) 31:100663. doi: 10.1016/j.eclinm.2020.100663
31. Gordon LG, Battistutta D, Scuffham P, Tweeddale M, Newman B. The impact of rehabilitation support services on health-related quality of life for women with breast cancer. *Breast Cancer Res Treat.* (2005) 93:3. doi: 10.1007/s10549-005-5151-5
32. Halliday LJ, Doganay E, Wynter-Blyth V, Osborn H, Buckley J, Moorthy K. Adherence to pre-operative exercise and the response to prehabilitation in oesophageal cancer patients. *J Gastrointestinal Surg.* (2021) 25:4. doi: 10.1007/s11605-020-04561-2
33. Halliday LJ, Doganay E, Wynter-Blyth VA, Hanna GB, Moorthy K. The impact of prehabilitation on post-operative outcomes in oesophageal cancer surgery: a propensity score matched comparison. *J Gastrointestinal Surg.* (2020) 1–19. doi: 10.1007/s11605-020-04881-3
34. Hanssens S, Luyten R, Watthy C, Fontaine C, Decoster L, Baillon C, et al. Evaluation of a comprehensive rehabilitation program for post-treatment patients with cancer. *Oncol Nurs Forum.* (2011) 38:6. doi: 10.1188/11.ONF.E418-E424
35. Heim ME, Malsburg MLE, vd Niklas A. Randomized controlled trial of a structured training program in breast cancer patients with tumor-related chronic fatigue. *Onkologie.* (2007) 30:8–9. doi: 10.1159/000104097
36. Janssen SMJ, Abbink JJ, Lindeboom R, Vliet Vlieland TPM. Outcomes of pulmonary rehabilitation after treatment for non-small cell lung cancer stages i to IIIa: an observational study. *J Cardiopulm Rehabil Prev.* (2017) 37:1. doi: 10.1097/HCR.0000000000000227
37. Kirkham AA, Klika RJ, Ballard T, Downey P, Campbell KL. Effective translation of research to practice: Hospital-based rehabilitation program improves health-related physical fitness and quality of life of cancer survivors. *JNCCN.* (2016) 14:12. doi: 10.6004/jnccn.2016.0167
38. Korstjens I, Mesters I, Gijsen B, van den Borne B. Cancer patients' view on rehabilitation and quality of life: a programme audit: original article. *Eur J Cancer Care.* (2008) 17:3. doi: 10.1111/j.1365-2354.2007.00864.x
39. Korstjens I, Mesters I, van der Peet E, Gijsen B, van den Borne B. Quality of life of cancer survivors after physical and psychosocial rehabilitation. *Eur J Cancer Prevent.* (2006) 15:6. doi: 10.1097/01.cej.0000220625.77857.95
40. Kröz M, Reif M, Glinz A, Berger B, Nikolaou A, Zerm R, et al. Impact of a combined multimodal-aerobic and multimodal intervention compared to standard aerobic treatment in breast cancer survivors with chronic cancer-related fatigue - results of a three-armed pragmatic trial in a comprehensive cohort design. *BMC Cancer.* (2017) 17:1. doi: 10.1186/s12885-017-3142-7
41. Marhic A, Dakhil B, Plantefeve G, Zaimi R, Oltean V, Bagan P. Long-term survival following lung surgery for cancer in high-risk patients after perioperative pulmonary rehabilitation. *Interact Cardiovasc Thorac Surg.* (2019) 28:2. doi: 10.1093/icvts/ivy225
42. Morris GS, Gallagher GH, Baxter MF, Brueilly KE, Scheetz JS, Ahmed MM, et al. Pulmonary rehabilitation improves functional status in oncology patients. *Arch Phys Med Rehabil.* (2009) 90:5. doi: 10.1016/j.apmr.2008.12.005
43. O'Neill LM, Guinan E, Doyle SL, Bennett AE, Murphy C, Elliott JA, et al. The RESTORE randomized controlled trial: Impact of a multidisciplinary rehabilitative program on cardiorespiratory fitness in esophagogastric cancer survivorship. *Ann Surg.* (2018) 268:5. doi: 10.1097/SLA.0000000000002895
44. Rossen S, Trier K, Christensen B, Eriksen MA, Zwisler AD, Vibe-Petersen J. Municipality-based pragmatic rehabilitation stratified in accordance with individual needs—results from a longitudinal survey study. *Support Care Cancer.* (2020) 28:4. doi: 10.1007/s00520-019-04993-w
45. Rothe D, Cox-Kennett N, Buijs DM, Venner CP, Paterson DI, Gyenes GT, et al. Cardiac rehabilitation in patients with lymphoma undergoing autologous hematopoietic stem cell transplantation: a cardio-oncology pilot project. *Canad J Cardiol.* (2018) 34:10. doi: 10.1016/j.cjca.2018.07.001
46. Sterzi S, Cesario A, Cusumano G. Dall'Armi V, Lapenna LM, Cardaci V, et al. Post-operative rehabilitation for surgically resected non-small cell lung cancer patients: Serial pulmonary functional analysis. *J Rehabilit Med.* (2013) 45:9. doi: 10.2340/16501977-1192
47. Velthuis MJ, Peeters PH, Gijsen BC, van den Berg JP, Koppejan-Rensenbrink RA, Vlaeyen JW, et al. Role of fear of movement in cancer survivors participating in a rehabilitation program: a longitudinal cohort study. *Arch Phys Med Rehabil.* (2012) 93:2. doi: 10.1016/j.apmr.2011.08.014
48. Wu F, Laza-Cagigas R, Pagarkar A, Olaoke A, el Gammal M, Rampal T. The feasibility of prehabilitation as part of the breast cancer treatment pathway. *PM and R.* (2020). doi: 10.1002/pmrj.12543
49. Young-McCaughan S, Mays MZ, Arzola SM, Yoder LH, Dramiga SA, Leclerc KM, et al. Research and commentary: change in exercise tolerance, activity and sleep patterns, and quality of life in patients with cancer participating in a structured exercise program. *Oncol Nurs Forum.* (2003) 30:3. doi: 10.1188/03.ONF.441-454
50. Zhou K, Su J, Lai Y, Li P, Li S, Che G. Short-term inpatient-based high-intensive pulmonary rehabilitation for lung cancer patients: Is it feasible and effective? *J Thorac Dis.* (2017) 9:11. doi: 10.21037/jtd.2017.10.105
51. Zvinovski F, Stephens JA, Ramaswamy B, Reinbolt RE, Noonan AM, Vandeusen JB, et al. A cardiac rehabilitation program for breast cancer survivors: a feasibility study. *J Oncol.* (2021) 2021:9965583. doi: 10.1155/2021/9965583
52. Bonsignore A, Marzolini S, Oh P. Cardiac rehabilitation for women with breast cancer and treatmentrelated heart failure compared with

coronary artery disease: a retrospective study. *J Rehab Med.* (2017) 49:3. doi: 10.2340/16501977-2203
53. Groarke JD, Payne DL, Claggett B, Mehra MR, Gong J, Caron J, et al. Association of post-diagnosis cardiorespiratory fitness with cause-specific mortality in cancer. *Eur Heart J Quality Care Clin Outcom.* (2020) 6:4. doi: 10.1093/ehjqcco/qcaa015
54. Scott JM, Zabor EC, Schwitzer E, Koelwyn GJ, Adams SC, Nilsen TS, et al. Efficacy of exercise therapy on cardiorespiratory fitness in patients with cancer: a systematic review and meta-analysis. *J Clin Oncol.* (2018) 36:22. doi: 10.1200/JCO.2017.77.5809
55. Kasymjanova G, Correa JA, Kreisman H, Dajczman E, Pepe C, Dobson S, et al. Prognostic value of the six-minute walk in advanced non-small cell lung cancer. *J Thoracic Oncol.* (2009) 4:5. doi: 10.1097/JTO.0b013e31819e77e8
56. Schmidt K, Vogt L, Thiel C, Jäger E, Banzer W. Validity of the six-minute walk test in cancer patients. *Int J Sports Med.* (2013) 34:7. doi: 10.1055/s-0032-1323746
57. Inoue T, Ito S, Kanda M, Niwa Y, Nagaya M, Nishida Y, et al. Preoperative six-minute walk distance as a predictor of postoperative complication in patients with esophageal cancer. *Dis Esophagus.* (2020) 33:2. doi: 10.1093/dote/doz050
58. Granger CL, Holland AE, Gordon IR, Denehy L. Minimal important difference of the 6-minute walk distance in lung cancer. *Chron Respir Dis.* (2015) 12:2. doi: 10.1177/1479972315575715
59. Muscaritoli M, Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, et al. ESPEN practical guideline: clinical Nutrition in cancer. *Clin Nutr.* (2021) 40:5. doi: 10.1016/j.clnu.2021.02.005
60. Burgess C, Cornelius V, Love S, Graham J, Richards M, Ramirez A. Depression and anxiety in women with early breast cancer: five year observational cohort study. *Br Med J.* (2005) 330:7493. doi: 10.1136/bmj.38343.670868.D3
61. Yusuf PS, Hawken S, Ôunpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *Lancet.* (2004) 364:9438. doi: 10.1016/S0140-6736(04)17018-9
62. Chaddha A, Robinson EA, Kline-Rogers E, Alexandris-Souphis T, Rubenfire M. Mental health and cardiovascular disease. *Am J Med.* (2016) 129:11. doi: 10.1016/j.amjmed.2016.05.018
63. Swardfager W, Herrmann N, Marzolini S, Saleem M, Farber SB, Kiss A, et al. Major depressive disorder predicts completion, adherence, and outcomes in cardiac rehabilitation: a prospective cohort study of 195 patients with coronary artery disease. *J Clin Psychiat.* (2011) 72:9. doi: 10.4088/JCP.09m05810blu
64. Grace SL, Turk-Adawi KI, Contractor A, Atrey A, Campbell N, Derman W, et al. Cardiac rehabilitation delivery model for low-resource settings. Heart (2016) 102(18). doi: 10.1136/heartjnl-2015-309209
65. Kirkham AA. Supervised, multimodal exercise: the chemotherapy supportive therapy that almost does it all. *Oncologist.* (2020) 25:1. doi: 10.1634/theoncologist.2019-0628
66. Norris CM, Jensen LA, Galbraith PD, Graham MM, Daub WD, Knudtson ML, et al. Referral rate and outcomes of cardiac rehabilitation after cardiac catheterization in a large Canadian city. *J Cardiopulm Rehabil.* (2004) 24:6. doi: 10.1097/00008483-200411000-00006
67. Milner SC, Boruff JT, Beaurepaire C, Ahmed S, Janaudis-Ferreira T. Rate of, and barriers and enablers to, pulmonary rehabilitation referral in COPD: A systematic scoping review. *Respir Med.* (2018) 137:103–14. doi: 10.1016/j.rmed.2018.02.021
68. Covington KR, Hidde MC, Pergolotti M, Leach HJ. Community-based exercise programs for cancer survivors: a scoping review of practice-based evidence. *Support Care Cancer.* (2019) 27:12. doi: 10.1007/s00520-019-05022-6
69. American College of Sports Medicine. ACSM/ACS Certified Cancer Exercise Trainer (2021). Available online at: https://www.acsm.org/get-stay-certified/get-certified/specialization/cet/ (accessed July 9, 2021).
70. Hayward R. Clinical Cancer Exercise Specialist Workshop (2020). Available online at: https://www.unco.edu/nhs/cancer-rehabilitation-institute/education/workshop/ (accessed July 9, 2021).
71. Commission on Dietetic Registration. Board Certification as a Specialist in Oncology Nutrition (2021). Available online at: https://www.cdrnet.org/certifications/board-certification-as-a-specialist-in-oncology-nutrition (accessed July 9, 2021).
72. Association of Oncology Social Work. Oncology Social Work Certification (2021). Available online at: https://aosw.org/publications-media/oncology-social-work-specialty-certification/ (accessed July 9, 2021).
73. Shields GE, Wells A, Doherty P, Heagerty A, Buck D, Davies LM. Cost-effectiveness of cardiac rehabilitation: a systematic review. *Heart.* (2018) 104:1403–10. doi: 10.1136/heartjnl-2017-312809
74. Gubler-Gut BE, Pöhlmann J, Flatz A, Schwenkglenks M, Rohrmann S. Cost-effectiveness of physical activity interventions in cancer survivors of developed countries: a systematic review. *J Cancer Survivorship.* (2021) 23:1–5. doi: 10.1007/s11764-021-01002-0
75. Tran M, Pesah E, Turk-Adawi K, Supervia M, Lopez Jimenez F, Oh P, et al. Cardiac rehabilitation availability and delivery in Canada: how does it compare with other high-income countries? *Canad J Cardiol.* (2018) 34:S252–62. doi: 10.1016/j.cjca.2018.07.413

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 04 October 2021
doi: 10.3389/fcvm.2021.735485

Treadmill Exercise Attenuates Cerebral Ischemia–Reperfusion Injury by Promoting Activation of M2 Microglia via Upregulation of Interleukin-4

Juanjuan Lu[1,2†], *Jie Wang*[1†], *Long Yu*[1†], *Rong Cui*[1,2†], *Ying Zhang*[1*], *Hanqing Ding*[3*] and *Guofeng Yan*[4]

[1] Department of Rehabilitation, Shanghai Xuhui Central Hospital, Shanghai, China, [2] School of Kinesiology, Shanghai University of Sport, Shanghai, China, [3] Academy of Integrative Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China, [4] School of Medicine, Shanghai Jiao Tong University, Shanghai, China

OPEN ACCESS

Edited by:
Jian Yang,
Fudan University, China

Reviewed by:
Gilbert Lee,
Taipei Medical University, Taiwan
Yulong Bai,
Huashan Hospital Affiliated to Fudan University, China

***Correspondence:**
Ying Zhang
ZhangYing032317@163.com
Hanqing Ding
dudu_paredise@126.com

[†]These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to General Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

Received: 02 July 2021
Accepted: 13 September 2021
Published: 04 October 2021

Citation:
Lu J, Wang J, Yu L, Cui R, Zhang Y, Ding H and Yan G (2021) Treadmill Exercise Attenuates Cerebral Ischemia–Reperfusion Injury by Promoting Activation of M2 Microglia via Upregulation of Interleukin-4. Front. Cardiovasc. Med. 8:735485. doi: 10.3389/fcvm.2021.735485

Background: Exercise has been proven to be an effective therapy for stroke by reducing the microglia-initiated proinflammatory response. Few studies, however, have focused on the phenotypic changes in microglia cells caused by exercise training. The present study was designed to evaluate the influence of treadmill exercise on microglia polarization and the molecular mechanisms involved.

Methods: Male Sprague-Dawley rats were randomly assigned into 3 groups: sham, MCAO and exercise. The middle cerebral artery occlusion (MCAO) and exercise groups received MCAO surgery and the sham group a sham operation. The exercise group also underwent treadmill exercise after the surgery. These groups were studied after 4 and 7 days to evaluate behavioral performance using a modified neurological severity score (mNSS), and infarct conditions using 2,3,5-triphenyl tetrazolium chloride. Quantitative real-time polymerase chain reaction (qRT-PCR) and Luminex was employed to determine the expressions of markers of microglia phenotypes. Western blotting was employed to identify the phosphorylation levels of Janus kinase1 (JAK1) and signal transducer and activator of transcription 6 (STAT6). Immunofluorescence was conducted to identify microglia phenotypes.

Results: Treadmill exercise was found to improve neurobehavioral outcomes, mainly motor and balance functions, reduce infarct volumes and significantly increase interleukin-4 (IL-4) expression. In addition, treadmill exercise inhibited M1 microglia and promoted M2 microglia activation as evidenced by decreased M1 and increased M2 markers. Furthermore, an obvious increase in p-JAK1 and p-STAT6 was observed in the exercise group.

Conclusions: Treadmill exercise ameliorates cerebral ischemia–reperfusion injury by enhancing IL-4 expression to promote M2 microglia polarization, possibly via the JAK1-STAT6 pathway.

Keywords: treadmill exercise, anti-inflammation, cerebral ischemia–reperfusion injury, M2 microglia, interleukin-4

INTRODUCTION

Clinically, early exercise has been proven to be an effective method to promote motor recovery in patients with ischemic stroke (1, 2). Experimental studies have also demonstrated that treadmill training is beneficial in ameliorating neurological deficits in rats after cerebral ischemia (3, 4). Further analysis of the mechanism of exercise-induced neuroprotection revealed decreased activation of resident cells such as microglia and astrocytes (5, 6), suppressed expression of pro-inflammatory cytokines (6, 7), and reduced leukocyte infiltration in the penumbra (8, 9), results consistent with our previous findings (10).

It has been shown that activated microglia become rapidly polarized into different phenotypes in response to ischemic conditions (11). The anti-inflammatory phenotype, known as M2, emerged at the border of the ischemic area from the 1 day, reached a peak expression at 5 days after MCAO, then decreased over 7 to 14 days after MCAO, but was still higher than in the sham group. By comparison, the inflammatory phenotype M1, appeared in the penumbra after 3 days and was maintained at a high level until day 14 after MCAO (12). These data suggested that the M1 phenotype gradually took the place of the M2 phenotype, dominating at the infarct border. Therefore, maintaining the M2 phenotype and inhibiting the M1 phenotype in the penumbra is crucial for the attenuation of cerebral ischemia reperfusion (CI/RP) injury. Our previous study found that treadmill exercise effectively inhibited microglia activation and diminished the expression of pro-inflammatory mediators, including interleukin-1β (IL-1β) and monocyte chemotactic protein-1 (MCP-1), at 3 and 6 days post-injury (10). Since the M1 phenotype is able to produce pro-inflammatory cytokines, it is reasonable to link the exercise-induced neuroprotection to a significant decline in the M1 phenotype in the penumbra. Even so, the effects of treadmill exercise on anti-inflammatory cytokines and the M2 microglia associated with these cytokines still remains unknown.

To date, IL-4 has been reported to participate in neuroprotection against cerebral ischemia and that the upregulation of M2 microglia induced by IL-4 treatment has a neuroprotective effect (13, 14). Liu et al. reported that IL-4 deficiency disrupted neurological functions and impaired microglia M2 polarization in mice after stroke (15). These investigations suggested that IL-4 is actively involved in promoting functional recovery through induction of the M2 phenotype. Recently, testing with a customized magnetic rat premixed multi analyte kits for multiple anti-inflammatory cytokines, including interleukin-10 (IL-10), interleukin-4 (IL-4), interleukin-13 (IL-13), and so on, we discovered a significant increase in the protein level of IL-4 after 3- and 6-days of treadmill exercise. We speculated that IL-4 might be involved in the process by which treadmill exercise exerts a beneficial effect after CI/RP injury. Thus, this question deserves further study of the anti-inflammatory mechanisms involved in treadmill training after MCAO and in particular the potential role of IL-4.

The Janus kinase (JAK) signal transducer and activator of transcription 6 (STAT6) signaling is acknowledged as the primary pathway involved in IL-4 responsiveness and its effects in modulating inflammatory events (16–18). Koh et al. discovered that IL-4 activated STAT6 to regulate M1/M2 polarization in various diseases arising as a result of inflammation (19). He et al. found that the administration of IL-4 led to a transition between M1 and M2a phenotypes through the JAK1/STAT6 pathway to promote post stroke recovery (20). Therefore, elucidation of the IL-4 and related signaling pathways involved in the protective effect induced by treadmill exercise in a stroke model is needed.

In the present study, we evaluated the mechanisms underlying the improvements in neurobehavioral deficits after treadmill training and whether IL-4 boosted microglia to polarize from the M1 to M2 phenotype in exercise-mediated neuroprotection in MCAO rats.

MATERIALS AND METHODS

Animals

Adult, male Sprague Dawley (weighing 250–320 g) rats were obtained from the Slack Experimental Animal Company (Shanghai, China). The rats were housed in cages (4 rats per cage) at 23°C in a 12/12 h light/dark cycle, with *ad libitum* access to food and water. In total 117 rats were familiarized with the environment for 1 week prior to operations and then were randomly allocated into a treadmill exercise, MCAO or sham operation group. All the experimental procedures were carried out according to the National Institutes of Health (NIH) guidelines for the care and use of laboratory animals. The experimental protocols were approved by the Ethics Committee of Shanghai Jiao Tong University (Ethical code: 2019027). All efforts were made to minimize the number of animals used and their suffering.

Middle Cerebral Artery Occlusion Model

Rats in the exercise and MCAO groups underwent right middle cerebral artery occlusion-reperfusion surgery. After accurate weighing, rats were anesthetized intraperitoneally before surgery. Subsequently, they were position on the operating table in a supine position and shaved to expose the neck. An incision was made in the neck skin and the right common cervical artery (CCA), external carotid artery (ECA), internal carotid artery (ICA) and wing palatine artery isolated. A filament with a silicone tip of 2.0 cm was inserted through the incision into the lumen of the ICA and when it reached 1.8–2.0 cm it occluded the ostium of the right middle cerebral artery (MCA) to produce cerebral ischemia for 120 min; then the filament was removed to enable reperfusion. The rats underwent the Zea-Longa test (21) after reperfusion for 24 h and only those with scores of 1–3 were used for experiments. The same operation procedure was performed in rats of the sham operation group except that the filament was advanced into the ICA. The chosen area of penumbra in the cortex and striatum was as follows (**Figure 1**).

Exercise Intervention

A motorized treadmill (ZH-PT/5s, Huaibei Zhenghua, Anhui) was used in the present study. Before surgery, rats in the exercise group were familiarized with treadmill running over a 3-day

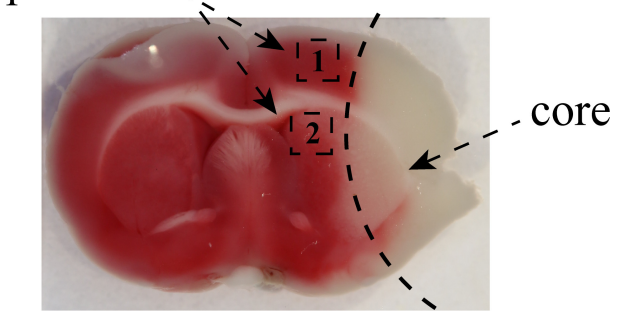


FIGURE 1 | The images of the penumbra after MCAO. The images showed that the black zone marked as "1" represented the selected cortex region near the infarct core and the area labeled as "2" was marginal striatum around the infarct core. We used the brain tissue from penumbra to perform qRT-PCR, Luminex multiplex assay, and Western blotting. The area of penumbra in the cortex and striatum for immunofluorescence staining was chosen as shown.

period (12 m/min, 10 min/day). Twenty four hour after the MCAO procedure, rats in the exercise group were trained on the treadmill (0° slope) for 30 min for 3 or 6 consecutive days. The treadmill velocity was increased every 10 min from 5 to 9 m/min and finally to 12 m/min. Rats in the MCAO and sham groups remained on the treadmill for 30 min without running.

Evaluation of Neurological Scores

For neurological deficit assessment, all rats were scored using an 18-point modified neurological severity score (mNSS) 1, 4, and 7 days after CI-RP by an operator who had no knowledge of the treatment allocation. mNSS is comprised of motor, sensory, reflex and balance tests (22). The score was graded from 0 to 18 points, where 0 represents normality with no neurological signs and a higher score indicates a more severe neurological injury.

Infarct Assessment

2,3,5-triphenyltetrazolium chloride (TTC) was used to estimate the volume of the brain infarct. When the last neuro-score was completed, the rats were deeply anesthetized. The brains were rapidly removed and kept at −20°C for 10 min and then sequentially sliced into 2-mm coronal sections. The sections were immersed in 2% TTC and incubated at 37°C for 30 min in the dark. Then, the brain sections were fixed in 4% paraformaldehyde for 24 h and images were recorded using a digital camera.

Quantitative Real-Time Polymerase Chain Reaction Analysis

Total RNA was extracted from the penumbra and its concentration and purity examined using BioPhotometer plus (Eppendorf). Subsequently, RNA (1 μg) was reverse transcribed into cDNA, which was then added to a reaction system that included primers and SYBR Green. The quantity of IL-4 was determined using the Applied Biosystems (7500 Real-Time PCR Software, RRID:SCR_014596). The kits used for total RNA extraction, cDNA synthesis and rt-PCR were all obtained from Tiangen Biotech (Beijing, China). U6 (Cat#B661602-0002, Sangon, Shanghai) served as the internal control and mRNA expression was determined using the $2^{-\Delta\Delta CT}$ method (23). The forward primer sequence for IL-4 was: GTACCGGGAACGGTATCCAC, which was designed based on previous studies (24). All experiments were repeated three times.

Luminex Multiplex Assay

The supernatants from the isolated brain tissue were collected. The concentrations of cytokines including IL-4, IL-10, IL-13, IL-1a, IL-1b, IL-6, and MCP-1 were measured using the Bio-Plex Pro™ Rat Cytokine 23-Plex Assay (Cat#12005641, Bio-Rad, Hercules, CA) by Luminex technology, following the manufacturer's instructions. The cytokine concentrations were determined using a Luminex 200 instrument. The expression of proteins is given in units of pg/mg.

Western Blotting

The extracted protein of the penumbra was homogenized in RIPA lysis buffer (Yamei, Suzhou) according to the manufacturer's instructions. The supernatant of proteins was subjected to 10% sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to nitrocellulose membranes, which were sealed with 5% skimmed milk for 2 h at room temperature. The rinsed membrane and primary antibody were incubated together overnight at 4°C, including p-JAK1 (Cat#YP0154, Immunoway, dilution 1:500), p-STAT6 (Cat#YP0256, Immunoway, dilution 1:400) and GAPDH (Cat#YM3029, Immunoway, dilution 1:5000). After 3 washes with TBST, samples were exposed for 2 h at room temperature to secondary antibodies (Immunoway, dilution 1:10,000). The bands were observed using an Odyssey Infrared Imaging System 3.0.29 (LICOR, Nebraska). All experiments were repeated three times.

Double Immunofluorescence Staining

The brains of every group were sectioned coronally at 40 μm intervals using a freezing microtome. Slices were soaked in 0.1% Triton X-100 in PBS for 10 min and then blocked for 1 h. Subsequently, let the slices incubate overnight at 4°C in the mixed solution of rabbit anti-Iba1 (Cat# 019-19741, Wako, RRID: AB_839504, dilution 1:500) and mouse anti-CD68 (Cat# MCA341R, Bio-Rad, RRID: AB_2291300, dilution 1:50) or mouse anti-Arg-1 (Cat# sc-271430, Santa Cruz Biotechnology, RRID: AB_10648473, dilution 1:25). After rinsing 3 times with PBS the next day, incubation fluid was replaced with corresponding secondary antibodies labeled with goat anti-rabbit IgG–Alexa Fluor 555 (Cat# A-21428, Thermo Fisher Scientific, RRID: AB_2535849, dilution 1:1000) and goat anti-mouse IgG–Alexa Fluor 488 (Cat# A-11029, Thermo Fisher Scientific, RRID: AB_2534088, dilution 1:500). DAPI (Cat#G1012, Servicebio, Wuhan) counterstaining was applied to label the cell nuclei for 10 min. Images were captured using a Zeiss confocal microscope (LSM 800) and ZEN imaging systems (ZEN Digital Imaging for Light Microscopy, RRID:SCR_013672) at ×100 magnification and the number of CD68 and Arg-1 in $Iba1^+$ cells in the cerebral

cortex and striatum were quantified with Image-J 1.51 software (Media Cybernetics Inc. Co., Shanghai, China).

Statistical Analysis

All data were evaluated using SPSS version 26.0 (IBM SPSS Statistics, RRID:SCR_019096) or GraphPad Prism version 8.3.0 (GraphPad Prism, RRID:SCR_002798). Mean ± standard deviation (SD) was used to describe the results. Student's *t*-test was adopted to analyze data quantitatively between 2 groups and one-way ANOVA for multiple group comparisons, followed by LSD as the *post-hoc* test. A $P < 0.05$ was considered to be a statistically significant finding.

RESULTS

Treadmill Exercise Alleviated Neurological Deficits and Reduced the Infarct Volume After MCAO

To identify the neuroprotective effects of treadmill exercise, the functional deficits and infarct volume at the indicated time points were evaluated. As shown in **Figure 2A**, the difference in baseline of mNSS between the MCAO and exercise groups was not remarkable. The rats treated with treadmill exercise for 4 days did not exhibit a significant decrease in neurological scores ($P > 0.05$), but showed a greater reduction at 7 days compared to the MCAO group ($P < 0.01$), especially in the motor ($P < 0.01$) and balance ($P < 0.05$) subitems. Since rats in the sham operation group had no deficit, their mNSS scores were 0, which are not reported in this paper. These data indicated that treadmill exercise was effective in promoting functional recovery after MCAO.

The TTC analysis revealed that MCAO surgery produced histologically proven damage to the cortex and striatum in the MCAO group. The increased infarct volume induced in the MCAO group appeared to be attenuated by the treadmill exercise intervention, an effect which was not quantified in the present study (**Figure 2B**).

Treadmill Exercise Inhibited M1 Microglia Polarization and Promoted Microglia Polarization Toward M2 Phenotype After MCAO

To determine which subtype of microglia was activated in the cortex and striatum in response to MCAO and treadmill exercise, double immunostaining for microglial biomarker Iba1$^+$ and M1-like marker CD68 or M2-like marker Arg-1 was performed in this study, respectively. As expected, CD68$^+$ M1 microglia in the cortex (**Figure 3A**) and striatum (**Figure 3B**) was observed with a smaller number at 24 h and gradually increased over time, especially at 7 d ($P < 0.01$ for cortex, and striatum) after MCAO. Three-day ($P < 0.05$ for striatum) and 6-day ($P < 0.01$ for cortex, and striatum) of treadmill exercise significantly curbed this growing tendency. In contrast, among 24 h, 4, and 7 d after MCAO, the highest level of Arg-1$^+$ M2 microglia of the cortex (**Figure 3C**) and striatum (**Figure 3D**) was observed at 4 d ($P < 0.01$ for cortex, $P < 0.05$ for striatum) and treadmill exercise lasting for 6 d raised it to a much higher level compared to the corresponding time point in the MCAO group ($P < 0.05$ for cortex, $P < 0.01$ for striatum). These data suggested that there is a fair chance that treadmill exercise suppressed inflammation by reducing M1 microglia and facilitating the expression of M2 microglia.

Treadmill Exercise Altered the Levels of M1/M2 Markers

To explore further the effects of treadmill exercise on microglia polarization, we analyzed the expression of surface markers on M1/M2 phenotypes in the penumbra using Luminex Multiplex Assays. As shown in **Figure 4**, the level of M1-like markers, including IL-1a, IL-1b, IL-6, and MCP-1, and the M2-like marker IL-10 were strongly affected by the treadmill exercise intervention. IL-1a expression (**Figure 4A**) reached the highest level at 24 h ($P < 0.05$), then continued decreasing to the lowest level ($P < 0.05$) at 7 d after MCAO compared to the sham group. It was found that IL-1b expression (**Figure 4B**) was induced and elevated at 24 h, further increased and peaked at day 4 ($P < 0.05$) and then decreased at day 7 after MCAO compared to the sham group. The levels of IL-6 (**Figure 4C**) and MCP-1 (**Figure 4D**) reached their peaks at 24 h ($P < 0.01$ for IL-6, $P < 0.05$ for MCP-1) after MCAO and then rapidly declined, but still remained elevated compared to the sham group. The expression of IL-10 (**Figure 4E**) increased at 24 h, with a peak at 4 days ($P < 0.01$), and decreased rapidly by day 7 ($P < 0.01$) in the MCAO group. Treadmill exercise significantly reduced the protein expression of IL-1a, IL-1b, IL-6, and MCP-1 on day 4 ($P < 0.05$ for IL-1a, $P < 0.01$ for IL-1b and IL-6) and day 7 ($P < 0.05$ for IL-1a and MCP-1, $P < 0.01$ for IL-1b and IL-6), except for the MCP-1 expression at 4 d post-surgery compared to the MCAO group. In contrast to the levels of M1-like markers, the protein level of IL-10 was significantly higher only on day 7 post-surgery ($P < 0.01$) in the exercise group. These results indicated that treadmill exercise contributed to inhibiting the M1 phenotype at first and in addition then resulted in an enhancement of M2 polarization.

Treadmill Exercise Increased the Expression of IL-4 After MCAO

To determine whether IL-4 or IL-13 promoted M2 polarization in the penumbra after treadmill exercise, Luminex Multiplex Assays were developed to establish the protein levels of IL-13 (**Figure 5A**) and IL-4 (**Figure 5B**) at the indicated time points among the sham, MCAO and exercise groups, respectively. The results suggested that the level of IL-4 increased significantly after the 6-day treadmill exercise ($P < 0.01$) compared to the MCAO group. Subsequently, we used qRT-PCR to measure the gene level of IL-4. Data analysis clearly revealed a significant gain in the mRNA level of IL-4 in the exercise group on both day 4 ($P < 0.01$) and day 7 ($P < 0.01$) post-surgery compared to the MCAO group (**Figure 5C**). These findings suggested that upregulation of IL-4 signaling is involved in exercise-mediated functional recovery after MCAO.

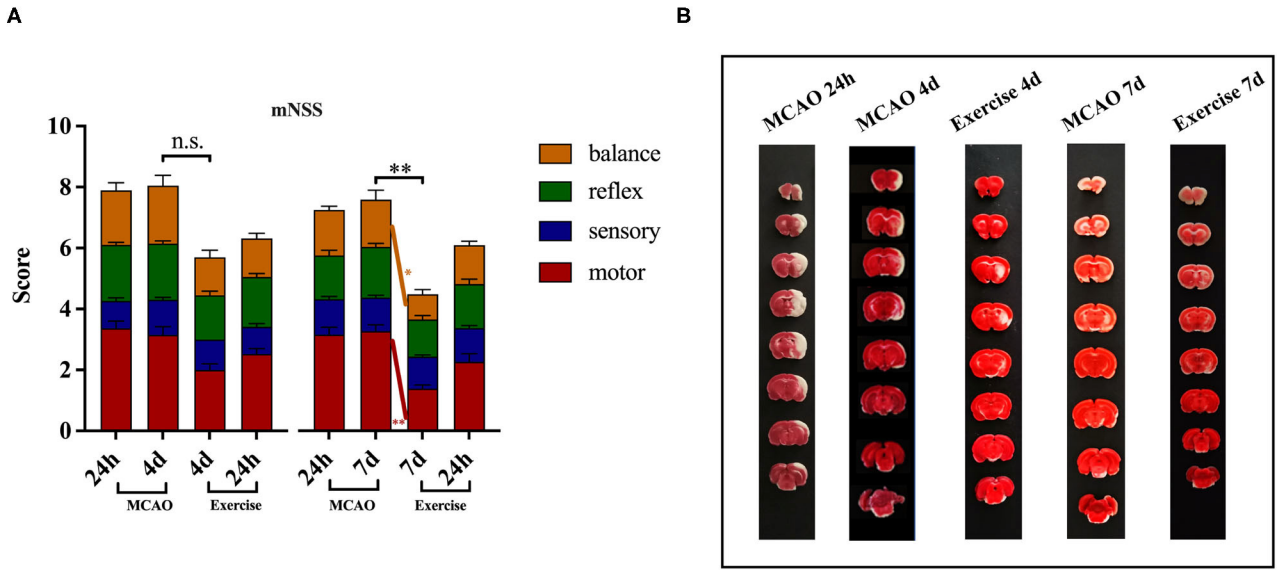


FIGURE 2 | Treadmill exercise alleviated neurological deficits and reduced infarct volume after MCAO. **(A)** Behavioral functions were assessed using mNSS in the MCAO and exercise groups 24 h post-surgery before the animals were humanely killed (MCAO group: $n = 19$ for 4-day time points, $n = 18$ for 7-day time points; Exercise group: $n = 20$ for 4-day, $n = 18$ for 7-day time points). The data are presented as the mean ± SD. n.s.: $p > 0.05$, $^{*}P < 0.05$, $^{**}P < 0.01$ vs. MCAO group. **(B)** Representative images of brain sections (8 consecutive sections at 2.0 mm intervals from bregma) obtained after TTC staining from rats in the MCAO and exercise groups before they were humanely killed ($n = 1$ per group).

Treadmill Exercise Regulated Microglia Polarization Through the JAK1/STAT6 Pathway After MCAO

Treadmill exercise enhanced IL-4 expression, stimulating the upregulation of the M2 phenotype. To establish whether JAK1/STAT6 pathway activation was involved, the protein levels of p-JAK1 and p-STAT6 were detected using western blot analysis. The results showed that the p-JAK1 expression was significantly increased in the exercise vs. MCAO group on day 4 ($P < 0.01$, **Figures 6A,B**) and day 7 ($P < 0.01$, **Figures 6A,B**) post-surgery. The p-STAT6 was markedly increased at 7 d in the exercise group in comparison to the MCAO group ($P < 0.01$, **Figures 6A,C**). These data suggested that JAK1/STAT6 was activated after treadmill exercise intervention.

DISCUSSION

In the present study, we verified that treadmill exercise could exert its neuroprotective effects by downregulating the levels of the M1 microglia phenotype. To our surprise, treadmill exercise played a role in facilitating the anti-inflammatory reaction by accelerating the polarization from the M1 to M2 phenotype and by upregulating the production of the anti-inflammatory cytokine IL-4. We showed that treadmill exercise intervention significantly elevated the level of IL-4 to promote M2 polarization for brain repair and suggest that the JAK1-STAT6 pathway might be involved in mediating the IL-4 effect.

Previous reports have concluded that the onset time of therapeutic exercise did not show any benefit either within 3 h or 3 days after modeling (25). Li et al. conducted several animal studies and found that 6 h after reperfusion that inflammatory injury was exacerbated, but 24 h and 3 days stroke recovery was enhanced (26, 27). These findings are consistent with results from other studies in which exercise beginning 24 h post-surgery produced beneficial effects (28, 29). In addition, Morrison et al. showed the morphology of microglia was changed and that microglia activity was greatly decreased after 24 h of reperfusion (30). Temporal profile analysis of microglia expression and activation in ischemic animals revealed that both were significantly increased in the peri-ischemic area at 96 h and especially 7 days after reperfusion (31). Therefore, we chose 24 h after CI/RP as exercise initiation timing and day 4 and day 7 post-surgery to investigate the effects of treadmill exercise on microglia polarization and inflammatory responses.

Previous studies have shown that a long-lasting inflammatory response contributes to neurodegeneration and the aggravation of brain injury after stroke (32, 33). Exercise has been reported to induce anti-microglial activation which may effectively modulate inflammation in different diseases of the central nervous system (34–36), at least partly because of the increased secretion of anti-inflammatory factors (37–39) and a decrease in pro-inflammatory cytokines (40–42). For example, Zhang et al. found that swimming inhibited microglia activation in the hippocampus via upregulation of IL-4 after global cerebral ischemia (34). It has been reported that treadmill exercise suppressed microglia-induced neuroinflammation via

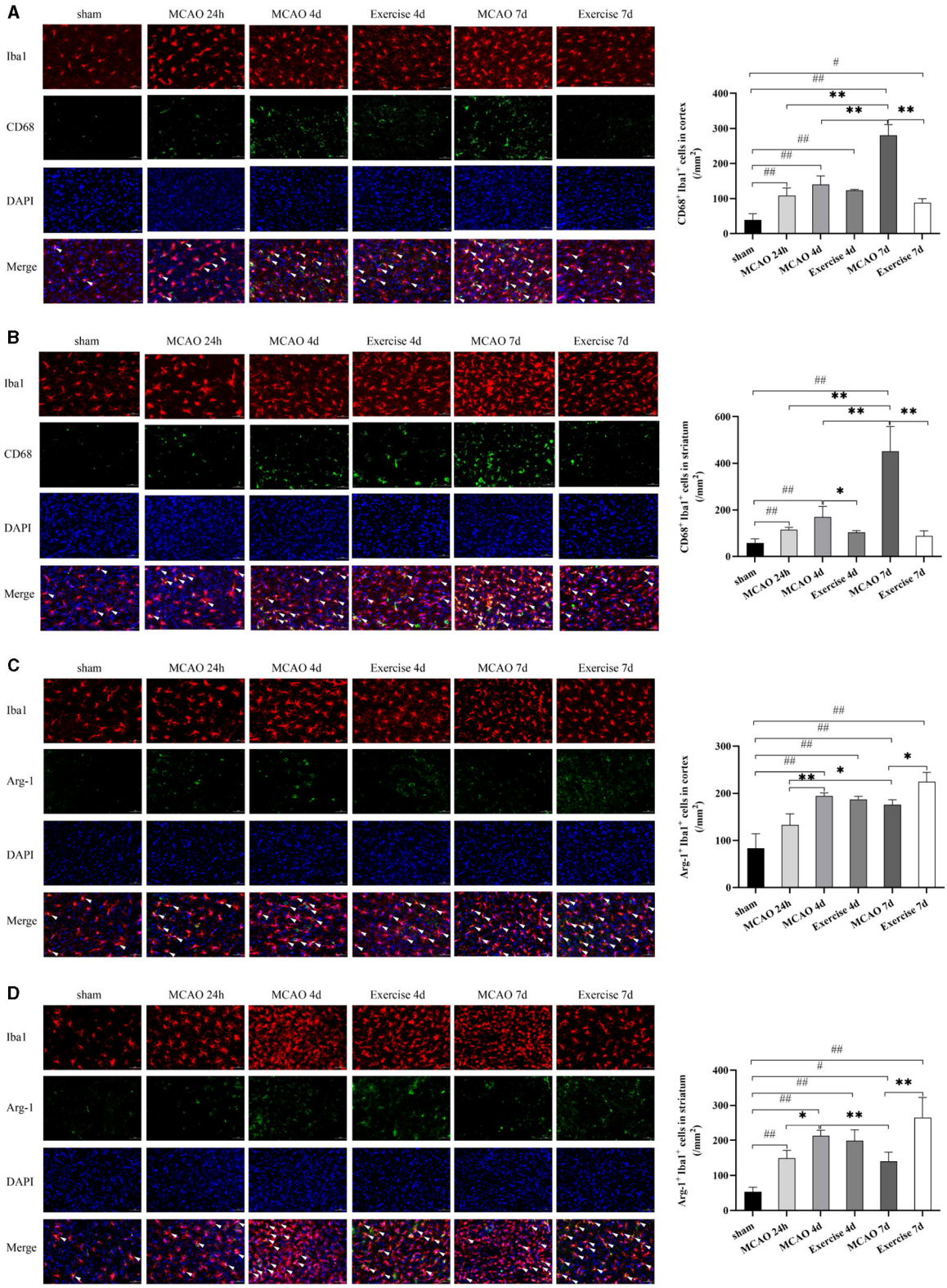


FIGURE 3 | Treadmill exercise inhibited M1 microglia polarization and promoted microglia polarization toward M2 Phenotype after MCAO. Double immunostaining with Iba1 and CD68 or Arg-1 at 24 h, 4, and 7d among the sham, MCAO and exercise groups was performed in this study. **(A,B)** representative images of immunostaining with Iba1 and CD68 in the cortex **(A)** and striatum **(B)** and the corresponding histogram was shown on the right side. **(C,D)** representative images of immunostaining with Iba1 and Arg-1 in the cortex **(C)** and striatum **(D)** and the number of double-positive cells was shown on the right side. White arrows indicated the double-positive cells. Bar = 50 μm for all images, $n = 3$ per group. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs. sham group; $^{*}P < 0.05$, $^{**}P < 0.01$ vs. MCAO group.

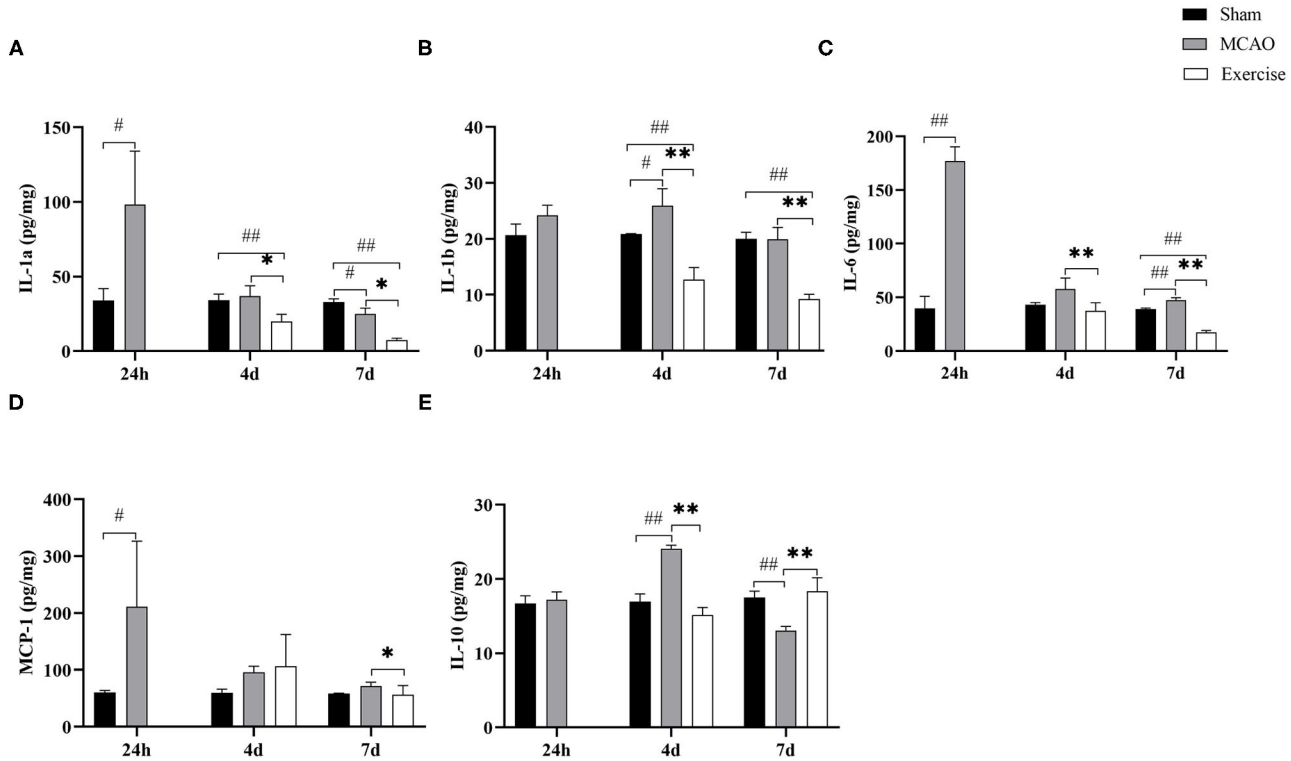


FIGURE 4 | Treadmill exercise altered the levels of M1/M2 markers. The levels of M1 markers, including **(A)** IL-1a, **(B)** IL-1b, **(C)** IL-6, **(D)** MCP-1, and M2 marker **(E)** IL-10 in the penumbra at 1-, 4-, and 7-days post-surgery among the sham, MCAO and exercise groups were examined by Luminex Multiplex Assays. Data are presented as the mean SD, $n = 3$/group. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs. sham group; $^{*}P < 0.05$, $^{**}P < 0.01$ vs. MCAO group.

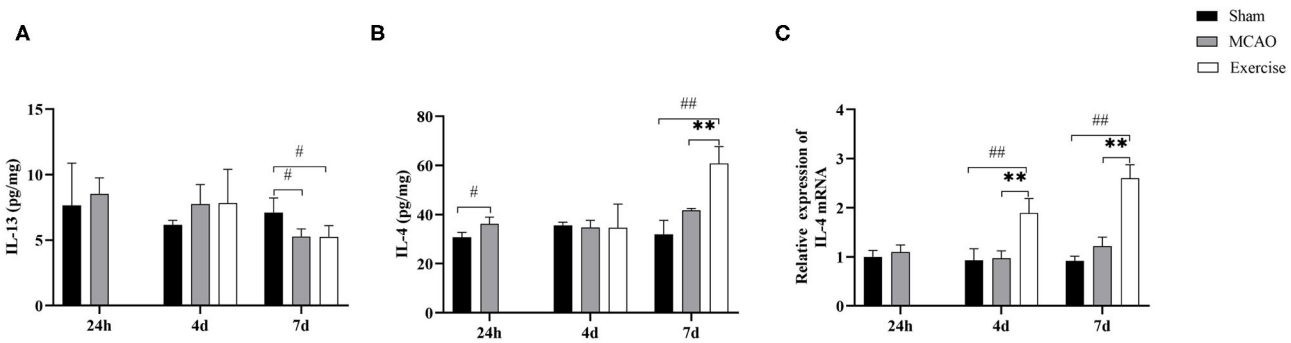


FIGURE 5 | Treadmill exercise increased the expression of IL-4 after MCAO. Protein concentrations of IL-13 **(A)** and IL-4 **(B)** in the penumbra were measured by Luminex Multiplex Assays on day 1, 4, and 7 post-surgery in the sham, MCAO and exercise groups. **(C)** RNA extracts were prepared from the penumbra and mRNA analysis of IL-4 was detected by real-time PCR at the same time points in the 3 groups. Data are given as the mean ± SD. $n = 3$/group. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs. sham group; $^{**}P < 0.01$ vs. MCAO group.

CD200/CD200R signaling pathway by decreasing the level of IL-1β and TNF-α in a mouse model of MCAO (43). Although it has already been established that exercise has an effect on microglia activation, these studies did not explore the changing phenotype of microglia. An increasing body of evidence suggests that there is a dynamic microglial phenotypic polarization in the penumbra, and whether these microglia exacerbate or alleviate tissue damage is associated with their different polarization (44, 45). In agreement with these findings, we showed here that microglia express predominantly M2 markers in the penumbra between day 1 and day 4 after CI/RP, whereas the expression of M1 markers progressively increased over 7 days, suggesting a M2-to-M1 phenotype shift. Therefore, it is necessary to search for a link that would associate the neuroprotective effects of exercise to microglia polarization in the penumbra at different time points after CI/RP.

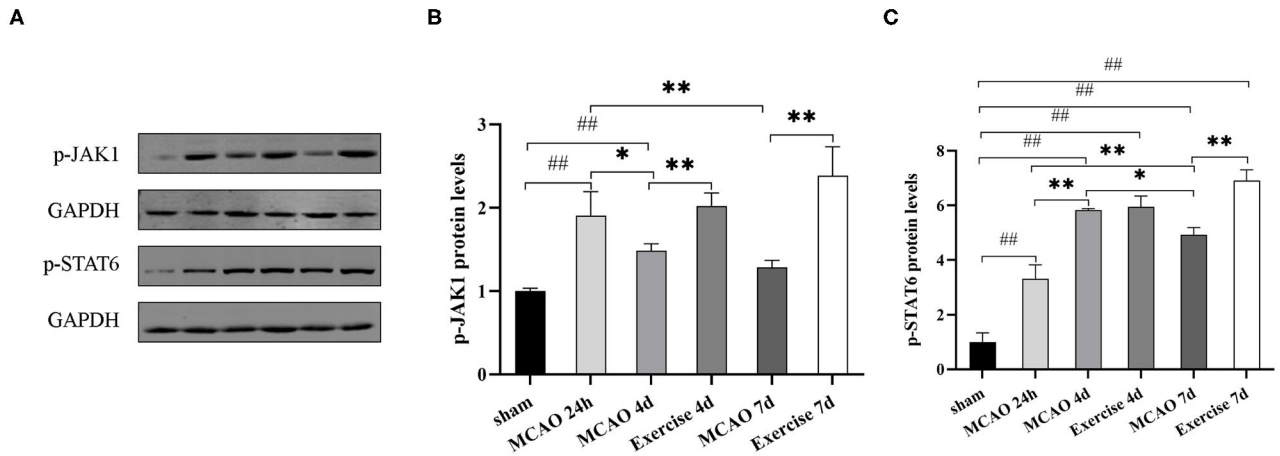


FIGURE 6 | Treadmill exercise regulated microglia polarization through the JAK1/STAT6 pathway after MCAO. **(A)** The representative protein band of p-JAK1 and p-STAT6 was acquired by western blotting with the protein GAPDH serving as the control. Relative protein level of p-JAK1 **(B)** and p-STAT6 **(C)** in the penumbra on the 1st, 4th, and 7th day among the sham, MCAO and exercise groups are shown. Data are presented as the mean ± SD, $n = 3$/group. $^{\#\#}P < 0.01$ vs. sham group; $^{*}P < 0.05$, $^{**}P < 0.01$ vs. MCAO group.

Some drugs have shown neuroprotective effects in animal models of stroke by affecting the type of microglia. For instance, melatonin treatment has been shown to ameliorate brain damage by shifting the microglia phenotype from pro-inflammatory to anti-inflammatory polarity (46). Curcumin was also found to improve functional outcomes via M1–M2 microglial switching (47). At present, M2a microglia are mainly considered to suppress inflammation (11). The M2a phenotype may be the main cell subtype involved in the processes we studied and the surface marker Arg-1 was selected as the surface marker of M2a microglia for immunofluorescence staining (48). In the present study, we found that 3- and 6-day treadmill exercise did indeed promote an M1-to-M2 phenotype shift in the penumbra, which was correlated with greater improvements in neurological scores (particularly in motor and balance) and reduced infarct volumes compared to the MCAO group. These data support the benefit of M2 induction on treadmill exercise for stroke recovery. It is worth noting that in order to induce overall beneficial effects, it is not enough to simply suppress M1 activation to block inflammation (49). Nevertheless, treadmill exercise appears to be a good therapeutic option for stroke rehabilitation.

Based on stimulation of diverse cytokines, microglia could generally polarize into the M1 or M2 phenotypes. IL-4 and IL-13 are essential effectors that polarize microglia to the M2a phenotype (50). An M2a phenotype was indeed induced after IL-4 application both *in vitro* and *in vivo* (51). In our study, the data obtained by Luminex Multiplex Assays and real-time PCR revealed a dramatic increase in IL-4 rather than IL-13 in the exercise compared to the MCAO group. In summary, treadmill exercise increased IL-4 concentrations, which was accompanied by decreased numbers of $CD68^{+}$ M1 microglia and increased $Arg\text{-}1^{+}$ M2 microglia. Consistent with the results of immunofluorescence staining, Luminex Assays revealed a decreased expression of M1 markers (IL-1a, IL-1b, IL-6, and MCP-1) and the increased levels of the M2 marker IL-10. Therefore, IL-4 is likely to be involved in the M2 polarization induced by treadmill exercise. IL-4 is widely recognized as a protective and pleiotropic cytokine in CI/RP, which plays an important role in inflammatory reactions by modulating microglia polarization (52, 53). Yang et al. used intracranially injection of interleukin-4 and verified that an IL-4 supplement could promote neuro-functional recovery and enhanced microglia M2 polarization *in vivo* (54). Zhao et al. reached the same conclusion from the results of *in vivo* experiments and also ascertained that IL-4 administration converted the surrounding microglia to the M2 phenotype *in vitro* (55), a finding consistent with conclusions reached after *in vi*tro experiments carried out by Ting et al. (56). These data demonstrate the importance of IL-4 in eliciting M2 polarization after CI/RP.

Binding of IL-4 to its receptor (IL-4R) elicits stimulation of intracellular signaling, such as the JAK/STAT pathway, which involves IL-4-specific transcription factor STAT6 (17). The role of STAT6 in M2 phenotype switching following IL-4 stimulation was consistently confirmed (57–59). Cai et al. discovered that knockout of STAT6 significantly reduced the positive effect on M2 microglia induction (60). Data from one study demonstrated that IL-4 could promote M2 polarization via activation of the JAK1/STAT6 pathway (61), while JAK1 inhibition would block IL-4-dependent STAT6 activation (62), suggesting that JAK1 is a key molecule downstream of IL-4 signaling. In our study, we detected the protein levels of p-JAK1 and p-STAT6 and observed that treadmill exercise markedly increased JAK1 and STAT6 phosphorylation. Taken together, it is possible that treadmill exercise elicits its favorable effects via the IL-4-JAK1/STAT6 pathway to induce M2 polarization.

Our data clearly showed that IL-4 did not greatly increase M2 induction until the 6-day treadmill exercise intervention. Recent studies also highlighted the effect of IL-4 on long-term behavioral performance after cerebral ischemia (15, 55). The evidence implied that the therapeutic effects of IL-4 polarization to an M2 phenotype is likely to accumulate over time, thereby promoting a greater degree of neurological recovery. Hence, it will be prudent to investigate further the long-term effects of treadmill exercise on IL-4 activity and the consequent alterations in microglia polarization and functional recovery; indeed the degree of exercise may be a factor leading to stress (25). Further studies should proceed more cautiously by additionally increasing the intensity and duration of exercise. Furthermore, in order to prove further the reliability of the present findings, IL-4 knockout (KO) mice or inhibitors of JAK1/STAT6 pathways should be applied in subsequent experiments for comparison.

In summary, the results support the hypothesis that treadmill exercise can alleviate inflammatory injury and promote microglia polarization to the M2 phenotype by increasing the expression of IL-4, which may activate downstream the JAK1/STAT6 pathway. Our study has identified the anti-inflammatory feature of treadmill exercise. As far as we are aware, this study is the first to show that IL-4 is an effective factor in treadmill exercise-mediated anti-inflammation, involving the induction of the M2 phenotype in microglia.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The animal study was reviewed and approved by the Ethics Committee of Shanghai Jiao Tong University.

AUTHOR CONTRIBUTIONS

The overall conception and supervision of this experiment was from YZ and experimental details was designed by YZ and HD. The animal experiment was carried out by JL, JW, LY, and GY and the samples' analysis was completed by JL, JW, LY, and RC. JL wrote the manuscript. JW, LY, and RC participated in the data interpretation and image acquisition. YZ revised and approved the final version. All authors read and agreed on the submitted manuscript.

FUNDING

This research was supported by the National Natural Science Foundation of China (81973612) and the Science and Technology Commission of Shanghai Municipality (21ZR1459200) to YZ.

ACKNOWLEDGMENTS

We expressed our gratitude to Zunji Ke for providing valuable suggestions to the experimental design. We also appreciated the assistance from seniors of laboratories of the Academy of Integrative Medicine of Shanghai University of Traditional Chinese Medicine and the School of Medicine of Shanghai Jiao Tong University.

REFERENCES

1. Billinger SA, Arena R, Bernhardt J, Eng JJ, Franklin BA, Johnson CM, et al. Physical activity and exercise recommendations for stroke survivors: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* (2014) 45:2532–53. doi: 10.1161/STR.0000000000000022
2. Middleton LE, Corbett D, Brooks D, Sage MD, Macintosh BJ, McIlroy WE, et al. Physical activity in the prevention of ischemic stroke and improvement of outcomes: a narrative review. *Neurosci Biobehav Rev.* (2013) 37:133–7. doi: 10.1016/j.neubiorev.2012.11.011
3. Chang MC, Park CR, Rhie SH, Shim WH, Kim DY. Early treadmill exercise increases macrophage migration inhibitory factor expression after cerebral ischemia/reperfusion. *Neural Regen Res.* (2019) 14:1230–6. doi: 10.4103/1673-5374.251330
4. Yang L, Zhang J, Deng Y, Zhang P. The effects of early exercise on motor, sense, and memory recovery in rats with stroke. *Am J Phys Med Rehabil.* (2017) 96:e36–43. doi: 10.1097/PHM.0000000000000670
5. Zhang Q, Zhang J, Yan Y, Zhang P, Zhang W, Xia R. Proinflammatory cytokines correlate with early exercise attenuating anxiety-like behavior after cerebral ischemia. *Brain Behav.* (2017) 7:e00854. doi: 10.1002/brb3.854
6. Zhang P, Zhang Q, Pu H, Wu Y, Bai Y, Vosler PS, et al. Very early-initiated physical rehabilitation protects against ischemic brain injury. *Front Biosci (Elite Ed).* (2012) 4:2476–89. doi: 10.2741/e559
7. Farokhi-Sisakht F, Sadigh-Eteghad S, Mohaddes G, Ebrahimi-Kalan A, Karimi P, Farhoudi M. Physical and cognitive training attenuate hippocampal ischemia-induced memory impairments in rat. *Brain Res Bull.* (2020) 155:202–10. doi: 10.1016/j.brainresbull.2019.10.007
8. Curry A, Guo M, Patel R, Liebelt B, Sprague S, Lai Q, et al. Exercise pre-conditioning reduces brain inflammation in stroke via tumor necrosis factor-alpha, extracellular signal-regulated kinase 1/2 and matrix metalloproteinase-9 activity. *Neurol Res.* (2010) 32:756–62. doi: 10.1179/174313209X459101
9. Ding Y-H, Young CN, Luan X, Li J, Rafols JA, Clark JC, et al. Exercise preconditioning ameliorates inflammatory injury in ischemic rats during reperfusion. *Acta Neuropathol.* (2005) 109:237–46. doi: 10.1007/s00401-004-0943-y
10. Zhang Y, Cao RY, Jia X, Li Q, Qiao L, Yan G, et al. Treadmill exercise promotes neuroprotection against cerebral ischemia-reperfusion injury via downregulation of pro-inflammatory mediators. *Neuropsychiatr Dis Treat.* (2016) 12:3161–73. doi: 10.2147/NDT.S121779
11. Ma Y, Wang J, Wang Y, Yang G-Y. The biphasic function of microglia in ischemic stroke. *Prog Neurobiol.* (2017) 157:247–72. doi: 10.1016/j.pneurobio.2016.01.005
12. Hu X, Li P, Guo Y, Wang H, Leak RK, Chen S, et al. Microglia/macrophage polarization dynamics reveal novel mechanism of injury expansion after focal cerebral ischemia. *Stroke.* (2012) 43:3063–70. doi: 10.1161/STROKEAHA.112.659656
13. Gadani SP, Cronk JC, Norris GT, Kipnis J. IL-4 in the brain: a cytokine to remember. *J Immunol.* (2012) 189:4213–9. doi: 10.4049/jimmunol.1202246
14. Sica A, Mantovani A. Macrophage plasticity and polarization: *in vivo* veritas. *J Clin Invest.* (2012) 122:787–95. doi: 10.1172/JCI59643

15. Liu X, Liu J, Zhao S, Zhang H, Cai W, Cai M, et al. Interleukin-4 is essential for microglia/macrophage M2 polarization and long-term recovery after cerebral ischemia. *Stroke.* (2016) 47:498–504. doi: 10.1161/STROKEAHA.115.012079
16. Quarta A, Berneman Z, Ponsaerts P. Neuroprotective modulation of microglia effector functions following priming with interleukin 4 and 13: current limitations in understanding their mode-of-action. *Brain Behav Immun.* (2020) 88:856–66. doi: 10.1016/j.bbi.2020.03.023
17. McCormick SM, Heller NM. Commentary: IL-4 and IL-13 receptors and signaling. *Cytokine.* (2015) 75:38–50. doi: 10.1016/j.cyto.2015.05.023
18. Murata T, Obiri NI, Puri RK. Structure of and signal transduction through interleukin-4 and interleukin-13 receptors (review). *Int J Mol Med.* (1998) 1:551–7. doi: 10.3892/ijmm.1.3.551
19. Koh Y-C, Yang G, Lai C-S, Weerawatanakorn M, Pan M-H. Chemopreventive effects of phytochemicals and medicines on M1/M2 polarized macrophage role in inflammation-related diseases. *Int J Mol Sci*. (2018) 19:2208. doi: 10.3390/ijms19082208
20. He Y, Gao Y, Zhang Q, Zhou G, Cao F, Yao S. IL-4 switches microglia/macrophage M1/M2 polarization and alleviates neurological damage by modulating the JAK1/STAT6 pathway following ICH. *Neuroscience.* (2020) 437:161–71. doi: 10.1016/j.neuroscience.2020.03.008
21. Longa EZ, Weinstein PR, Carlson S, Cummins R. Reversible middle cerebral artery occlusion without craniectomy in rats. *Stroke.* (1989) 20:84–91. doi: 10.1161/01.STR.20.1.84
22. Chen J, Sanberg PR Li Y, Wang L, Lu M, Willing AE, et al. Intravenous administration of human umbilical cord blood reduces behavioral deficits after stroke in rats. *Stroke.* (2001) 32:2682–8. doi: 10.1161/hs1101.098367
23. Schmittgen TD, Livak KJ. Analyzing real-time PCR data by the comparative C(T) method. *Nat Protoc.* (2008) 3:1101–8. doi: 10.1038/nprot.2008.73
24. Saleem M, Iftikhar A, Asif M, Hussain K. Alamgeer, Shah PA, et al. Asphodelus tenuifolius extracts arrested inflammation and arthritis through modulation of TNF-α, NF-κB, ILs, and COX-2 activities in *in vivo* models. *Inflammopharmacology.* (2021) 29:483–97. doi: 10.1007/s10787-020-00761-z
25. Austin MW, Ploughman M, Glynn L, Corbett D. Aerobic exercise effects on neuroprotection and brain repair following stroke: a systematic review and perspective. *Neurosci Res.* (2014) 87:8–15. doi: 10.1016/j.neures.2014.06.007
26. Li F, Pendy JT, Ding JN, Peng C, Li X, Shen J, et al. Exercise rehabilitation immediately following ischemic stroke exacerbates inflammatory injury. *Neurol Res.* (2017) 39:530–7. doi: 10.1080/01616412.2017.1315882
27. Li F, Shi W, Zhao EY, Geng X, Li X, Peng C, et al. Enhanced apoptosis from early physical exercise rehabilitation following ischemic stroke. *J Neurosci Res.* (2017) 95:1017–24. doi: 10.1002/jnr.23890
28. Himi N, Takahashi H, Okabe N, Nakamura E, Shiromoto T, Narita K, et al. Exercise in the early stage after stroke enhances hippocampal brain-derived neurotrophic factor expression and memory function recovery. *J Stroke Cerebrovasc Dis.* (2016) 25:2987–94. doi: 10.1016/j.jstrokecerebrovasdis.2016.08.017
29. Zhang Y, Zhang P, Shen X, Tian S, Wu Y, Zhu Y, et al. Early exercise protects the blood-brain barrier from ischemic brain injury via the regulation of MMP-9 and occludin in rats. *Int J Mol Sci.* (2013) 14:11096–112. doi: 10.3390/ijms140611096
30. Morrison HW, Filosa JA, A. quantitative spatiotemporal analysis of microglia morphology during ischemic stroke and reperfusion. *J Neuroinflammation.* (2013) 10:4. doi: 10.1186/1742-2094-10-4
31. Ito D, Tanaka K, Suzuki S, Dembo T, Fukuuchi Y. Enhanced expression of Iba1, ionized calcium-binding adapter molecule 1, after transient focal cerebral ischemia in rat brain. *Stroke.* (2001) 32:1208–15. doi: 10.1161/01.STR.32.5.1208
32. Shi K, Tian D-C, Li Z-G, Ducruet AF, Lawton MT, Shi F-D. Global brain inflammation in stroke. *Lancet Neurol.* (2019) 18:1058–66. doi: 10.1016/S1474-4422(19)30078-X
33. DiSabato DJ, Quan N, Godbout JP. Neuroinflammation: the devil is in the details. *J Neurochem.* (2016) 139 (Suppl. 2):136–53. doi: 10.1111/jnc.13607
34. Zhang M, Zhai Y, Sun Y, Zhang W, Li Q, Brann D, et al. Swimming improves cognitive reserve in ovariectomized rats and enhances neuroprotection after global cerebral ischemia. *Brain Res.* (2018) 1692:110–7. doi: 10.1016/j.brainres.2018.05.020
35. Li D-J, Li Y-H, Yuan H-B, Qu L-F, Wang P. The novel exercise-induced hormone irisin protects against neuronal injury via activation of the Akt and ERK1/2 signaling pathways and contributes to the neuroprotection of physical exercise in cerebral ischemia. *Metabolism.* (2017) 68:31–42. doi: 10.1016/j.metabol.2016.12.003
36. Lovatel GA, Bertoldi K, Elsnerb VR, Piazza FV, Basso CG, Moysés FDS, et al. Long-term effects of pre and post-ischemic exercise following global cerebral ischemia on astrocyte and microglia functions in hippocampus from Wistar rats. *Brain Res.* (2014) 1587:119–26. doi: 10.1016/j.brainres.2014.08.068
37. Bobinski F, Teixeira JM, Sluka KA, Santos ARS. Interleukin-4 mediates the analgesia produced by low-intensity exercise in mice with neuropathic pain. *Pain.* (2018) 159:437–50. doi: 10.1097/j.pain.0000000000001109
38. Cianciulli A, Dragone T, Calvello R, Porro C, Trotta T, Lofrumento DD, et al. IL-10 plays a pivotal role in anti-inflammatory effects of resveratrol in activated microglia cells. *Int Immunopharmacol.* (2015) 24:369–76. doi: 10.1016/j.intimp.2014.12.035
39. Rosenzweig JM, Lei J, Burd I. Interleukin-1 receptor blockade in perinatal brain injury. *Front Pediatr.* (2014) 2:108. doi: 10.3389/fped.2014.00108
40. Zhang X, He Q, Huang T, Zhao N, Liang F, Xu B, et al. Treadmill exercise decreases aβ deposition and counteracts cognitive decline in APP/PS1 mice, possibly hippocampal microglia modifications. *Front Aging Neurosci.* (2019) 11:78. doi: 10.3389/fnagi.2019.00078
41. Wang Y, Xu Y, Sheng H, Ni X, Lu J. Exercise amelioration of depression-like behavior in OVX mice is associated with suppression of NLRP3 inflammasome activation in hippocampus. *Behav Brain Res.* (2016) 307:18–24. doi: 10.1016/j.bbr.2016.03.044
42. Carlin JL, Grissom N, Ying Z, Gomez-Pinilla F, Reyes TM. Voluntary exercise blocks Western diet-induced gene expression of the chemokines CXCL10 and CCL2 in the prefrontal cortex. *Brain Behav Immun.* (2016) 58:82–90. doi: 10.1016/j.bbi.2016.07.161
43. Sun H, Li A, Hou T, Tao X, Chen M, Wu C, et al. Neurogenesis promoted by the CD200/CD200R signaling pathway following treadmill exercise enhances post-stroke functional recovery in rats. *Brain Behav Immun.* (2019) 82:354–71. doi: 10.1016/j.bbi.2019.09.005
44. Kim J-Y, Kim N, Yenari MA. Mechanisms and potential therapeutic applications of microglial activation after brain injury. *CNS Neurosci Ther.* (2015) 21:309–19. doi: 10.1111/cns.12360
45. Hu X, Liou AKF, Leak RK, Xu M, An C, Suenaga J, et al. Neurobiology of microglial action in CNS injuries: receptor-mediated signaling mechanisms and functional roles. *Prog Neurobiol.* (2014) 119–120:60–84. doi: 10.1016/j.pneurobio.2014.06.002
46. Liu Z-J, Ran Y-Y, Qie S-Y, Gong W-J, Gao F-H, Ding Z-T, et al. Melatonin protects against ischemic stroke by modulating microglia/macrophage polarization toward anti-inflammatory phenotype through STAT3 pathway. *CNS Neurosci Ther.* (2019) 25:1353–62. doi: 10.1111/cns.13261
47. Liu Z, Ran Y, Huang S, Wen S, Zhang W, Liu X, et al. Curcumin protects against ischemic stroke by titrating microglia/macrophage polarization. *Front Aging Neurosci.* (2017) 9:233. doi: 10.3389/fnagi.2017.00233
48. Chhor V, Le Charpentier T, Lebon S, Oré M-V, Celador IL, Josserand J, et al. Characterization of phenotype markers and neuronotoxic potential of polarised primary microglia *in vitro*. *Brain Behav Immun.* (2013) 32:70–85. doi: 10.1016/j.bbi.2013.02.005
49. Becker C, Jick SS, Meier CR, NSAID. use and risk of Parkinson disease: a population-based case-control study. *Eur J Neurol.* (2011) 18:1336–42. doi: 10.1111/j.1468-1331.2011.03399.x
50. Qin C, Zhou L-Q, Ma X-T, Hu Z-W, Yang S, Chen M, et al. Dual functions of microglia in ischemic stroke. *Neurosci Bull.* (2019) 35:921–33. doi: 10.1007/s12264-019-00388-3
51. Latta CH, Sudduth TL, Weekman EM, Brothers HM, Abner EL, Popa GJ, et al. Determining the role of IL-4 induced neuroinflammation in microglial activity and amyloid-β using BV2 microglial cells and APP/PS1 transgenic mice. *J Neuroinflammation.* (2015) 12:41. doi: 10.1186/s12974-015-0243-6
52. Xie L, Zhang N, Zhang Q, Li C, Sandhu AF Iii GW, et al. Inflammatory factors and amyloid β-induced microglial polarization promote inflammatory crosstalk with astrocytes. *Aging (Albany NY).* (2020) 12:22538–49. doi: 10.18632/aging.103663
53. Girard S, Brough D, Lopez-Castejon G, Giles J, Rothwell NJ, Allan SM. Microglia and macrophages differentially modulate cell death after brain injury caused by oxygen-glucose deprivation in organotypic brain slices. *Glia.* (2013) 61:813–24. doi: 10.1002/glia.22478

54. Yang J, Ding S, Huang W, Hu J, Huang S, Zhang Y, et al. Interleukin-4 ameliorates the functional recovery of intracerebral hemorrhage through the alternative activation of microglia/macrophage. *Front Neurosci.* (2016) 10:61. doi: 10.3389/fnins.2016.00061
55. Zhao X, Wang H, Sun G, Zhang J, Edwards NJ, Aronowski J. Neuronal interleukin-4 as a modulator of microglial pathways and ischemic brain damage. *J Neurosci.* (2015) 35:11281–91. doi: 10.1523/JNEUROSCI.1685-15.2015
56. Ting S-M, Zhao X, Zheng X, Aronowski J. Excitatory pathway engaging glutamate, calcineurin, and NFAT upregulates IL-4 in ischemic neurons to polarize microglia. *J Cereb Blood Flow Metab.* (2020) 40:513–27. doi: 10.1177/0271678X19838189
57. Karpathiou G, Papoudou-Bai A, Ferrand E, Dumollard JM. Peoc'h M. STAT6: a review of a signaling pathway implicated in various diseases with a special emphasis in its usefulness in pathology. *Pathol Res Pract*. (2021) 223:153477. doi: 10.1016/j.prp.2021.153477
58. Bai J-Y, Li Y, Xue G-H, Li K-R, Zheng Y-F, Zhang Z-Q, et al. Requirement of Gαi1 and Gαi3 in interleukin-4-induced signaling, macrophage M2 polarization and allergic asthma response. *Theranostics.* (2021) 11:4894–909. doi: 10.7150/thno.56383
59. Sheldon KE, Shandilya H, Kepka-Lenhart D, Poljakovic M, Ghosh A, Morris SM. Shaping the murine macrophage phenotype: IL-4 and cyclic AMP synergistically activate the arginase I promoter. *J Immunol.* (2013) 191:2290–8. doi: 10.4049/jimmunol.1202102
60. Cai W, Dai X, Chen J, Zhao J, Xu M, Zhang L, et al. STAT6/Arg1 promotes microglia/macrophage efferocytosis and inflammation resolution in stroke mice. *JCI Insight*. (2019) 4:e131355. doi: 10.1172/jci.insight.131355
61. Im JH, Yeo IJ, Park PH, Choi DY, Han S-B, Yun J, et al. Deletion of chitinase-3-like 1 accelerates stroke development through enhancement of neuroinflammation by STAT6-dependent M2 microglial inactivation in Chitinase-3-like 1 knockout mice. *Exp Neurol.* (2020) 323:113082. doi: 10.1016/j.expneurol.2019.113082
62. Deszo EL, Brake DK, Kelley KW, Freund GG. IL-4-dependent CD86 expression requires JAK/STAT6 activation and is negatively regulated by PKCdelta. *Cell Signal.* (2004) 16:271–80. doi: 10.1016/S0898-6568(03)00137-2

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 08 October 2021
doi: 10.3389/fcvm.2021.732076

Regulation of Cardiac-Specific Proteins Expression by Moderate-Intensity Aerobic Exercise Training in Mice With Myocardial Infarction Induced Heart Failure Using MS-Based Proteomics

Shouling Mi[1,2†], *Hao Jiang*[1,2†], *Lei Zhang*[3†], *Zhonglei Xie*[1,2], *Jingmin Zhou*[1,2], *Aijun Sun*[1,2,3], *Hong Jin*[3,4*] *and Junbo Ge*[1,2,3*]

[1] Department of Cardiology, Zhongshan Hospital, Fudan University, Shanghai, China, [2] Shanghai Institute of Cardiovascular Diseases, Shanghai, China, [3] Institutes of Biomedical Sciences, Fudan University, Shanghai, China, [4] Stomatological Hospital, Fudan University, Shanghai, China

This study aims to systematically reveal the changes in protein levels induced by regular exercise in mice with ischemic-induced heart failure (HF). Aerobic exercise training for the ischemic-induced HF mice lasted for 4 weeks and then we used the liquid chromatography-mass spectrometry method to identify and quantify the protein profile in the myocardium of mice. As a whole, 1,304 proteins (597 proteins up-regulated; 707 proteins down-regulated) were differentially expressed between the exercise group and the sedentary group, including numerous proteins related to energy metabolism. The significant alteration of the component (E1 component subunit alpha and subunit beta) and the activity-regulating enzyme (pyruvate dehydrogenase kinase 2 and pyruvate dehydrogenase kinase 4) of pyruvate dehydrogenase complex and poly [ADP-ribose] polymerase 3, a nicotinamide adenine dinucleotide(+)-consuming enzymes, was further verified in targeted analysis. Generally, this proteomics profiling furnishes a systematic insight of the influence of aerobic exercise on HF.

Keywords: aerobic exercise, mice, myocardial infarction, heart failure, proteomics

OPEN ACCESS

Edited by:
Richard Yang Cao, Shanghai Xuhui Central Hospital, China

Reviewed by:
Masato Mashimo, Doshisha Women's College of Liberal Arts, Japan
Yinlong Guo, Shanghai Institute of Organic Chemistry (CAS), China

***Correspondence:**
Junbo Ge
jbge@zs-hospital.sh.cn
Hong Jin
jinhong@fudan.edu.cn

[†]These authors share first authorship

Specialty section:
This article was submitted to General Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

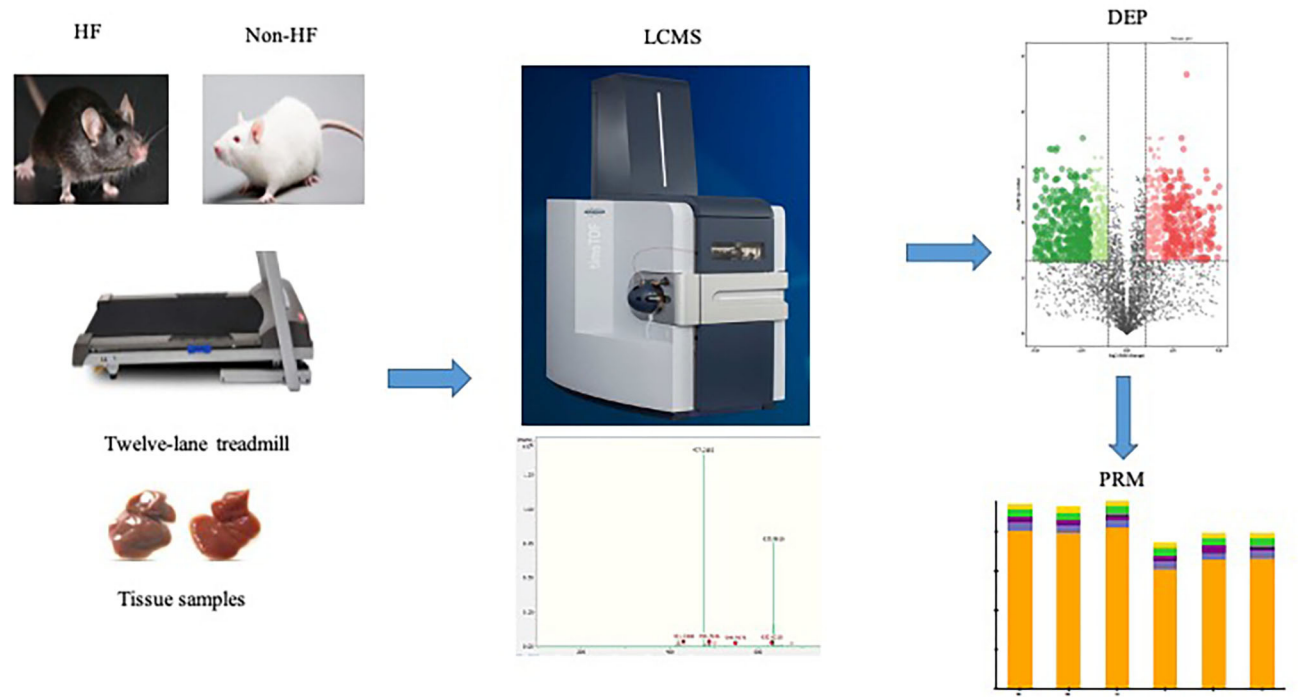
Received: *28 June 2021*
Accepted: *18 August 2021*
Published: *08 October 2021*

Citation:
Mi S, Jiang H, Zhang L, Xie Z, Zhou J, Sun A, Jin H and Ge J (2021) Regulation of Cardiac-Specific Proteins Expression by Moderate-Intensity Aerobic Exercise Training in Mice With Myocardial Infarction Induced Heart Failure Using MS-Based Proteomics. Front. Cardiovasc. Med. 8:732076. doi: 10.3389/fcvm.2021.732076

INTRODUCTION

With the increase of life-expectancy and underlying risk factors, heart failure (HF) is emerging as a major public health issue with the prevalence estimated to be 56 million patients worldwide (1). In the past few decades,pharmacotherapeutics has made great progress for HF from initial neuro-hormonal blockade of the cardiovascular system to additional neurohormonal regulation, as well as some recent anti-hyperglycemic drugs. However, the prognosis of HF patients remains less satisfactory. It is a challenge that the reductionist approach in this high clinical heterogeneity disease is due to the diverse therapy responding and treatment intolerance (2). Further multivariate therapeutic interventions are essential to improve the clinical outcomes of HF patients.

There is strong evidence that cardiac rehabilitation, especially the achievable non-pharmacological intervention training, could improve functional ability, relieve symptoms as



GRAPHICAL ABSTRACT | The heart failure model was induced by myocardial infarction in male C57BL/6N mice and then the mice with established HF were randomly assigned to the sedentary group or the exercise group in the 12-lane treadmill for 4 weeks. Myocardium samples of both exercise groups mice and sedentary groups mice were harvested, respectively. The LC-MS method was adopted for identification and quantification of the protein expression profile in the myocardium of mice. The retrieved protein peak area was used for subsequent statistical analysis. With the predetermined criterion ($P < 0.05$; fold change >2 or <0.5), 1,304 differentially expressed proteins were detected between the exercise group and the sedentary group, among which 597 proteins were up-regulated after exercise training and 707 proteins were down-regulated. Further targeted analysis was conducted to verify the expression changes in several key components of mitochondrial metabolism identified in the preliminary LC-MS analysis. HF, heart failure; LC-MS, liquid chromatography-mass spectrometry; DEP, differentially expressed protein; PRM, parallel reaction monitor.

well as reduce hospitalization, mortality, and ejection fraction for HF patients (3–7). Given the significant effectiveness and safety, training in the management of HF patients has been an alternative recommendation by authoritative guidelines (8, 9). Recently, more clinical trials began to focus on exercise intervention in different HF populations. For example, among HF patients with preserved ejection fraction, exercise training also yielded a beneficial effect on cardio-respiratory fitness and quality of life (10, 11) and the TOPCAT study further suggests that higher levels of physical activity have the potential to reduce the risk of adverse outcomes, which may attribute to the better indices of diastolic function (12, 13). In addition, exercise-based cardiac rehabilitation was also found to be feasible as an adjuvant treatment option with multiple HF groups with diverse complications (14, 15). That is to say, exercise may benefit more different subgroups of HF patients with discrepant pathophysiological settings, suggesting the multi-target effects of exercise training on HF condition. Experimental studies on the molecular mechanism of exercise intervention in HF may bring new enlightenment to the treatment strategies.

It was shown that several preclinical studies have already provided molecular insights for the beneficial effect of exercise in various induced HF animal models. As a whole, exercise training can ameliorate HF-induced dysfunctions by acting on the current standard pharmacological care-targeted pathways (16, 17) or non-pharmacological available targets correcting the inflammatory response, skeletal myopathy, and vagal outflow (16, 17). More recently, exercise was demonstrated to activate cardio-myogenesis in adult mice and the robust cardiomyogenic response was also observed in the adjacent area of the infarcted zone (18). Further, evidence indicates metabolic remodeling also contributes to the exercise-induced cardio-protection (19, 20). Chicco et al. demonstrated that low-intensity exercise could restore the mitochondrial energy metabolism via improving the activity of mitochondrial cytochrome oxidase (COx) and increasing the cardiolipin biosynthesis in the failing heart (20). In line with a previous result, it was also found that the cardiac function in myocardial infarction (MI)-induced HF model was improved after moderate-intensity exercise via upregulating mitochondrial respiration and glycolysis in our

Abbreviations: HF, heart failure; MI, myocardial infarction; MS, mass spectrometry; LC, liquid chromatography; GO, gene ontology; DEPs, differentially expressed proteins; ATP, adenosine triphosphate; NAD, nicotinamide adenine dinucleotide; PDC, pyruvate dehydrogenase complex; PARP3, poly [ADP-ribose] polymerase 3; DCA, dichloroacetate.

previous work (19). Just as the extensive effects in different HF groups, exercise training exerts its beneficial effects via different molecular mechanisms.

However, the abovementioned experimental trials were conducted in diverse animal models and the global alteration at the molecule level in an individual trial is scarce. Whether there is a critical target responsible for the effect of exercise on HF condition remains elusive. To date, no study has systematically revealed a global view for the alteration of protein expression regarding the cardiovascular adaptive response to exercise training in the setting of HF. Hence, in the present study, we used untargeted mass spectrometry (MS)-based proteomics to explore the moderate-intensity aerobic exercise-induced changes in expression level of proteins in mice with ischemic HF, aiming at a comprehensive understanding on the molecular basis for exercise-induced regulation of HF.

METHODS

Experimental Animals and Models

In this study, only the male mice were used to avoid possible interference on exercise response from estrogen. Male C57BL/6N mice (21–25 g; 8–10 weeks) were purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd. All experimental mice were treated in a uniform environment (22°C constant temperature; 12/12-h light/dark cycle; standard laboratory chow and tap water). The experimental procedures of animals strictly comply with the U.S. National Institutes of Health-published Guide for the Care and Use of Laboratory Animals (NIH publication no. 85–23, revised 1996). All experiments involving animals were reviewed and approved by the animal ethics committee at Zhongshan Hospital, Fudan University, China. Mice were subjected to either a surgery by ligation of the left anterior descending artery to induce MI and subsequent HF or sham surgery as previously described (21). All survived mice had echocardiography performed 1 week after surgery and mice with reduced left ventricular ejection fraction (EF<40%) were regarded as established HF. Then the mice with established HF were randomly assigned to sedentary group or exercise group. In addition, the same number of non-HF mice were also randomly divided into exercise groups and sedentary groups as controls.

Aerobic Exercise Training and Materials Preparation

The 12-lane treadmill was utilized to conduct aerobic exercise 1 week after MI surgery. The first 3 days were the adaptative process of the exercise training in treadmill for mice (10 m/min; 1 h/day). After the adaptative process, regular exercise began at the fourth day and last 4 weeks (15 m/min; 1 h/day; 5 days/week). Mice that did not run in the treadmill were gently pushed and those manifesting the exhaustion condition (i.e., mice did not follow the running protocol even after 10 times gently push) were taken away from the treadmill to rest. The exercise capacity of all mice was tested by increasing the treadmill speed with a gradient of 5 m/min until exhaustion condition at the last training and the total running distance until exhaustion was recorded. Cardiac function of all mice was further tested by echocardiography after the exercise training and test process. Then, all mice were euthanized, and organs were dissected and rapidly frozen in liquid nitrogen.

Sample Preparation for Mass Spectrometry-Based Quantitative Proteomic Analysis

The samples were combined, shredded in phosphate buffer saline, and ground with liquid nitrogen to mix. The lysate (7 M urea, 2 M thiourea, 0.1% phenylmethanesulfonyl fluoride-a protease inhibitor, 65 mM dithiothreitol [DTT]) was added at a ratio of 5:1 (lysate volume: sample weight) and then suspended and cracked on ice for half an hour. Next, samples were centrifuged at 12,000 g for 15 min. The supernatant was extracted, and the protein content was determined by the Bradford method. Two hundred microgram protein dissolved in lysate was taken to react with 10 mM DTT at 37°C for 1 h, 20 mM iodoacetamide in the dark at room temperature for 0.5 h and 4 times the volume of ice acetone for overnight precipitation at −80°C. The supernatant was extracted after centrifugation at 12,000 g for 15 min and resuspended with the 200 UL 50 mM ammonium bicarbonate. Trypsin was added at 1:50 for enzymolysis overnight at 37°C, which was terminated when the final concentration of formic acid was added to 5%. Finally, the final samples were desalted with the Sepak desalination column (Waters, U.S.) and prepared for mass spectrometry analysis.

Inverse Separation at High pH

A 100-ug protein was extracted for high pH 2D separation on chromatographic column (BEH C18,300 Å, 1.7 um, 2.1 mm × 150 mm; Waters, U.S.) and concatenated into 20 fractions, which were finally combined into 4 fractions. Mobile phase A is water with 5 mM ammonium formate (pH 10.3), and B phase is acetonitrile. Within 20 min, B phase increased linearly from 5 to 45%. The fractions were lyophilized and redissolved in an aqueous solution of 1‰ formic acid.

The Chromatographic Conditions

We performed the second-dimensional separation using nano Elute liquid chromatography (LC) system (Bruker Daltonics). A 250 mm×75 um column (Inopticks) was employed, in which the mobile phase A and B were water and acetonitrile of 1‰ formic acid, respectively. Peptide separation was conducted at a flow rate of 300 nL/min within 90 min. The mobile phase B concentration increased from 2 to 22% in the first 45 min, followed by an increase to 37% within 5 min and another increase to 80% within 5 min before the last 5 min for maintenance rinsing. A 200-ng peptide fragment was used for LC-MS analysis.

Mass Spectrometry Conditions

All fractions were analyzed by a hybrid trapped ion mobility spectrometry (TIMS) quadrupole time-of-flight mass spectrometer (TIMS-TOF Pro, Bruker Daltonics) using a nano electrospray ion source with a scanning range of 100–1,700 m/z and a trip range of 0.7–1.3 VS/cm^2. The collection time of a single cycle was 1.16 s comprising 1 MS scan and 10 PASEF secondary scans. The intense threshold is 5,000 and we set the

accumulation and release time as 100 ms, ion source voltage as 1,500 V, the auxiliary gas as 3 L/min, and the temperature of the ion source as 180°C.

Data Analysis

The data were analyzed by Peaks Online software (Bioinformatics Solutions, Inc.) with the mouse database downloaded from SwissProt (17,046 proteins, 20,200,820 download). The MS1 error was 15 ppm, the MS2 error was 0.05 Dalton, and the trypsinase was set at half enzyme digestion. Carbamidomethylation protein C-term was set as fixed modification and acetylation (protein N-term), oxidation (M) and deamidation (NQ) were set as variable modification. The retrieved protein peak area was used for subsequent statistical analysis.

Statistical Analysis

Proteins with an overall missing value of more than 50% are removed, and the remaining blank values are filled with a random number between 0 and the minimum area. *T*-test and fold-change values of proteins were used to screen differential proteins, and the GO (gene ontology) was analyzed using R package clusterProfiler, version 3.16.1.

Verify the Differentially Expressed Proteins

To verify the up and down regulated proteins, we use the prmPASEF method based on the timsTOF Pro mass spectrum (22). For each protein, we choose a unique and high scored peptide to perform the prmPASE experiment; then check the peptide areas manually, and the areas are exported to plot the histogram.

RESULTS

Study Overview

Aerobic exercise training for the ischemic-induced HF mice lasted for 4 weeks, and then myocardial samples of both the exercise group and sedentary group were harvested, respectively. Significant improvement in cardiac function was observed in the HF-exercise group compared with the HF-sedentary group as has been demonstrated in our preliminary work, including EF, fractional shortening, and exercise endurance (19). All samples were pre-separated by high pH reverse phase chromatography after enzymolysis, and each group of samples was finally combined into four fractions. The LC-MS method was adopted for further identification and quantification of the protein expression profile in the myocardium of mice. As a result, a total of 6,297 proteins were steadily identified in this experiment, among which proteins with missing values greater than 50% were directly deleted and the remaining blank values were filled by KNN algorithm, finally retaining 4,260 proteins for further differential analysis (**Supplementary Table 1**).

Evaluation of the Proteomic Results

Reliability of the LC-MS results was evaluated. The peak intensity distribution of samples was exhibited in **Figure 1A**. We observed that the intensity distribution of 4,260 identified proteins spanning 6 magnitude orders,which was almost similar and balanced among these different groups, indicating the high reproducibility and sensitivity of the LC-MS method. Moreover, reproducibility of the results was also evaluated by calculating the correlation of peak intensity between any two samples among exercise groups or sedentary groups. As presented in **Figure 1B**, the adopted LC-MS method revealed excellent repeatability and reliability in the identification and quantification of protein expression profile in different samples with an average correlation coefficient (R package corrplot, version 0.84) of 0.8. The exercise group and sedentary group could be exactly divided according to the hierarchical clustering analysis (**Figure 1C**) and principal component analysis (**Figure 1D**) based on the quantitative data of identified proteins.

DEPs and Pathway Analysis

We further analyzed the alterations of the protein expression profile induced by regularly aerobic exercise in ischemic-induced HF mice following the predetermined criterion (adj. $P < 0.05$; fold change > 2 or < 0.5) (23). As a whole, 1,304 proteins were differentially expressed between the exercise group and the sedentary group (**Figure 2A**), among which 597 proteins were up-regulated after exercise training and 707 proteins were down-regulated (**Supplementary Table 2**). GO analysis (**Figure 2B**) for the biological process revealed that these DEPs play crucial roles in material and energy metabolism especially the mitochondrial-related energy metabolism. Indeed, the cellular components analysis (**Figure 2B**) for the altered proteins further verified that those DEPs were significantly enriched in numerous structural and functional components of mitochondria, including the matrix and inner membrane of mitochondrial, mitochondrial respirasome, mitochondrial protein complex, and inner mitochondrial membrane protein complex. Moreover, ribosome and ribosomal subunit, the molecular machinery for protein synthesis in cells, are also significantly enriched by differential proteins. Whereas, the molecular function analysis (**Figure 2B**) indicated that those DEPs were associated with oxidoreductase activity (acting on the aldehyde or oxo group of donors, NAD or NADP as acceptor), electron transfer activity, and translation regulator activity. In summary, our research provided a comprehensive elucidation for the impact of regular exercise on multiple proteins in the ischemic-induced HF mice model. Metabolic-related pathways especially the energy metabolism pathways were significantly regulated by aerobic exercise training in the HF condition, which usually was characterized by insufficient energy supply.

Verification of the Expression Changes of Key Proteins Involved in Energy Metabolism

The previous analysis has found that a variety of altered proteins is related to mitochondrial metabolism, which is usually impaired in a state of HF. Further study of the key molecules in this vital transition may provide more intuitive mechanism insight into the metabolic remodeling process of HF induced by aerobic exercise. Therefore, we conducted targeted MS analysis to verify the expression changes in several key

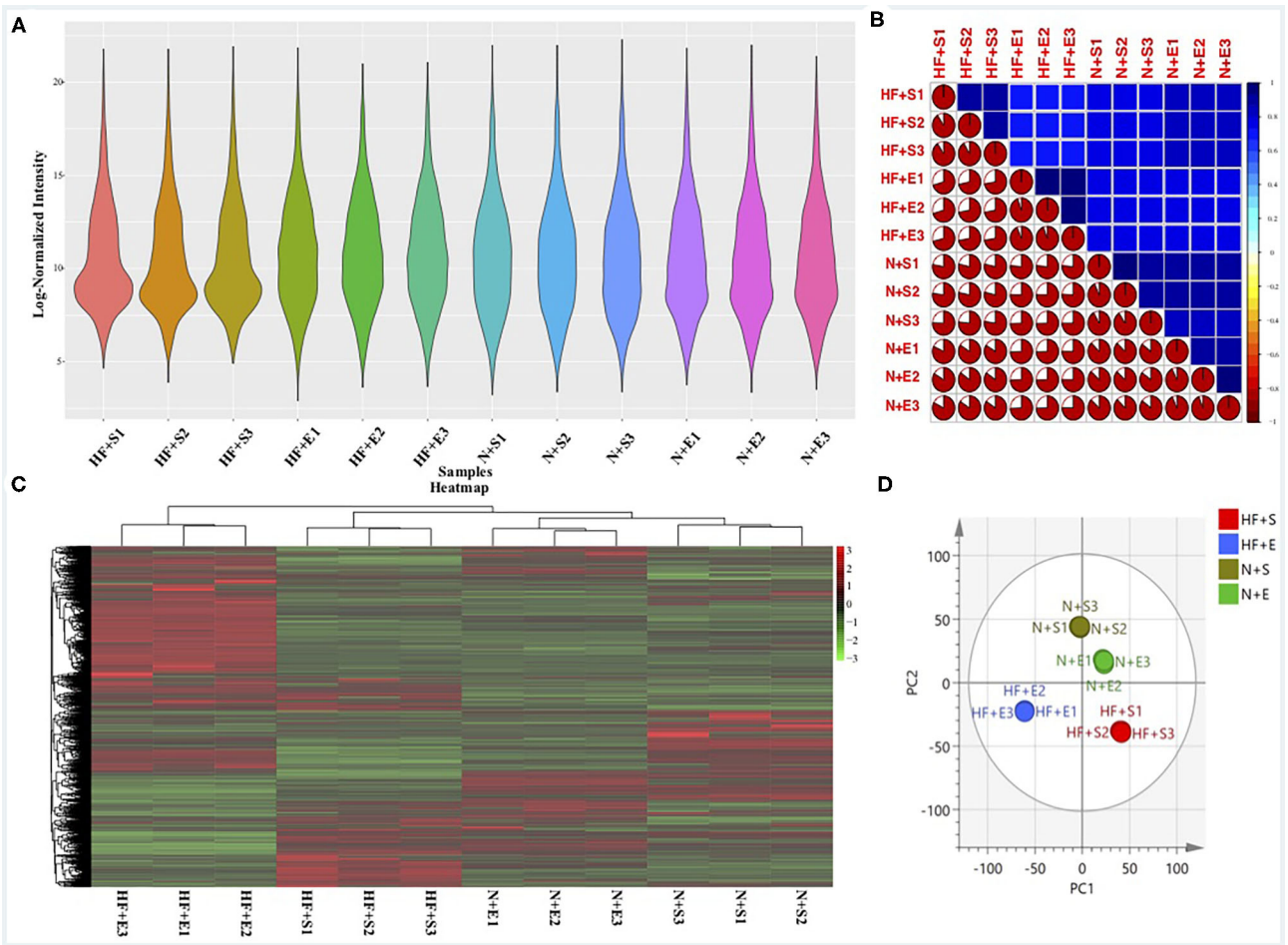


FIGURE 1 | The sensitivity and reliability of the LC-MS results. **(A)** The peak intensity distribution of all samples. **(B)** The correlation of all samples using the peak intensity data. **(C)** Heatmap of differential expressed proteins within the four experimental groups and hierarchical clustering analysis. **(D)** O2PLS-DA of the four experimental groups by the identified protein data. LC-MS, liquid chromatography-mass spectrometry; HF+S, sedentary groups of heart failure mice; HF+E, exercise groups of heart failure mice; N+S, sedentary groups of non-heart failure mice; N+E, exercise groups of non-heart failure mice.

components of mitochondrial metabolism identified in the preliminary LC-MS analysis. Finally, we observed that the expression level off our proteins involving the metabolism of adenosine triphosphate (ATP) and nicotinamide adenine dinucleotide (NAD) had consistent direction with the discovery stage (**Figure 3**). The expression of pyruvate dehydrogenase complex E1 component subunit alpha (PDC E1α) and subunit beta (PDC E1β) were both downregulated to almost the normal level especially the PDC E1β in the exercise-treated HF mice compared with the sedentary groups. Two phosphorylase isoforms of PDC, the pyruvate dehydrogenase kinase 2 (PDK2) and pyruvate dehydrogenase kinase 4 (PDK4), were also significantly downregulated in the HF compared to the normal mice and their levels were further downregulated after exercise. Whereas, there was no significant change observed for the other PDK isoforms. The verification of NAD(+)-consuming enzymes exhibited a dramatic increase of poly [ADP-ribose] polymerase 3 (PARP3) after exercise in HF mice but not poly [ADP-ribose] polymerase 1 (PARP1).

DISCUSSION

Overall, this study provides a global view of exercise-induced protein-level alterations by LC-MS methods in the murine model of MI-induced HF. The MS analysis finally reveals that the significant shift of 1,304 functional proteins in the adaptive regulation was induced by exercise in a failing heart. The differential proteins were mainly related to cardiac metabolism especially the structure and function of mitochondria. Further confirmation experiments by targeted MS analysis demonstrated the significant downregulation of the component (PDC E1α; PDC E1β) and activity-regulating enzyme (PDK2; PDK4) of PDC and the significant upregulation NAD(+)-consuming enzymes (PARP3). Generally, illustration of the cardiac metabolism-related changes after regular exercise further deepens our understanding of the cardio-regulation mechanisms of aerobic exercise in HF, which may prompt better use of this non-pharmacological intervention and lead to novel alternative therapeutic targets for HF patients.

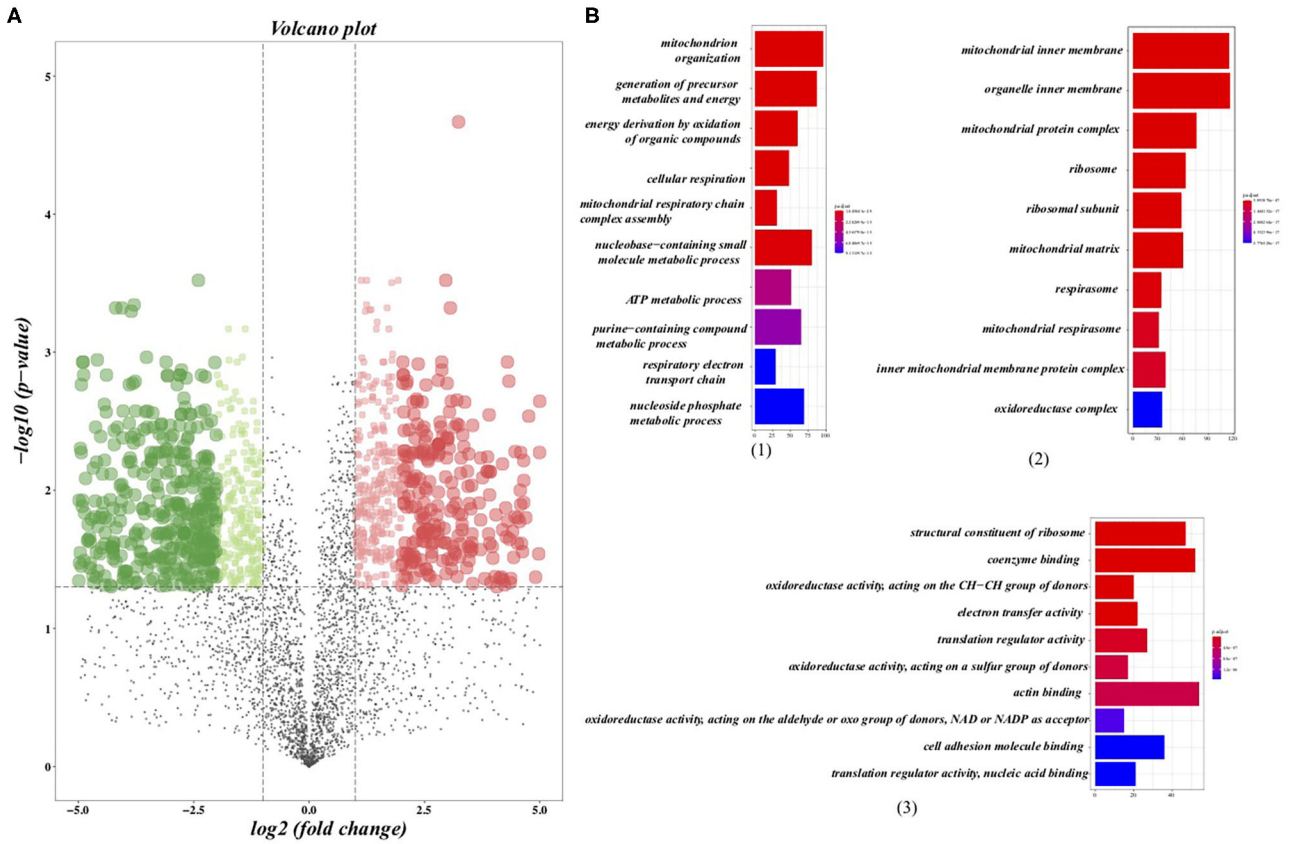


FIGURE 2 | Differentially expressed proteins (DEPs) and the gene ontology (GO) analysis. **(A)** Volcano plots presented the DEPs between the sedentary group and the exercise group in HF mice, in which the x axis presented the fold change and the *y*-axis presented the *p*-value after adjustment. The dotted lines show selection threshold (adj. $P < 0.05$; fold change >2 or <0.5). **(B)** GO analysis: (1) Top 10 of enriched biological processes of DEPs; (2) Top 10 of enriched cellular components of DEPs; (3) Top 10 of enriched molecular function of DEPs.

We employed advanced MS strategies with high sensitivity for this proteomic study. The results were generally reliable based on the repeatability and accurate discrimination between groups. As far as we know, this is the first comprehensive study to explore the effect of exercise on ischemic-induced HF at the molecular level, although the results need to be further verified in humans. Many previous studies have shown the beneficial effect of exercise training on HF, but our understanding of its mechanism is still insufficient due to some discrete individual mechanism studies. Through the analysis of global protein alterations, the study found significant differences in a large number of metabolism-related proteins after 4 weeks of aerobic exercise, especially the proteins involving mitochondrial metabolism, hinting at the crucial role of metabolism remodeling in the regulation of exercise on HF. PDC, which has a central effect on the control of anaerobic metabolism or aerobic metabolic flux, has also been verified to have significant alteration, which suggests that the aerobic metabolism impaired in HF condition after exercise has undergone a significant change after regular exercise.

PDC is the gatekeeper enzyme linking glycolysis and the Krebs cycle by catalyzing the oxidative decarboxylation of pyruvate to acetyl-CoA in mitochondria and comprises three proportional catalytic components including pyruvate dehydrogenase (E1), dihydrolipoamide transacetylase (E2), and dihydrolipoamide dehydrogenase (E3) (24, 25). PDC is subject to inactivation at E1α by four PDK isoforms (PDK 1–4) (24). The E2-lipoyl domains serve as the binding and integrational regions between the regulatory enzymes and PDC (26). A growing body of evidence proved the vital role of the adaptive change in the total level and activity of PDC understanding severely impaired energy metabolic conditions in a failing heart. Recently, an elaborate study comprehensively examined the expression of PDC component proteins and its regulatory proteins found the increased expression levels of E1α, diminished expression of PDK4, and indifferent levels of E1β, PDK1, and PDK2 in the myocardia of HF patients compared to the nonfailing heart, which support sustained adaptive capacity for PDC to facilitate glucose metabolism facing the energy deficiency condition in the failing heart (27). Our results in the mice model are generally similar to this finding in human myocardium except the increased level of E1β, suggesting the consistency of PDC regulation in different species and further serving as a confirmation of our results in the HF condition. More importantly, we further supplemented that exercise could

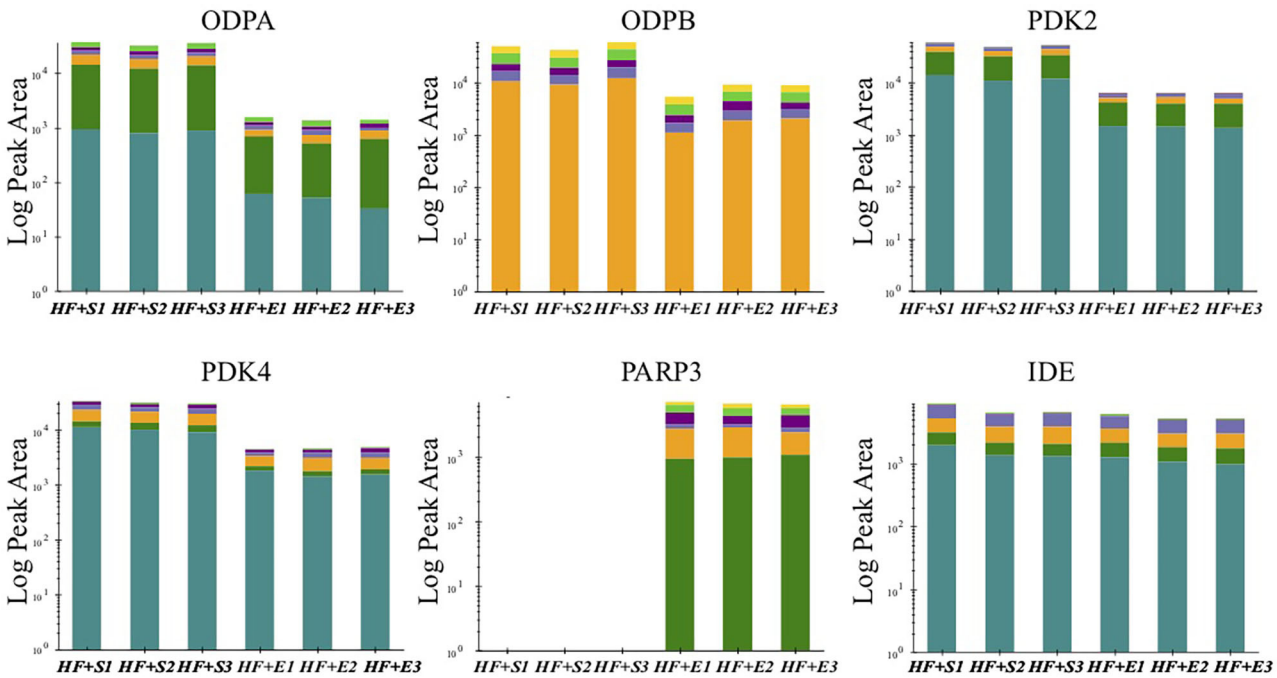


FIGURE 3 | The peak area of verified proteins involved in energy metabolism in the sedentary group and the exercise group of HF mice. ODPA, pyruvate dehydrogenase E1 component subunit alpha; ODPB, pyruvate dehydrogenase E1 component subunit beta; PDK2, pyruvate dehydrogenase (acetyl-transferring)] kinase isozyme 2; PDK4, pyruvate dehydrogenase (acetyl-transferring)] kinase isozyme 4; PARP3, poly [ADP-ribose] polymerase 3; IDE, insulin-degrading enzyme.

normalize the expression of E1α and E1β to nonfailing condition and further decreased the expression level of PDK2 and PDK4. To date, this is the first study revealing the exercise-induced regulation of PDC activity in the HF condition.

Generally, the complex regulation of PDC includes the long-term transcriptional regulation of component subunits or regulatory enzymes and short-term enzymatic activity regulation by reversible phosphorylation or metabolic intermediates (28). Our study found the transcriptional regulation of both component subunits and PDK after exercise. The expression of four PDK isoenzymes is regulated diversely and the changeable characteristic of PDK2 and PDK4 have been identified previously (29). PDK1 is mostly sensitive to low oxygen supply and the expression of PDK1 is generally activated by hypoxia-inducible factor 1 (HIF-1) in hypoxic conditions acting to the shunting of glucose metabolites away from the mitochondria in the case of ROS accumulation (30, 31). Expression of the other three PDKs are all directly under the upstream regulation by the peroxisome-proliferator-activated receptor (PPAR), a critical factor involved in the control of metabolism (32). While they are sensitive to various stimulating factors, which, respectively, are high concentration of NADH and high acetyl-CoA to CoA ratios for PDK2, high concentration of ATP for PDK3, and energy deprivation for PDK4 (26–28). In our study, the expression of PDK1 was unchanged in the exercise-treated group, suggesting that PDH expression is not significantly modulated by the oxygen supply condition of myocardium. The expression level of PDK3 is too low to be measured due to the overly high affinity to PDC (33). The co-instantaneous downregulation of PDK2 and PDK4 suggests the metabolic markers conventionally believed didn't exert a driving role in the transcriptional regulation of PDC considering the elevated ATP level after exercise in the HF mice (19). By which the expression of PDK2 and PDK4 are regulated and whether PPAR plays dominant roles deserve future works. Subunits of PDC will be downregulated when deprivation or diminishment of energy supplement and vice versa (34). Hence, a higher level of E1αin HF serves as an adaptive response to the energy depletion condition and its normalization after exercise may represent positive feedback after the relative restoration of energy supplement. Broadly speaking, lower expression of PDK suggests a higher proportion of active PDC, whereas the lower E1α and E1β suggest a lower total PDC level. Combined with our previous findings that the glucose metabolism was significantly elevated after exercise (19), we speculated that the total activity of PDC increased after exercise and the rapid control of PDC activity by PDK-mediated in activation rather the PDC component proteins play essential roles in the biological process.

PDC has been increasingly studied as a promising intervention target to restore cardiac function via regulating the oxidation of glucose (35). A recent study on a PDC stimulator, dichloroacetate (DCA), proved its therapeutic effects in restoring the glycolytic flux, maintaining the levels of ATP and improving cardiac function in the chronically hypoxic hearts by inhibiting PDK in mitochondria (36). However, the short half-life limits the clinical practice of DCA in a large scale and diverse drugs targeted on PDC are needed. Exercise has also been shown to regulate metabolism by increasing the expression levels of glycolytic oxidation-related enzymes (37). However, previous

evidence on the role of exercise on PDC in HF condition is limited. Our study fills the gaps for the first time and found that regular aerobic exercise regulates PDC not only by the expression of its functional subunits but also the activity-related enzymes. The results enlighten us not only about the molecular insight of exercise on HF but also about future therapeutic selection on PDC. Except the nonpharmacological treatments, more drug targets could be identified by further exploring delicate molecular mechanism for the expression changes and multi-target drugs on PDC may also be a selection.

Nicotinamide adenine dinucleotide (NAD) is a cofactor for energy metabolism in redox reactions. The reduced form (NADH) contributes most electrons to the respiratory chain and the oxidized form (NAD+) is commonly shared as a substrate by several enzymes including the PARPs (38), which play pivotal roles in cardiac metabolism by the function as metabolic sensors (39, 40). PARP, as a ubiquitous nuclear protein, is mainly responsible for DNA repair of injured cells as pathophysiological activation (41) but can also lead to NAD^+ depletion and cell death (42). Numerous studies have focused on the regulation of NAD homeostasis in cardiac diseases (43). For example, it was found that inhibition of PARP1 exerted cardioprotective roles in post-MI mediated possibly by attenuating cardiac fibrosis, regulating autophagy or reducing apoptosis in some pre-clinical trials (44, 45). In line with previous studies, we observed the decreasing expression level of PARP1 and PARP3 in the MI-induced HF mice model. The upregulation of PARP1 after regular exercise was not verified in subsequent experiments. However, the expression of PARP3 is significantly upregulated in the confirmatory experiment. Considering the detrimental effects of the PARP's over-activation, we can't exclude the possibility that the overexpression of PARP3 after exercise will exacerbate cardiac fibrosis like PARP1 (46). This may be the unusual obstacle hanging over the beneficial role of regular exercise on HF and we should treat it seriously.

LIMITATIONS

Major limitations of our study reflect on the exercise training mode and HF model. More exercise types including resistance training or wheel-running, diverse training duration, and intensity may induce different proteomic alterations in the same HF model. Moreover, repeatability in other nonischemic HF models of the metabolic alterations in the current study remains elusive.

CONCLUSION

Our study exhibits the shift of proteomic profiles induced by aerobic exercise in the setting of MI-induced HF, which furnishes not only the systematic insight of the influence of aerobic exercise on HF but also ample molecular targets for future mechanism's experiments. The significant changes of several functional proteins involving energy metabolism support the pivotal role of metabolic remodeling in the regulation of exercise on HF. Adaptive regulations of PDC induced by exercise manifested the downregulating expression of both PDC protein and PDKs. The seemingly reverse regulation suggests the possibly dominant role of PDK in the activation of PDC and further work to elucidate the mechanism of the altered expression response to exercise treatment in the setting of HF is of great benefit for the mitochondrial energy regulation and viable novel drug developments. Further study on the PARP3 is also essential, especially its effect on the cardiac function.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by Zhongshan Hospital, Fudan University, China.

AUTHOR CONTRIBUTIONS

SM: conceptualization, project administration, and writing-review and editing. HJia: methodology, project administration, and writing-review and editing. LZ: methodology, project administration, and data analysis. ZX: investigation, data curation, writing-original draft, and writing-review and editing. JZ: data curation and writing-review. AS: investigation, data curation, and writing-review. HJin: resources and data curation. JG: supervision, project administration, and writing-review and editing. All authors contributed to the article and approved the submitted version.

FUNDING

This research received a grant from Major Research Plan of the National Natural Science Foundation of China (91639104), a grant to AS from the National Science Fund for Distinguished Young Scholars (81725002), National Natural Science Foundation of China (81800348), and Shanghai Science and Technology Commission(No. 19JC1411302).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.732076/full#supplementary-material

REFERENCES

1. Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet.* (2020) 396:1204–22. doi: 10.1016/S0140-6736(20)30925-9
2. Andries G, Yandrapalli S, Aronow WS. Benefit-risk review of different drug classes used in chronic heart failure. *Expert*

Opin Drug Saf. (2019) 18:37–49. doi: 10.1080/14740338.2018.1512580
3. Smart N, Marwick TH. Exercise training for patients with heart failure: a systematic review of factors that improve mortality and morbidity. *Am J Med.* (2004) 116:693–706. doi: 10.1016/j.amjmed.2003.11.033
4. Lewinter C, Doherty P, Gale C, Crouch S, Stirk L, Lewin R, et al. Exercise-based cardiac rehabilitation in patients with heart failure: a meta-analysis of randomised controlled trials between 1999 and 2013. *Eur J Prevent Cardiol.* (2015) 22:1504–12. doi: 10.1177/2047487314559853
5. Sagar V, Davies E, Briscoe S, Coats A, Dalal H, Lough F, et al. Exercise-based rehabilitation for heart failure: systematic review and meta-analysis. *Open Heart.* (2015) 2:e000163. doi: 10.1136/openhrt-2014-000163
6. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA.* (2009) 301:1439–50. doi: 10.1001/jama.2009.454
7. Belardinelli R, Georgiou D, Cianci G, Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. *Circulation.* (1999) 99:1173–82. doi: 10.1161/01.CIR.99.9.1173
8. Ponikowski P, Voors A, Anker S, Bueno H, Cleland J, Coats A, et al. 2016 ESC Guidelines for the diagnosis treatment of acute chronic heart failure: the Task Force for the diagnosis treatment of acute chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* (2016) 37:2129–200. doi: 10.1093/eurheartj/ehw128
9. Yancy C, Jessup M, Bozkurt B, Butler J, Casey D, Drazner M, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American heart association task force on practice guidelines. *J Am Coll Cardiol.* (2013) 62:e147–239. doi: 10.1161/CIR.0b013e31829e8776
10. Schmidt C, Moreira-Goncalves D, Santos M, Leite-Moreira A, Oliveira J. Physical activity and exercise training in heart failure with preserved ejection fraction: gathering evidence from clinical and pre-clinical studies. *Heart Fail Rev.* (2020) doi: 10.1007/s10741-020-09973-5. [Epub ahead of print].
11. Dieberg G, Ismail H, Giallauria F, Smart N. Clinical outcomes and cardiovascular responses to exercise training in heart failure patients with preserved ejection fraction: a systematic review and meta-analysis. *J Appl Physiol (1985).* (2015) 119:726–33. doi: 10.1152/japplphysiol.00904.2014
12. Hegde S, Claggett B, Shah A, Lewis E, Anand I, Shah S, et al. Physical activity and prognosis in the TOPCAT trial (treatment of preserved cardiac function heart failure with an aldosterone antagonist). *Circulation.* (2017) 136:982–992. doi: 10.1161/CIRCULATIONAHA.117.028002
13. Brinker S, Pandey A, Ayers C, Barlow C, DeFina L, Willis B, et al. Association of cardiorespiratory fitness with left ventricular remodeling and diastolic function: the cooper center longitudinal study. *JACC Heart Fail.* (2014) 2:238–46. doi: 10.1016/j.jchf.2014.01.004
14. Luo N, Merrill P, Parikh KS, Whellan DJ, Pina IL, Fiuzat M, et al. Exercise training in patients with chronic heart failure and atrial fibrillation. *J Am Coll Cardiol.* (2017) 69:1683–91. doi: 10.1016/j.jacc.2017.01.032
15. Morris JH, Chen L. Exercise training and heart failure: a review of the literature. *Card Fail Rev.* (2019) 5:57–61. doi: 10.15420/cfr.2018.31.1
16. Ichige MHA, Pereira MG, Brum PC, Michelini LC. Experimental evidences supporting the benefits of exercise training in heart failure. *Adv Exp Med Biol.* (2017) 999:181–206. doi: 10.1007/978-981-10-4307-9_11
17. Patel HC, Kaye DM. Exercise training in heart failure: a long way to go yet. *Eur J Heart Fail.* (2018) 20:1744–5. doi: 10.1002/ejhf.1332
18. Vujic A, Lerchenmuller C, Wu TD, Guillermier C, Rabolli CP, Gonzalez E, et al. Exercise induces new cardiomyocyte generation in the adult mammalian heart. *Nat Commun.* (2018) 9:1659. doi: 10.1038/s41467-018-04083-1
19. Jiang H, Jia D, Zhang B, Yang W, Dong Z, Sun X, et al. Exercise improves cardiac function and glucose metabolism in mice with experimental myocardial infarction through inhibiting HDAC4 and upregulating GLUT1 expression. *Basic Res Cardiol.* (2020) 115:28. doi: 10.1007/s00395-020-0787-1
20. Chicco A, McCune S, Emter C, Sparagna G, Rees M, Bolden D, et al. Low-intensity exercise training delays heart failure and improves survival in female hypertensive heart failure rats. *Hypertension (1979).* (2008) 51:1096–102. doi: 10.1161/HYPERTENSIONAHA.107.107078
21. Gao E, Lei Y, Shang X, Huang Z, Zuo L, Boucher M, et al. A novel and efficient model of coronary artery ligation and myocardial infarction in the mouse. *Circ Res.* (2010) 107:1445–53. doi: 10.1161/CIRCRESAHA.110.223925
22. Lesur A, Schmit PO, Bernardin F, Letellier E, Brehmer S, Decker J, et al. Highly multiplexed targeted proteomics acquisition on a TIMS-QTOF. *Anal Chem.* (2021) 93:1383–92. doi: 10.1021/acs.analchem.0c03180
23. Tian W, Zhang N, Jin R, Feng Y, Wang S, Gao S, et al. Immune suppression in the early stage of COVID-19 disease. *Nat Commun.* (2020) 11:5859. doi: 10.1038/s41467-020-19706-9
24. Patel M, Nemeria N, Furey W, Jordan F. The pyruvate dehydrogenase complexes: structure-based function and regulation. *J Biol Chem.* (2014) 289:16615–23. doi: 10.1074/jbc.R114.563148
25. Patel M, Roche T. Molecular biology and biochemistry of pyruvate dehydrogenase complexes. *FASEB J.* (1990) 4:3224–33. doi: 10.1096/fasebj.4.14.2227213
26. Harris R, Bowker-Kinley M, Huang B, Wu P. Regulation of the activity of the pyruvate dehydrogenase complex. *Adv Enzyme Regul.* (2002) 42:249–59. doi: 10.1016/S0065-2571(01)00061-9
27. Sheeran FL, Angerosa J, Liaw NY, Cheung MM, Pepe S. Adaptations in protein expression and regulated activity of pyruvate dehydrogenase multienzyme complex in human systolic heart failure. *Oxid Med Cell Longev.* (2019) 2019:4532592. doi: 10.1155/2019/4532592
28. Patel M, Korotchkina L. Regulation of the pyruvate dehydrogenase complex. *Biochem Soc Trans.* (2006) 34:217–22. doi: 10.1042/BST0340217
29. Strumiło S. Short-term regulation of the mammalian pyruvate dehydrogenase complex. *Acta Biochim Polonica.* (2005) 52:759–64. doi: 10.18388/abp.2005_3387
30. DeBerardinis R, Lum J, Hatzivassiliou G, Thompson C. The biology of cancer: metabolic reprogramming fuels cell growth and proliferation. *Cell Metab.* (2008) 7:11–20. doi: 10.1016/j.cmet.2007.10.002
31. Kim J, Tchernyshyov I, Semenza G, Dang C. HIF-1-mediated expression of pyruvate dehydrogenase kinase: a metabolic switch required for cellular adaptation to hypoxia. *Cell Metab.* (2006) 3:177–85. doi: 10.1016/j.cmet.2006.02.002
32. Degenhardt T, Saramäki A, Malinen M, Rieck M, Väisänen S, Huotari A, et al. Three members of the human pyruvate dehydrogenase kinase gene family are direct targets of the peroxisome proliferator-activated receptor beta/delta. *J Mol Biol.* (2007) 372:341–55. doi: 10.1016/j.jmb.2007.06.091
33. Bowker-Kinley M, Davis W, Wu P, Harris R, Popov K. Evidence for existence of tissue-specific regulation of the mammalian pyruvate dehydrogenase complex. *Biochem J.* (1998) 329:191–6. doi: 10.1042/bj3290191
34. Zhang F, Xu X, Zhou B, He Z, Zhai Q. Gene expression profile change and associated physiological and pathological effects in mouse liver induced by fasting and refeeding. *PLoS ONE.* (2011) 6:e27553. doi: 10.1371/journal.pone.0027553
35. Ussher J, Wang W, Gandhi M, Keung W, Samokhvalov V, Oka T, et al. Stimulation of glucose oxidation protects against acute myocardial infarction and reperfusion injury. *Cardiovasc Res.* (2012) 94:359–369. doi: 10.1093/cvr/cvs129
36. Handzlik M, Constantin-Teodosiu D, Greenhaff P, Cole M. Increasing cardiac pyruvate dehydrogenase flux during chronic hypoxia improves acute hypoxic tolerance. *J Physiol.* (2018) 596:3357–69. doi: 10.1113/JP275357
37. Kim D, Chauhan S. The role of dichloroacetate in improving acute hypoxic tolerance and cardiac function: translation to failing hearts? *J Physiol.* (2018) 596:2967–8. doi: 10.1113/JP276217
38. Alemasova E, Lavrik O. Poly(ADP-ribosyl)ation by PARP1: reaction mechanism and regulatory proteins. *Nucleic Acids Res.* (2019) 47:3811–27. doi: 10.1093/nar/gkz120
39. Houtkooper R, Cantó C, Wanders R, Auwerx J. The secret life of NAD+: an old metabolite controlling new metabolic signaling pathways. *Endocr Rev.* (2010) 31:194–223. doi: 10.1210/er.2009-0026
40. Tannous C, Booz G, Altara R, Muhieddine D, Mericskay M, Refaat M, et al. Nicotinamide adenine dinucleotide: biosynthesis, consumption and therapeutic role in cardiac diseases. *Acta Physiol (Oxf).* (2020) 231:e13551. doi: 10.1111/apha.13551
41. Jagtap P, Szabó C. Poly(ADP-ribose) polymerase and the therapeutic effects of its inhibitors. *Nat Rev Drug Discov.* (2005) 4:421–40. doi: 10.1038/nrd1718

42. Alano C, Garnier P, Ying W, Higashi Y, Kauppinen T, Swanson R. NAD+ depletion is necessary and sufficient for poly(ADP-ribose) polymerase-1-mediated neuronal death. *J Neurosci.* (2010) 30:2967–78. doi: 10.1523/JNEUROSCI.5552-09.2010
43. Mericskay M. Nicotinamide adenine dinucleotide homeostasis and signalling in heart disease: pathophysiological implications and therapeutic potential. *Arch Cardiovasc Dis.* (2016) 109:207–15. doi: 10.1016/j.acvd.2015.10.004
44. Wang J, Hao L, Wang Y, Qin W, Wang X, Zhao T, et al. Inhibition of poly (ADP-ribose) polymerase and inducible nitric oxide synthase protects against ischemic myocardial damage by reduction of apoptosis. *Mol Med Rep.* (2015) 11:1768–76. doi: 10.3892/mmr.2014.2977
45. Wang H, Yang X, Yang Q, Gong L, Xu H, Wu Z. PARP-1 inhibition attenuates cardiac fibrosis induced by myocardial infarction through regulating autophagy. *Biochem Biophys Res Commun.* (2018) 503:1625–32. doi: 10.1016/j.bbrc.2018.07.091
46. Sun S, Hu Y, Zheng Q, Guo Z, Sun D, Chen S, et al. Poly(ADP-ribose) polymerase 1 induces cardiac fibrosis by mediating mammalian target of rapamycin activity. *J Cell Biochem.* (2019) 120:4813–26. doi: 10.1002/jcb.26649

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Cardiovascular Medicine

SYSTEMATIC REVIEW
published: 11 October 2021
doi: 10.3389/fcvm.2021.734687

Differences in Peak Oxygen Uptake in Bicycle Exercise Test Caused by Body Positions: A Meta-Analysis

Xiaohua Wan[1,2], *Chang Liu*[1,2], *Thomas P. Olson*[3], *Xiankun Chen*[2,4,5], *Weihui Lu*[1,2*] *and Wei Jiang*[1,2,6*]

[1] Department of Cardiology, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, China, [2] The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China, [3] Division of Cardiovascular Diseases, Department of Internal Medicine, Mayo Clinic and Foundation, Rochester, MN, United States, [4] Healthy Systems and Policy, Department of Global Public Health, Karolinska Institutet, Stockholm, Sweden, [5] Key Unit of Methodology in Clinical Research, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, China, [6] Guangdong Provincial Key Laboratory of Chinese Medicine for Prevention and Treatment of Refractory Chronic Diseases, Guangzhou, China

Background: As demand for cardiopulmonary exercise test using a supine position has increased, so have the testing options. However, it remains uncertain whether the existing evaluation criteria for the upright position are suitable for the supine position. The purpose of this meta-analysis is to compare the differences in peak oxygen uptake (VO_{2peak}) between upright and supine lower extremity bicycle exercise.

Methods: We searched PubMed, Web Of Science and Embase from inception to March 27, 2021. Self-control studies comparing VO_{2peak} between upright and supine were included. The quality of the included studies was assessed using a checklist adapted from published papers in this field. The effect of posture on VO_{2peak} was pooled using random/fixed effects model.

Results: This meta-analysis included 32 self-control studies, involving 546 participants (63% were male). 21 studies included only healthy people, 9 studies included patients with cardiopulmonary disease, and 2 studies included both the healthy and cardiopulmonary patients. In terms of study quality, most of the studies ($n = 21$, 66%) describe the exercise protocol, and we judged theVO_{2peak} to be valid in 26 (81%) studies. Meta-analysis showed that the upright VO_{2peak} exceeded the supine VO_{2peak} [relative VO_{2peak}: mean difference (MD) 2.63 ml/kg/min, 95% confidence interval (CI) 1.66-3.59, $I^2 = 56\%$, $p < 0.05$; absolute VO_{2peak}: MD 0.18 L/min, 95% CI 0.10-0.26, $I^2 = 63\%$, $p < 0.05$). Moreover, subgroup analysis showed there was more pooled difference in healthy people (4.04 ml/kg/min or 0.22 L/min) than in cardiopulmonary patients (1.03 ml/kg/min or 0.12 L/min).

Conclusion: VO_{2peak} in the upright position is higher than that in supine position. However, whether this difference has clinical significance needs further verification.

Systematic Review Registration: identifier, CRD42021233468.

Keywords: cardiopulmonary exercise test, peak oxygen uptake, bicycle, posture difference, meta-analysis

OPEN ACCESS

Edited by:
Jian Yang,
Fudan University, China

Reviewed by:
Candela Diaz Canestro,
The University of Hong Kong, Hong Kong, SAR China
YuQin Shen,
Tongji Hospital Affiliated to Tongji University, China

***Correspondence:**
Weihui Lu
weihui.lu@163.com
Wei Jiang
drjiangwei@126.com

Specialty section:
This article was submitted to General Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

Received: *01 July 2021*
Accepted: *13 September 2021*
Published: *11 October 2021*

Citation:
Wan X, Liu C, Olson TP, Chen X, Lu W and Jiang W (2021) Differences in Peak Oxygen Uptake in Bicycle Exercise Test Caused by Body Positions: A Meta-Analysis. Front. Cardiovasc. Med. 8:734687. doi: 10.3389/fcvm.2021.734687

INTRODUCTION

The cardiopulmonary exercise test (CPET) is a non-invasive and safe method for comprehensive evaluation of cardiopulmonary function during exercise. It has been used in a variety of settings including differential diagnosis, surgical risk assessment, and prognosis evaluation. For example, patients with heart failure and chronic obstructive pulmonary disease with low peak oxygen uptake (VO_{2peak}) have low survival rates (1, 2).

The two most common modes of CPET are upright bicycle and treadmill, followed by supine bicycle. Because of less arm and torso movement during supine cycling compared to upright cycle or treadmill, there can be less artifact in collected metrics and greater ease in obtaining clear and stable cardiac imaging and circulatory measurements when patients are supine. Therefore, supine CPET combined with cardiac imaging is the most comprehensive and sensitive means to evaluate the state of cardiac chambers, cardiac hemodynamics, and valve function during exercise (3, 4). Due to this advantage, clinical demand for supine CPET has been on the rise. However, researchers have hypothesized that the two positions' CPET results may be different. This is because the change from the upright position to supine position will affect the venous return, cardiac output (CO), the lung ventilation/perfusion matching (V/Q), and skeletal muscle blood flow and perfusion (5–8).

Studies have compared the cardiovascular response between upright and supine cycle exercise tests, but the results have been inconsistent. For example, Kramer's study of 14 men with heart failure showed that the VO_{2peak} in the upright position exceeded that in the supine (9). Conversely, Bonzheim's study found that VO_{2peak} in the supine was slightly higher than that in upright in patients with coronary artery disease (10). Therefore, the objective of this study was to compare the VO_{2peak} attained from upright and supine lower extremity bicycle exercise.

METHODS

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (**Supplementary Materials S1**: PRISMA 2020 Checklist) and the Cochrane Handbook for Interventional Reviews and registered in PROSPERO (CRD42021233468).

Data Sources and Search Strategy

We searched PubMed, Web Of Science and Embase on March 27, 2021 using relevant keywords and a Boolean search string (see **Supplementary Materials S2** for the detailed search strategy): (((((“Exercise test”)) OR (“exercise test” OR “cardiopulmonary exercise test” OR “cycle exercise” OR “ergometer” OR “CPET” OR “CPX”)) AND (“position” OR “posture” OR “supine” OR “recumbent” OR “recline” OR “lean” OR “tilt” OR “clinostatism” OR “decubitus” OR “lie”)) AND (“erect” OR “upright” OR “orthostatic” OR “sit”)) AND (“VO_2” OR “oxygen uptake”). The search string consisted of MeSH and general search terms. Searches were restricted to English.

Inclusion and Exclusion Criteria

We included self-control trials, and selection criteria conformed to the PICOS approach, as described hereinafter.

Populations

There were no restrictions regarding subjects, except for persons with disabilities.

Intervention

Subjects completed an incremental maximum exercise test using a leg bicycle ergometer in a supine position. However, we excluded any studies if other interventions had been applied, such as the use of drugs that may affect hemodynamics, or lower limb negative pressure.

Comparators

The same subjects completed the exercise using a leg bicycle ergometer in an upright position with the same exercise protocol.

Outcomes

The outcome measure was absolute and/or relative VO_{2peak}.

Study Selection

After eliminating duplicate articles, XW and CL screened the titles and abstracts. Studies that did not mention VO_{2peak} or a synonym in the study title and/or abstracts, but were likely to have included them as a secondary measure, were also included. In the second step, XW and CL read the full texts of articles considered relevant based on title and abstract. There was full agreement on the inclusion of the full-text articles.

Assessing Methodological Quality

XW and CL assessed the quality of the included studies with a modified version of the Downs and Black checklist (see **Supplementary Materials S3**) (11). This checklist has been employed in several reviews in the field of sports science, which also uses cross-sectional studies for data retrieval. In our modified version, we considered four domains, including seven items, to evaluate the included studies' quality: (1) are the interventions of interest clarified? (2) are the test positions clarified? (3) is the time period the participants have between tests similar? (4) was the test order randomized? (5) how was VO_{2peak} defined? (6) was the VO_{2peak} test valid? and (7) are the characteristics of the participants included in the study clarified? All items were rated as “Yes,” “No,” or “Not sure.”

Data Extraction

We extracted data on VO_{2peak} in the respective positions and the characteristics of the participants (number of participants, sex, age, body mass, types of disease) as well as the starting workload, rotation rate, duration and workload increase of the increments used during the test protocols.

Abbreviations: C(a-v) O_2, arteriovenous oxygen difference; CO, cardiac output; CPET, cardiopulmonary exercise test; SD, standard deviation; MD, mean difference; VO_{2peak}, peak oxygen uptake; V/Q, Ventilation/perfusion ratio.

Statistical Analysis

We performed statistical analysis with RevMan version 5.3. The data are segmented or combined based on the angle between the upper body and the horizontal plane, or whether there is cardiopulmonary disease, and the calculation process is based on the formula in Cochrane 7.7. Continuous variables are expressed by means and standard deviation. We assessed heterogeneity across included studies using a Cochran chi-square test (with 0.1 as the cutoff for statistical significance) and an I^2 statistic test. We employed a random effects model where there was evidence of statistical heterogeneity (I^2 statistic $> 50\%$). Otherwise, we used a fixed effects model. If there was heterogeneity, we first analyzed the source of heterogeneity, and then used subgroup analysis or other methods to deal with it. After excluding obvious clinical heterogeneity, we conducted the meta-analysis with a random response model. The meta-analysis test level was $p = 0.05$.

RESULTS

Search Results

The detailed study search and selection process is outlined in **Figure 1**. In total, we retrieved 1,179 records from the database searches. After excluding duplicates, we screened 1,011 potentially relevant abstracts, and excluded 891 for failing to meet the inclusion criteria. We read the remaining 120 full texts, and deemed 32 self-control trials eligible for systematic review (9, 10, 12–41).

Methodological Quality of the Included Studies

The quality of the included studies is shown in **Table 1**. Only nine studies (28%) clarified the participants' inclusion and exclusion criteria. Most of the studies ($n = 21$, 66%) clarified the exercise protocol, but only about half ($n = 14$, 44%) clarified the body position during exercise. Twenty studies (62.5%) mentioned the use of randomization methods to determine the sequence of positions used in the CPET. In addition, the interval between the two tests was similar in 18 (56%) of the studies. Although the VO_{2peak} was clarified in 14(44%) studies, VO_{2peak} was judged to be valid in 26 (81%) studies where the criteria for verification of maximal effort were stated explicitly.

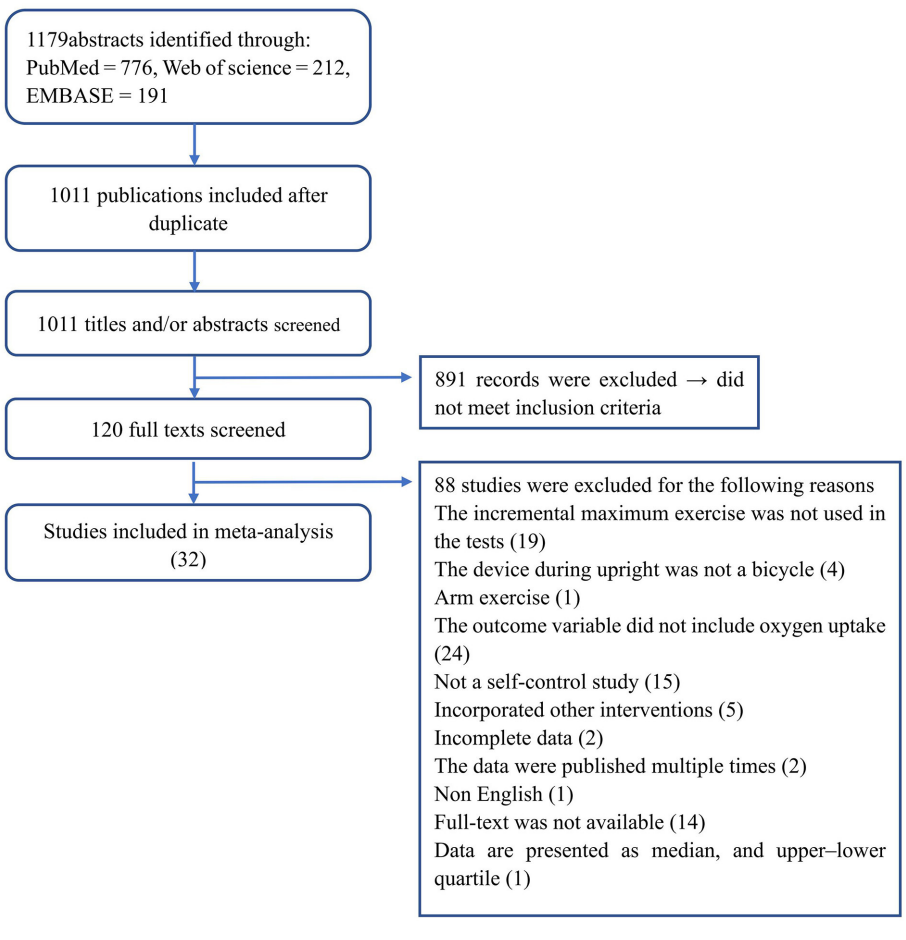


FIGURE 1 | Detailed literature search and study selection process.

TABLE 1 | Methodological quality evaluation for included studies ($n = 32$).

References	1. Participant's characteristics clarified?*	2. Test protocol clarified?*	3. Test positions clarified?*	4. Between tests period similar?*	5. Test order randomized?*	6. VO_{2peak} clarified?*	7. VO_{2peak} test valid?*
Ade et al. (15)	NS	Y	Y	N	Y	Y	Y
Armour et al. (16)	NS	NS	N	N	Y	N	Y
Bonzheim et al. (10)	Y	Y	Y	Y	Y	N	Y
Chesler and Stein (17)	Y	Y	Y	Y	Y	N	Y
Cornelis and Buys (18)	Y	Y	N	N	Y	Y	Y
DiMenna et al. (19)	N	Y	NS	N	N	Y	N
Egana et al. (20)	NS	Y	Y	N	Y	N	Y
Egana et al. (21)	N	Y	Y	Y	Y	Y	Y
Faulkner et al. (22)	Y	NS	N	Y	Y	N	Y
Forbregd et al. (23)	NS	Y	Y	Y	Y	Y	Y
Forton et al. (24)	NS	NS	Y	Y	Y	N	Y
Goldstein et al. (25)	NS	Y	N	Y	Y	N	Y
Greenleaf et al. (26)	N	NS	N	Y	N	Y	Y
Hughson et al. (27)	NS	NS	N	N	N	N	N
Hughson et al. (28)	NS	Y	NS	N	N	Y	Y
Jones et al. (29)	N	Y	Y	Y	N	Y	Y
Koga et al. (30)	NS	Y	NS	N	N	N	Y
Kramer et al. (9)	Y	NS	N	Y	N	N	N
Leyk et al. (31)	NS	Y	Y	Y	Y	N	Y
Magder et al. (32)	NS	NS	N	N	N	Y	N
May et al. (13)	Y	Y	N	N	Y	N	Y
Mizumi et al. (14)	Y	Y	Y	N	N	Y	Y
Pedersen et al. (33)	NS	NS	N	Y	Y	N	Y
Quinn et al. (12)	NS	Y	NS	Y	Y	N	Y
Rowland et al. (34)	NS	Y	NS	Y	N	Y	Y
Schulman et al. (35)	Y	NS	N	Y	Y	N	Y
Tempest et al. (36)	NS	NS	Y	N	Y	Y	Y
Terkelsen et al. (37)	NS	Y	N	N	Y	Y	N
Walsh-Riddle et al. (38)	NS	Y	Y	Y	Y	N	Y
Welbergen and Clijsen (39)	NS	Y	Y	Y	N	N	N
Yamada and Sumio (40)	Y	Y	Y	Y	N	Y	Y
Zhao et al. (41)	NS	NS	NS	N	Y	N	Y

VO_{2peak}, peak oxygen uptake; Y, Yes; N, No; NS, Not sure.
Rating criteria details are listed in **Supplementary Materials S3.*

Characteristics of the Included Studies

Details of the participants' characteristics are listed in **Table 2**. 546 participants were included in the meta-analysis, of which about 62% were male. 21 studies included only healthy people, 9 studies included patients with cardiopulmonary disease, and 2 studies included both the healthy and the patients with cardiopulmonary disease. The ages of the included population ranged from 9 to 72 years old. There were four articles on children (13, 23, 25, 34), one on both adults and children (41), and the remaining 27 articles were on adults.

Details on the exercise protocols used in the included studies are summarized in **Table 3**. All of the included studies used the continuous incremental exercise program, except for Quinn's study (12). The angle between the upper body and the horizontal in the supine position ranged from −6 to 65°. In some studies, there was only one position and one test for supine exercise, while in other studies, supine exercise contained multiple positions and multiple tests. For example, Egaña's study showed that the angles between the upper body and the horizontal plane in the supine position included zero, 15 and 30° (21). The interval between the two tests was within 1 month in all studies, except for May's and Mizumi's (13, 14).

Comparison of VO_{2peak} Between Positions

In terms of the relative VO_{2peak}, our pooled results showed that the upright VO_{2peak} was higher than the supine VO_{2peak} (relative VO_{2peak}: MD = 2.63 ml/kg/min, 95% CI: 1.66, 3.59, $I^2 = 56\%$, $p < 0.05$; **Figure 2**). In the healthy subgroup, the upright VO_{2peak} remained higher than supine and the effect size was larger without heterogeneity (relative VO_{2peak}: MD = 4.04

TABLE 2 | Characteristics of participants for the included studies ($n = 32$).

References	Population	Participants (*n*)	Males (*n*)	Age, years Mean ± SD (range)	BMI (kg/m^2)/Body mass (kg) Mean ± SD
Ade et al. (15)	Healthy	22	22	25 ± 3	23.8 ± 17.6/75.0 ± 17.6
Armour et al. (16)	HF	9	7	61.9 ± 6.1	29.1 ± 2.9/NA
	Healthy	10	6	63.8 ± 4.6	26.5 ± 3.1/NA
Bonzheim et al. (10)	CAD	14	14	60 ± 6	NA/85 ± 11
Chesler and Stein (17)	Healthy	21	0	39 ± 6 (30–50)	23.4 ± 0.43/66.2 ± 1.7
Cornelis and Buys (18)	Healthy	12	8	21.6 ± NA (21–24)	22.0 ± 1.2/NA
DiMenna et al. (19)	Healthy	8	8	35 ± 13	NA/80.3 ± 6.7
Egana et al. (20)	Healthy	22	11	25.1 ± 4.72	NA/67.9 ± 14.07
Egana et al. (21)	Healthy	10	10	24 ± 4	NA/74.4 ± 6.9
Faulkner et al. (22)	Healthy	17	17	24.6 ± 4.3	NA/76.5 ± 8.7
Forbregd et al. (23)	Healthy	31	NA	(9–15)	18.28 ± 2.4/NA
Forton et al. (24)	Healthy	26	13	23 ± 2	NA/67 ± 11
Goldstein et al. (25)	Fontan	29	18	13.4 ± 2.6	19.2 ± 3/NA
	Healthy	16	9	12.7 ± 4.9	19.6 ± 5.1/NA
Greenleaf et al. (26)	Healthy	4	4	38 ± 8 (26–45)	73.7 ± 7.8/NA
Hughson et al. (27)	Healthy	8	7	22.6 ± 0.9	NA/73.3 ± 2.8
Hughson et al. (28)	Healthy	12	12	22 ± 3	NA/74.6 ± 3.4
Jones et al. (29)	Healthy	8	8	24 ± 7	NA/75.0 ± 5.8
Koga et al. (30)	Healthy	9	8	23.8 ± 9.2	NA/65.8 ± 10.6
Kramer et al. (9)	HF	14	14	60 ± NA (48–72)	NA/NA
Leyk et al. (31)	Healthy	9	7	26 ± 6	NA/71 ± 8
Magder et al. (32)	CAD	8	8	59.1 ± 5.6 (49–66)	25.5 ± 1.8/76.75 ± 2.76
May et al. (13)	Healthy	80	40	13.1 ± 2.3 (8.4-17.8)	NA/49.3 ± 14.2
Mizumi et al. (14)	CTEPH	17	5	58 ± 14	NA/NA
Pedersen et al. (33)	Healthy	8	8	22 ± NA (19–27)	NA/73 ± NA
Quinn et al. (12)	Cardiac disease	9	NA	61.5 ± 8.8 (46–73)	NA/72.7 ± 14.4
Rowland et al. (34)	Healthy	13	13	12.5 ± 1.4 (10.3-14.8)	NA/45.5 ± 10.5
Schulman et al. (35)	Hypertension	20	10	55 ± 5	NA/NA
Tempest et al. (36)	Healthy	12	6	26.2 ± 3.0	NA/72.7 ± 9.1
Terkelsen et al. (37)	Healthy	10	5	22 ± NA (19–25)	NA/68.0 ± 3.3
Walsh-Riddle et al. (38)	Hypertension	20	10	47.9 ± NA (34–62)	NA/NA
Welbergen and Clijsen (39)	Healthy	6	6	28 ± 5 (23–34)	NA/83 ± 9
Yamada and Sumio1999 (40)	AMI	19	19	55.3 ± 7.8	NA/64.8 ± 6.8
Zhao et al. (41)	PE	13	11	19 ± 6 (10–31)	NA/56 ± 10

SD, standard deviation; BMI, body mass index; HF, heart failure; CAD, coronary artery disease; Fontan, Single Ventricle Receiving Fontan Palliation; CTEPH, chronic thromboembolic pulmonary hypertension; AMI, Acute Myocardial Infarction; PE, pectus excavatum. NA, not available.

ml/kg/min, 95% CI: 3.25, 4.83, $I^2 = 0\%$; **Figure 2**). Similarly, in patients with cardiopulmonary disease, upright VO_{2peak} was also higher than supine, however, the effect size was lower compared to the healthy subgroup (relative VO_{2peak}: MD = 1.03 ml/kg/min, 95% CI: 0.29, 1.76, $I^2 = 47\%$; **Figure 2**).

In terms of the absolute VO_{2peak}, our pooled results also showed that the upright VO_{2peak} was higher than the supine VO_{2peak} (absolute VO_{2peak}: MD = 0.18 L/min, 95% CI: 0.10, 0.26, $I^2 = 63\%$, $p < 0.05$; **Figure 3**). Again, the effect size was higher in the healthy subgroup (absolute VO_{2peak}: MD = 0.22 L/min, 95% CI: 0.12, 0.32, $I^2 = 69\%$; **Figure 3**), but lower in the cardiopulmonary disease subgroup (absolute VO_{2peak}: MD = 0.12 ml/kg/min, 95% CI: 0.02, 0.21 $I^2 = 31\%$; **Figure 3**).

Discussion

The purpose of this paper is to evaluate the effect of body position on VO_{2peak} in the CPET *via* meta-analysis. The results indicate that the VO_{2peak} measured by CPET in the upright position was higher than that of the supine position during an incremental cycling exercise test. Moreover, this difference exists in both healthy people and patients with cardiopulmonary disease.

Physiologic shifts in hemodynamic distribution occur with along with changes from supine to upright postures. This hemodynamic shift alters the preload to the right ventricle which subsequently affects preload to the left ventricle and the Frank-Starling mechanism associated with ventricular contraction and stroke volume. Thadani and Parker. have reported hemodynamic

TABLE 3 | Exercise protocol for the included studies ($n = 32$).

References	Angle[a], degrees	Protocol	Starting load	Cadence	Increments
Ade et al. (15)	−6	Continuous	20 W	60 rpm	25 W/min
Armour et al. (16)	NA	Continuous	0 W	NA	25 W/3 min
Bonzheim et al. (10)	65	Continuous	25 W	50 rpm	25 W/2 min
Chesler and Stein (17)	0	Continuous	0 W	50 rpm	25 W/2 min
Cornelis and Buys (18)	NA	Continuous	40-75 W	60-70 rpm	25 W or 30 W/min
DiMenna et al. (19)	0	Continuous	0 W	80 rpm	30 W/min
Egana et al. (20)	0	Continuous	M/F:60/30 W	60 rpm	M/F: 30 W/3 min
Egana et al. (21)	0 and 15 and 30	Continuous	60 W	60 rpm	30 W/3 min until 180 W, then 15 W/min
Faulkner et al. (22)	NA	Continuous	U/Rec:60/30 W	NA	U/REC: 1 W/5 s
Forbregd et al. (23)	0 and 45	Continuous	20 W	60 rpm	2 W/5 s
Forton et al. (24)	0 and 35	Continuous	M/F:60/30 W	NA	M/F: 30/20 W/min
Goldstein et al. (25)	NA	Continuous	200 kg·m/min	60-70 rpm	See the original for details
Greenleaf et al. (26)	NA	Continuous	0 W	NA	See the original for details
Hughson et al. (27)	0	Continuous	NA	NA	15 W/min
Hughson et al. (28)	NA	Continuous	25 W	60 rpm	20 W/min
Jones et al. (29)	0	Continuous	0 W	80-85 rpm	30 W/min
Koga et al. (30)	0	Continuous	0 W	60 rpm	25 W/min
Kramer et al. (9)	NA	Continuous	200 kpm/min	NA	100 kpm/min/3 min
Leyk et al. (31)	0	Continuous	20 W	1 Hz	20 W*5 min and 80 W*5 min, then 10 W/30 s until exhaustion
Magder et al. (32)	NA	Continuous	20 W	NA	10 W/min
May et al. (13)	NA	Continuous	0.25*body weight (kg)	50-60 rpm	0.25*body weight(kg)/min
Mizumi et al. (14)	0	Continuous	10 W	60 rpm	10 W/min
Pedersen et al. (33)	NA	Continuous	160 W	80 rpm	See the original for details
Quinn et al. (12)	0 and 35	Discontinuous	150 kg·m/min	50 rpm	150 kg·m/min
Rowland et al. (34)	0	Continuous	25 W	50 rpm	25 W/3min
Schulman et al. (35)	NA	Continuous	25 W	NA	25 W/3min
Tempest et al. (36)	45 and 65	Continuous	NA	70 rpm	20 W/min
Terkelsen et al. (37)	NA	Continuous	50 W	60 rpm	50 W/3min
Walsh-Riddle et al. (38)	45	Continuous	40 W	50 rpm	40 W*3min and 80 W*3min and 120 W*3min, then 20 W/min
Welbergen and Clijsen (39)	45	Continuous	100 W	90 rpm	100 W*3min and 200 W*3min, then give maximal effort
Yamada and Sumio (40)	0	Continuous	10 W	50 rpm	10 W/min
Zhao et al. (41)	0	Continuous	0 W	NA	15-30 W/min

[a]*Angle between upper body and horizontal plane in supine position.*

M, male; F, female; U, upright; REC, recumbent; W, watt; Kpm, Kilopounds; min, minute; s, second; rpm, revolutions per minute; NA, not available.

differences between the supine and upright positions in normal subjects. They found higher heart rates with lower left ventricular filling pressures and stroke volume index in the upright position, both at rest and during exercise. However, they noted no differences in cardiac index or peak work load between the two modes of exercise (42). Kramer's study of heart failure patients also showed significantly higher right atrial pressure in the supine position, but no differences in cardiac index or stroke index between the two positions. Further, these authors found significantly lower VO_{2peak} in the supine position (9). Moreover, in chronic thromboembolic pulmonary hypertension patients, Mizumi's study showed that CO at rest in the supine position was significantly higher than that in the upright. However, CO at peak exercise was comparable between the two positions, even though VO_{2peak} in the supine position tends to be lower than that of the upright (14). These studies suggest that increased ventricular preload caused by postural changes does not necessarily lead to an increase in stroke volume or CO as a key mechanism to facilitate increased oxygen uptake in the upright posture. In contrast, these data suggest that VO_{2peak} in the supine position may be limited by factors other than the effect of central hemodynamic shifts on CO.

According to the Fick principle, $VO_2 = CO * C(a\text{-}v)\ O_2$ (arteriovenous oxygen difference) (43). Therefore, the VO_2 is influenced by both central and peripheral components, including CO and $C(a\text{-}v)\ O_2$, during exercise. Studies have shown that VO_{2peak} in the upright position is higher than that in the supine position, and accompanied by higher $C(a\text{-}v)\ O_2$, while there is

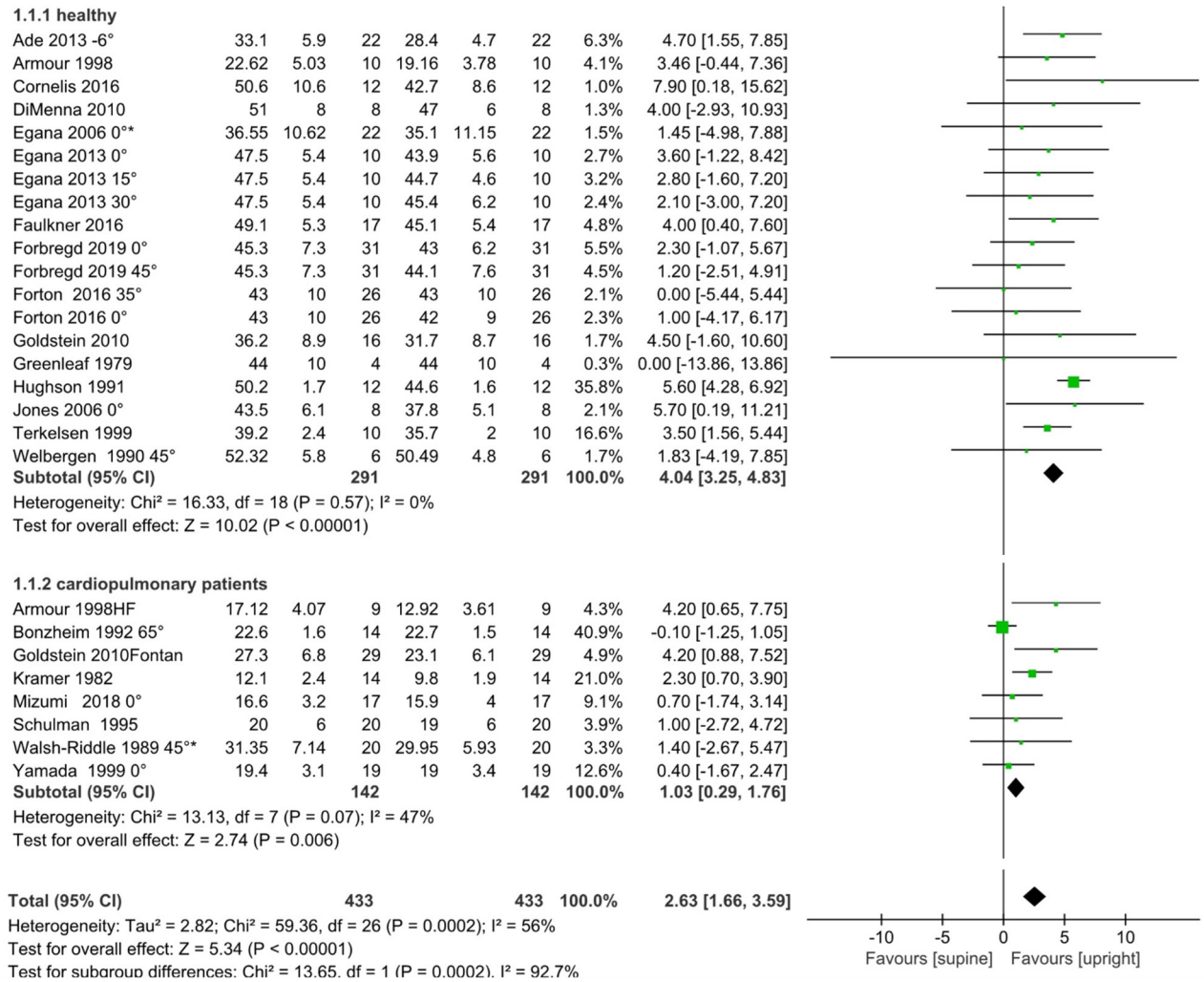


FIGURE 2 | Meta-analysis results for relative VO_{2peak} (ml/kg/min), including overall pooled effects and subgroup effects of the healthy and the cardiopulmonary disease patients. HF, heart failure; Fontan, Single Ventricle Receiving Fontan Palliation. A degree (°) symbol after the reference refers to the angle between upper body and horizontal plane in the supine position. A reference without a degree indicates that the details were unavailable in the original text. An asterisk means that the original text's grouping data are combined according to the formula in Cochrane 7.7, because the angle between the upper body and the horizontal plane is the same as in the supine position.

no difference in cardiac index between the two positions (9, 44). The change in C(a-v) O_2 is influenced by both muscle's ability to consume oxygen and the amount of muscle mass involved in the activity. The oxygen uptake in the muscles is determined by factors such as the amount of muscle work, perfusion pressure, blood flow and mitochondrial density and activity. With regards to muscle mass, the upright position requires greater muscle mass involvement, and thus more physiologic work. Research by Bouillon et al. has demonstrated that during upright cycling, the maximum voluntary isometric contraction of the gluteus maximus, gluteus medius, biceps femoris, lateral head of gastrocnemius, anterior tibialis, rectus femoris, lumbar erector spinalis and rectus abdominis exceed those measured in the semi-reclining position (45). Furthermore, when standing upright, the distribution of blood in the lower extremity vein increases due to increased orthostatic tension. Additionally, the arteries' diameter is wider than in the supine position, and the blood flow velocity is slower. This is conducive to the diffusion of more oxygen from hemoglobin to myoglobin (46). Furthermore, Eiken found that exposing working legs to sub-atmospheric pressure can increase perfusion pressure. This can improve motor ability in the supine position, and simulate upright exercise in normal gravity (47, 48). Further, several studies have used near-infrared spectroscopy illuminate the oxyhemoglobin relationship in the periphery during exercise. These studies suggest that muscle oxygen absorption capacity is higher in the upright position (49–51). Therefore, the C(a-v) O_2 during peak exercise is higher in the upright position,

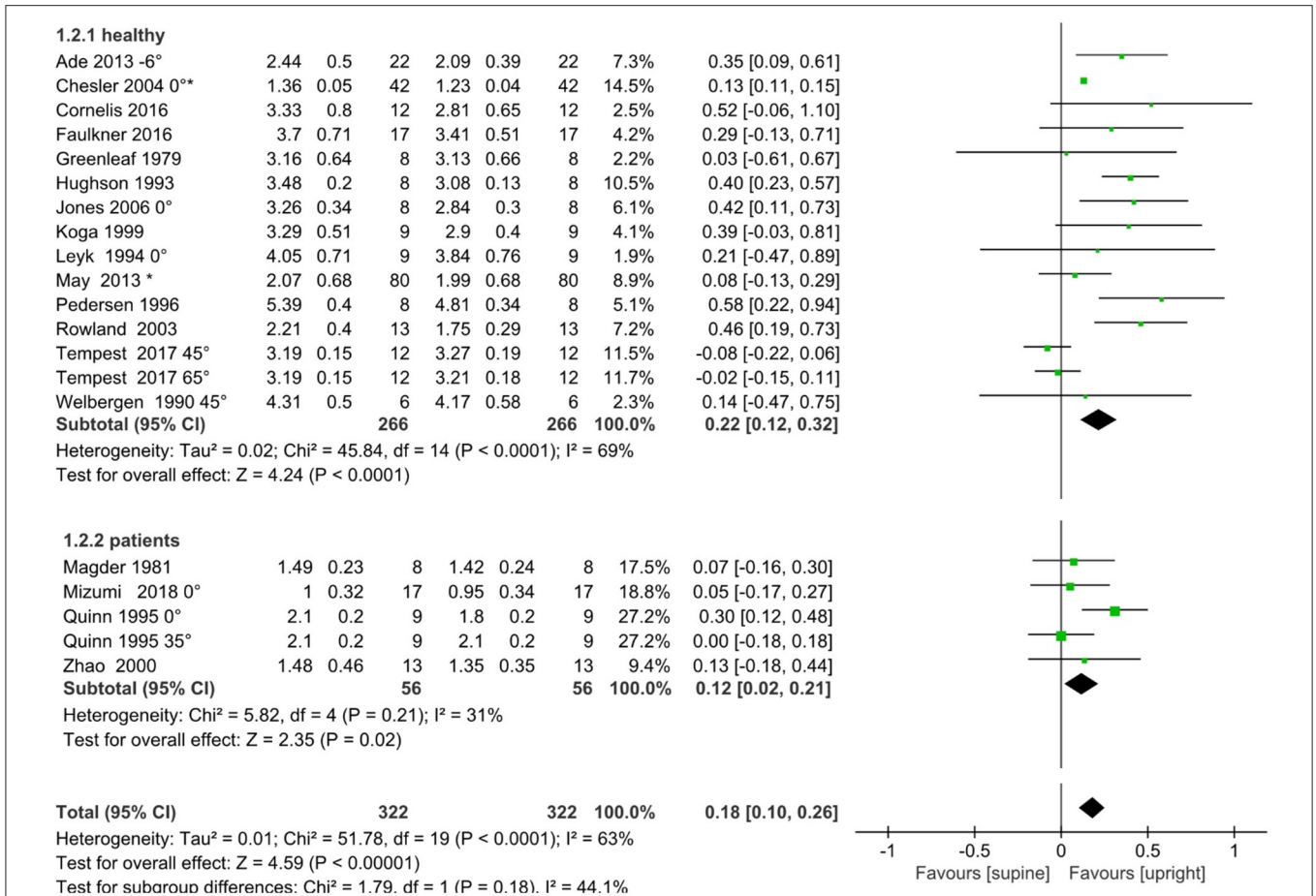


FIGURE 3 | Meta-analysis results for absolute VO_{2peak} (L/min), including overall pooled effects and subgroup effects of the healthy and the cardiopulmonary disease patients. A degree (°) marker after the reference refers to the angle between upper body and horizontal plane in the supine position. References without a degree symbol indicates that the details were unavailable in the original text. An asterisk means that the original text's grouping data are combined according to the formula in Cochrane 7.7, because the angle between upper body and horizontal plane is the same in the supine position.

and this may contribute to the increased VO_{2peak} noted in the upright position.

In addition, studies have shown that the increased venous return in the supine position is conducive to increasing the fluid shift to the pulmonary circulation and interstitium. This may compress small airways and/or blood vessels, unbalancing the overall pulmonary V/Q ratio and reducing ventilatory efficiency (52). Bryan et al. (5) demonstrated that the change from an upright position to the supine position in healthy individuals results in a decrease in the V/Q of the entire lung from 0.83 to 0.76. Further, Sandoval et al. have shown that even in the resting state, the change in body position causes significant changes in alveolar-arterial oxygen partial pressure difference in patients with Eisenmenger syndrome. This decreases oxygen saturation in the supine position (53). In contrast, other studies have shown that the change from an upright position to a supine does not cause significant reduction in ventilatory efficiency in healthy people, or even in patients with stable heart failure (16, 18, 24, 37). As such, the extent to which these components affect peak oxygen uptake in the supine position, and contribute to the lower values when compared to those measured in the upright position, remains unclear.

Limitations

It is important to acknowledge limitations associated with this study. First, the sample sizes of most studies in this meta-analysis were very small. Second, since this research is a self-control study, it is difficult to blind participants to the exercise condition, and therefore difficult to prevent unintentional bias. Third, the difference in VO_{2peak} between the upright position and the supine position may vary among patient groups, and the data for patients with cardiopulmonary disease was insufficient. Therefore, we could not conduct subgroup analysis according to specific disease types. In the future, with the increase in research data from patients with cardiopulmonary disease, subgroup analysis could be conducted according to specific disease types. Lastly, this analysis was unable to account for different supine position body angles. The body position of

research participants should be clarified in future clinical studies to facilitate subgroup analysis.

CONCLUSION

VO_{2peak} in the upright position is higher than that measured in the supine position, in both healthy subjects and patients with cardiopulmonary disease. However, additional verification is needed to determine whether this difference has clinical significance. Like bicycle and treadmill exercise modalities, both supine and upright exercise modalities can be applied for differential diagnosis, surgical risk assessment, prognosis, and to evaluate overall exercise capacity and therapeutic effects of a variety of clinical interventions. Researchers should consider these differences across exercise modalities, and choose the form of exercise which best suits their clinical requirements.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

XW and WJ contributed to the conception and design of the study. XW and CL contributed to the data acquisition, analysis, and interpretation. XW drafted the first version of the manuscript and revised it based on other authors' contributions. All authors contributed important intellectual content to the manuscript's critical revision, read, and approved the final manuscript.

FUNDING

This work was supported by the Guangdong Provincial Key Laboratory of Chinese Medicine for Prevention and Treatment of Refractory Chronic Diseases (grant number: 2018B030322012); the General Research Fund of Traditional Chinese Medicine Science and Technology from Guangdong Provincial Hospital of Chinese Medicine (YN2018ML02); and the Clinical Research Funding of Traditional Chinese Medicine Science and Technology (Project 1010) from Guangdong Provincial Hospital of Chinese Medicine (YN10101910).

ACKNOWLEDGMENTS

The authors wish to thank Dr. Xiaoguang Chen from the Department of Cardiology at GPHCM for his guidance in the use of RevMan, as well as research assistants from the GPHCM for their assistance with data collection.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.734687/full#supplementary-material

REFERENCES

1. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH Jr, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation.* (1991) 83:778-86. doi: 10.1161/01.CIR.83.3.778
2. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T. Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. *Am J Respir Crit Care Med.* (2003) 167:544-9. doi: 10.1164/rccm.200206-583OC
3. Badruddin SM, Ahmad A, Mickelson J, Abukhalil J, Winters WL, Nagueh SF, et al. Supine bicycle versus post-treadmill exercise echocardiography in the detection of myocardial ischemia: a randomized single-blind crossover trial [published correction appears in *J Am Coll Cardiol.* (1999) Aug;34:613]. *J Am Coll Cardiol.* (1999) 33:1485-90. doi: 10.1016/S0735-1097(99)00043-1
4. Skulstad H, Aakhus S. Stress echocardiography with semi-supine bicycle. *Tidsskrift for Den Norske Lgeforening Tidsskrift for Praktisk Medicin Ny Rkke.* (2012) 132:2175-8. doi: 10.4045/tidsskr.11.1538
5. Bryan AC, Bentivoglio LG, Beerel F, Macleish H, Zidulka A, Bates DV. Factors Affecting Regional Distribution of Ventilation and Perfusion in the Lung. *J Appl Physiol.* (1964) 19:395-402. doi: 10.1152/jappl.1964.19.3.395
6. Stanley A. Rubin, Harvey V. Brown. Ventilation and gas exchange during exercise in severe chronic heart failure. *Am Rev Respir Dis.* (1984) 129:63-4. doi: 10.1164/arrd.1984.129.2P2.S63
7. Sullivan MJ, Higginbotham MB. Increased exercise ventilation in patients with chronic heart failure: intact ventilatory control despite hemodynamic and pulmonary abnormalities. *Circulation.* (1988) 77:552-9. doi: 10.1161/01.CIR.77.3.552
8. Bønnelykke Sørensen V, Wroblewski H, Galatius S, Haunsø S, Kastrup J. Assessment of continuous skeletal muscle blood flow during exercise in humans. *Microvasc Res.* (2000) 59:301-9. doi: 10.1006/mvre.1999.2219
9. Kramer B, Massie B, Topic N. Hemodynamic differences between supine and upright exercise in patients with congestive heart failure. *Circulation.* (1982) 66:820-5. doi: 10.1161/01.CIR.66.4.820
10. Bonzheim SC, Franklin BA, DeWitt C, Marks C, Goslin B, Jarski R, et al. Physiologic responses to recumbent versus upright cycle ergometry, and implications for exercise prescription in patients with coronary artery disease. *Am J Cardiol.* (1992) 69:40-44. doi: 10.1016/0002-9149(92)90673-M
11. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* (1998) 52:377-84. doi: 10.1136/jech.52.6.377
12. Quinn TJ, Smith SW, Vroman NB, Kertzer R, Olney WB. Physiologic responses of cardiac patients to supine, recumbent, and upright cycle ergometry. *Arch Phys Med Rehabil.* (1995) 76:257-61. doi: 10.1016/S0003-9993(95)80612-1
13. May LJ, Punn R, Olson I, Kazmucha JA, Liu MY, Chin C. Supine cycling in pediatric exercise testing: disparity in performance measures. *Pediatr Cardiol.* (2014) 35:705-10. doi: 10.1007/s00246-013-0841-y
14. Mizumi S, Goda A, Takeuchi K, Kikuchi H, Inami T, Soejima K, et al. Effects of body position during cardiopulmonary exercise testing with right heart catheterization. *Physiol Rep.* (2018) 6:e13945. doi: 10.14814/phy2.13945
15. Ade CJ, Broxterman RM, Barstow TJ. Effects of body posture and exercise training on cardiorespiratory responses to exercise. *Respir Physiol Neurobiol.* (2013) 188:39-48. doi: 10.1016/j.resp.2013.04.023

16. Armour W, Clark AL, McCann GP, Hillis WS. Effects of exercise position on the ventilatory responses to exercise in chronic heart failure. *Int J Cardiol*. (1998) 66:59-63. doi: 10.1016/S0167-5273(98)00193-4
17. Chesler RM, Stein RA. The clinical use of supine left lateral leg cycle ergometry for exercise electrocardiographic testing in women, as used in exercise echocardiography [published correction appears in J Am Soc Echocardiogr. (2004) Jun;17:643]. *J Am Soc Echocardiogr*. (2004) 17:361-6. doi: 10.1016/j.echo.2003.12.002
18. Cornelis N, Buys R. The effects of exercise modality on maximal and submaximal exercise parameters obtained by graded maximal exercise testing. *Int J Cardiol*. (2016) 222:538-47. doi: 10.1016/j.ijcard.2016.07.190
19. DiMenna FJ, Wilkerson DP, Burnley M, Bailey SJ, Jones AM. Priming exercise speeds pulmonary O2 uptake kinetics during supine "work-to-work" high-intensity cycle exercise. *J Appl Physiol (1985)*. (2010) 108:283-92. doi: 10.1152/japplphysiol.01047.2009
20. Egaña M, Green S, Garrigan EJ, Warmington S. Effect of posture on high-intensity constant-load cycling performance in men and women. *Eur J Appl Physiol*. (2006) 96:1-9. doi: 10.1007/s00421-005-0057-9
21. Egaña M, Columb D, O'Donnell S. Effect of low recumbent angle on cycling performance, fatigue, and V·O(2) kinetics. *Med Sci Sports Exerc*. (2013) 45:663-73. doi: 10.1249/MSS.0b013e318279a9f2
22. Faulkner J, Lambrick D, Kaufmann S, Stoner L. Effects of upright and recumbent cycling on executive function and prefrontal cortex oxygenation in young healthy men. *J Phys Act Health*. (2016) 13:882-7. doi: 10.1123/jpah.2015-0454
23. Forbregd TR, Aloyseus MA, Berg A, Greve G. Cardiopulmonary capacity in children during exercise testing: the differences between treadmill and upright and supine cycle ergometry. *Front Physiol*. (2019) 10:1440. doi: 10.3389/fphys.2019.01440
24. Forton K, Motoji Y, Deboeck G, Faoro V, Naeije R. Effects of body position on exercise capacity and pulmonary vascular pressure-flow relationships. *J Appl Physiol (1985)*. (2016) 121:1145-50. doi: 10.1152/japplphysiol.00372.2016
25. Goldstein BH, Connor CE, Gooding L, Rocchini AP. Relation of systemic venous return, pulmonary vascular resistance, and diastolic dysfunction to exercise capacity in patients with single ventricle receiving fontan palliation. *Am J Cardiol*. (2010) 105:1169-75. doi: 10.1016/j.amjcard.2009.12.020
26. Greenleaf JE, Van Beaumont W, Brock PJ, Morse JT, Mangseth GR. Plasma volume and electrolyte shifts with heavy exercise in sitting and supine positions. *Am J Physiol*. (1979) 236:R206-14. doi: 10.1152/ajpregu.1979.236.3.R206
27. Hughson RL, Cochrane JE, Butler GC. Faster O2 uptake kinetics at onset of supine exercise with than without lower body negative pressure. *J Appl Physiol (1985)*. (1993) 75:1962-7. doi: 10.1152/jappl.1993.75.5.1962
28. Hughson RL, Xing HC, Borkhoff C, Butler GC. Kinetics of ventilation and gas exchange during supine and upright cycle exercise. *Eur J Appl Physiol Occup Physiol*. (1991) 63:300-7. doi: 10.1007/BF00233866
29. Jones AM, Berger NJ, Wilkerson DP, Roberts CL. Effects of "priming" exercise on pulmonary O2 uptake and muscle deoxygenation kinetics during heavy-intensity cycle exercise in the supine and upright positions. *J Appl Physiol (1985)*. (2006) 101:1432-41. doi: 10.1152/japplphysiol.00436.2006
30. Koga S, Shiojiri T, Shibasaki M, Kondo N, Fukuba Y, Barstow TJ. Kinetics of oxygen uptake during supine and upright heavy exercise. *J Appl Physiol (1985)*. (1999) 87:253-60. doi: 10.1152/jappl.1999.87.1.253
31. Leyk D, Essfeld D, Hoffmann U, Wunderlich HG, Baum K, Stegemann J. Postural effect on cardiac output, oxygen uptake and lactate during cycle exercise of varying intensity. *Eur J Appl Physiol Occup Physiol*. (1994) 68:30-5. doi: 10.1007/BF00599238
32. Magder S, Linnarsson D, Gullstrand L. The effect of swimming on patients with ischemic heart disease. *Circulation*. (1981) 63:979-86. doi: 10.1161/01.CIR.63.5.979
33. Pedersen PK, Mandøe H, Jensen K, Andersen C, Madsen K. Reduced arterial O2 saturation during supine exercise in highly trained cyclists. *Acta Physiol Scand*. (1996) 158:325-31. doi: 10.1046/j.1365-201X.1996.575323000.x
34. Rowland T, Garrison A, Delulio A. Circulatory responses to progressive exercise: insights from positional dif ferences. *Int J Sports Med*. (2003) 24:512-7. doi: 10.1055/s-2003-42016
35. Schulman DS, Tugoen JF, Flores AR, Dianzumba S, Reichek N. Left ventricular ejection fraction during supine and upright exercise in patients with systemic hypertension and its relation to peak filling rale. *Am J Cardiol*. (1995) 76:61-5. doi: 10.1016/S0002-9149(99)80802-9
36. Tempest GD, Eston RG, Parfitt G. A comparison of head motion and prefrontal haemodynamics during upright and recumbent cycling exercise. *Clin Physiol Funct Imaging*. (2017) 37:723-9. doi: 10.1111/cpf.12365
37. Terkelsen KE, Clark AL, Hillis WS. Ventilatory response to erect and supine exercise. *Med Sci Sports Exer*. (1999) 31:1429-32. doi: 10.1097/00005768-199910000-00011
38. Walsh-Riddle M, Blumenthal JA. Cardiovascular responses during upright and semi-recumbent cycle ergometry testing. *Med Sci Sports Exer*. (1989) 21:581-5. doi: 10.1249/00005768-198910000-00014
39. Welbergen E, Clijsen LP. The influence of body position on maximal performance in cycling. *Eur J Appl Physiol Occup Physiol*. (1990) 61:138-42. doi: 10.1007/BF00236708
40. Yamada, Sumio. Mechanism of increase in anaerobic threshold during recovery phase in patients with acute myocardial infarction. *Jpn Circ J*. (1999) 63:261-6. doi: 10.1253/jcj.63.261
41. Zhao L, Feinberg MS, Gaides M, Ben-Dov I. Why is exercise capacity reduced in subjects with pectus excavatum?. *J Pediatr*. (2000) 136:163-7. doi: 10.1016/S0022-3476(00)70096-5
42. Thadani U, Parker JO. Hemodynamics at rest and during supine and sitting bicycle exercise in normal subjects. *Am J Cardiol*. (1978) 41:52. doi: 10.1016/0002-9149(78)90131-5
43. Hamilton WF, Riley RL. Comparison of the Fick and dye injection methods of measuring the cardiac output in man. *Am J Physiol*. (1948) 153:309-21. doi: 10.1152/ajplegacy.1948.153.2.309
44. Takata T, Yamabe H, Fukuzaki H. The hemodynamic and metabolic basis for decreased aerobic capacity in the supine exercise compared with the upright exercise in coronary artery disease. *Jpn Circ J*. (1988) 52:495-502. doi: 10.1253/jcj.52.495
45. Bouillon L, Baker R, Gibson C, Kearney A, Busemeyer T. Comparison of trunk and lower extremity muscle activity among four stationary equipment devices: upright bike, recumbent bike, treadmill, and Elliptigo®. *Int J Sports Phys Ther*. (2016) 11:190-200.
46. MacDonald MJ, Shoemaker JK, Tschakovsky ME, Hughson RL. Alveolar oxygen uptake and femoral artery blood flow dynamics in upright and supine leg exercise in humans. *J Appl Physiol (1985)*. (1998) 85:1622-8. doi: 10.1152/jappl.1998.85.5.1622
47. Eiken O. Effects of increased muscle perfusion pressure on responses to dynamic leg exercise in man. *Eur J Appl Physiol Occup Physiol*. (1988) 57:772-6. doi: 10.1007/BF01076002
48. Murthy G, Watenpaugh DE, Ballard RE, Hargens AR. Supine exercise during lower body negative pressure effectively simulates upright exercise in normal gravity. *J Appl Physiol*. (1994) 76:2742-8. doi: 10.1152/jappl.1994.76.6.2742
49. DeLorey DS, Kowalchuk JM, Paterson DH. Relationship between pulmonary O2 uptake kinetics and muscle deoxygenation during moderate-intensity exercise. *J Appl Physiol*. (1985) (2003) 95:113-20. doi: 10.1152/japplphysiol.00956.2002
50. DiMenna FJ, Bailey SJ, Jones AM. Influence of body position on muscle deoxy [Hb+Mb] during ramp cycle exercise. *Respir Physiol Neurobiol*. (2010) 173:138-45. doi: 10.1016/j.resp.2010.07.005
51. Inglis EC, Iannetta D, Murias JM. Evaluating the NIRS-derived microvascular O2 extraction "reserve" in groups varying in sex and training status using leg blood flow occlusions. *PLoS ONE*. (2019) 14:e0220192. doi: 10.1371/journal.pone.0220192

52. Tedjasaputra V, Sá RC, Anderson KM, Kim Prisk G, Hopkins SR. Heavy upright exercise increases ventilation-perfusion mismatch in the basal lung: indirect evidence for interstitial pulmonary edema. *J Appl Physiol (1985)*. (2019) 127:473-81. doi: 10.1152/japplphysiol.00056.2019
53. Sandoval J, Alvarado P, Luisa M. Effect of body position changes on pulmonary gas exchange in Eisenmenger's syndrome. *Am J Respir Crit Care Med.* (1999) 159:1070-3. doi: 10.1164/ajrccm.159.4.9612071

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Cardiovascular Medicine

MINI REVIEW
published: 13 October 2021
doi: 10.3389/fcvm.2021.729073

Exercise-Based Rehabilitation Delivery Models in Comorbid Chronic Pulmonary Disease and Chronic Heart Failure

Audrey Borghi-Silva[1†], Adriana S. Garcia-Araújo[1†], Eliane Winkermann[2], Flavia R. Caruso[1], Daniela Bassi-Dibai[3†], Cássia da Luz Goulart[1], Snehil Dixit[4†], Guilherme Dionir Back[1] and Renata G. Mendes[1†]*

[1] Cardiopulmonary Physiotherapy Laboratory, Physiotherapy Department, Federal University of Sao Carlos, Sao Carlos, Brazil, [2] Graduate Program in Comprehensive Health Care, Universidade de Cruz Alta/Universidade Regional do Noroeste do Estado do Rio Grande do Sul, Ijuí, Brazil, [3] Postgraduate Program in Management and Health Services, Ceuma University, São Luís, Brazil, [4] Department of Medical Rehabilitation Sciences, College of Applied Medical Sciences, King Khalid University, Abha, Saudi Arabia

Among the most prevalent multimorbidities that accompany the aging process, chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF) stand out, representing the main causes of hospital admissions in the world. The prevalence of COPD coexistence in patients with CHF is higher than in control subjects, given the common risk factors associated with a complex process of chronic diseases developing in the aging process. COPD-CHF coexistence confers a marked negative impact on mechanical-ventilatory, cardiocirculatory, autonomic, gas exchange, muscular, ventilatory, and cerebral blood flow, further impairing the reduced exercise capacity and health status of either condition alone. In this context, integrated approach to the cardiopulmonary based on pharmacological optimization and non-pharmacological treatment (i.e., exercise-based cardiopulmonary and metabolic rehabilitation) can be emphatically encouraged by health professionals as they are safe and well-tolerated, reducing hospital readmissions, morbidity, and mortality. This review aims to explore aerobic exercise, the cornerstone of cardiopulmonary and metabolic rehabilitation, resistance and inspiratory muscle training and exercise-based rehabilitation delivery models in patients with COPD-CHF multimorbidities across the continuum of the disease. In addition, the review address the importance of adjuncts to enhance exercise capacity in these patients, which may be used to optimize the gains obtained in these programs.

Keywords: chronic heart failure, chronic obstructive pulmonary disease, rehabilitation, exercise, comorbidities, non-invasive ventilation, aging

OPEN ACCESS

Edited by:
Jian Yang,
Fudan University, China

Reviewed by:
I-Shiang Tzeng,
Chinese Culture University, Taiwan
Jingyi Ren,
China-Japan Friendship Hospital, China

****Correspondence:***
Audrey Borghi-Silva
audrey@ufscar.br

†These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to General Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

Received: *22 June 2021*
Accepted: *23 September 2021*
Published: *13 October 2021*

Citation:
Borghi-Silva A, Garcia-Araújo AS, Winkermann E, Caruso FR, Bassi-Dibai D, Goulart CL, Dixit S, Back GD and Mendes RG (2021) Exercise-Based Rehabilitation Delivery Models in Comorbid Chronic Pulmonary Disease and Chronic Heart Failure. Front. Cardiovasc. Med. 8:729073. doi: 10.3389/fcvm.2021.729073

HIGHLIGHTED

- Patients with coexistence of COPD-CHF present a further impaired exercise capacity and health status associated to mechanical-ventilatory, cardiocirculatory, autonomic, gas exchange, muscular, ventilatory, and cerebral blood flow disfunctions.
- COPD-CHF calls for a multifaceted and integrated disease management based on pharmacological and non-pharmacological treatment focused in an exercise-based cardiopulmonary rehabilitation delivered emphatically by professionals aware of multimorbidity care. Adjuncts as non-invasive ventilation, may enhance the exercise tolerability, performance, and consequently better physiological adaptations and outcomes.
- Further RCT studies are necessary to investigate randomized clinical trials to investigate the exercise-based rehabilitation in COPD-CHF overlap in a more systematically way in terms of criteria of inclusion, types of CHF (preserved or reduced), components, and outcomes.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF) are prevalent noncommunicable chronic conditions (1). Aging is a diverse and complex process related to chronic diseases developing, attributed in parts to the long exposure to an unhealthy lifestyle. This process favor the augment in the prevalence of mutually coexistence of diseases (2), as the COPD-CHF that has been highlighted in recent years and associated with poor adverse outcomes (3, 4).

COPD is characterized by chronic obstruction and progressive limitation to airflow, which is not fully reversible (5). On the other hand, CHF is a complex clinical syndrome in which the heart is unable to maintain tissue perfusion according to metabolic demands (6). CHF is defined according to left ventricular ejection fraction (EF) and although both types are possible to coexist, the reduced EF (HFrEF) is the most cited criterion to diagnose HF in patients with COPD.

Both COPD and CHF share the systemic inflammatory process and increased oxidative stress as a pathophysiological basis and smoking is the main etiology involved (7). This association imposes systemic consequences and impact on the quality of life, morbidity and mortality (3, 4). Systemic consequences include changes in cardiopulmonary and autonomic function, peripheral and respiratory muscle weakness (8) and can magnify the symptoms, leading to a marked negative impact on mechanical-ventilatory, cardiocirculatory, autonomic, gas exchange, muscular, ventilatory, and cerebral blood flow, further impairing the reduced exercise capacity and health status than either condition alone (9).

In the face of this complexity, the biggest challenge in the clinical practice involving patients with COPD-CHF is the establishment of an integrated and individualized approach focusing among other things on the management of dyspnea (3), exercise intolerance (10), functionality aimed to improve the survival and quality of life.

IMPACT OF COPD-CHF ON EXERCISE CAPACITY AND SYMPTOMS

Exercise intolerance may be considered multifactorial in COPD-CHF (11). Pathophysiological process of both diseases are related to imbalances of oxygen transport, cardiovascular, respiratory, muscle, and brain disorders (12). In this context, there are several lines of evidence suggesting that oxygen delivery to working muscles may be critically impaired during dynamic exercise in COPD-CHF patients (9). In addition, another impact in patients with COPD-CHF are ventilatory inefficiency and peripheral muscle dysfunction characterized by reduced muscle strength, promoting negative consequences on exercise performance (9, 13).

Studies have demonstrated that reduced oxygen supply (O_2), systemic inflammation and increased oxidative stress can contribute to respiratory muscle dysfunction (9, 12–14). In this context, an understanding of the interaction between the mechanisms that lead to symptoms during exercise such as dyspnea, can provide useful information about both diseases (15). Exercise intolerance may be due to critical mechanical-ventilatory restrictions or hypoxemia, demonstrating the contribution of COPD disease (16), or even exercise may be interrupted due to complaints of discomfort in the lower limbs, demonstrating the contribution of both diseases (9).

Cardiopulmonary rehabilitation (CR) for COPD and CHF patients consists of a program of structured, individualized, and supervised physical exercises, usually performed for a period of 6–12 weeks (17). Furthermore, CR in general is interdisciplinary, including health education measures, and its primary objective is to improve exercise capacity and, consequently, dyspnea (18), as well as preventing secondary cardiac events (19). CR may reduce the risk of hospital admissions for all causes, as well as specific hospital admissions for CHF in the short term (up to 12 months). Additionally, CR attributes an important improvement in the quality of life of these individuals (20). Prior to enrollment to exercise rehabilitation, patients should be clinically assessed, an exercise test and risk stratification is recommended. Patients should present clinical stability with no contraindications to exercise training (such as unstable angina, respiratory failure, and severe electrolyte imbalance) and should have optimized comorbidities and pharmacological treatment. Moreover, the risk stratification and need for electrocardiogram monitoring, oxygen supplementation and supervision level must be assessed and programmed individually. During the CR sessions, it is important to remain aware of signs regarding decompensating, such as disproportional increased shortness of breath and fatigue, increased body weight and edema, worsening of pulmonary auscultation, increased coughing, and intolerance to supine position. Breathing techniques, educational support, psychological support, lifestyle management and nutritional counseling are allied components. Desveaux et al. (21) also concluded that motivation and incentive, as well as access to appropriate facilities, are key resources to support adherence to the prescribed activity. Thus, the multifaceted approach achieved by the integration between physical training, pharmacological,

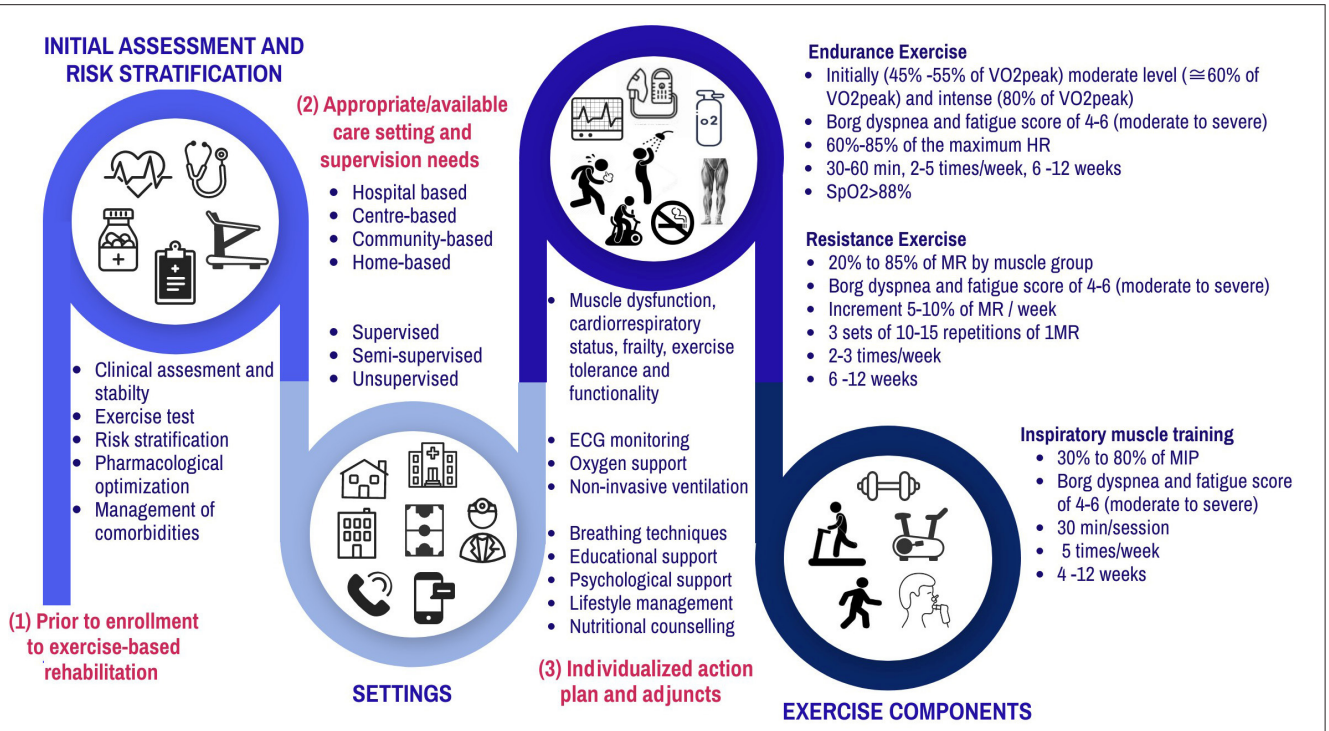


FIGURE 1 | Summary of components of Exercise-based rehabilitation on the population with COPD-CHF or COPD-Cardiovascular comorbidities. VO_{2peak}, oxygen consumption; HR, heart rate; MR, maximum repetition; MIP, maximum inspiratory pressure; SpO_2, Peripheral oxygen saturation.

and nutritional care in a personalized way (21) is warranted to these patients who present the coexistence of COPD-CHF. **Figure 1** summarizes the recommendations and components of an integrated CR.

A recent review conducted by Anderson et al. (22) highlights that home-based rehabilitation seem to be equally effective than those performed in CR centers when considering improving the quality of life in patients post myocardial infarction or revascularization and heart failure. In addition, it supports the continued expansion of home-based and evidence-based CR programs. Moreover, according to Anderson et al. (22) participating in a more traditional program with supervision carried out at a center or in a home program reflects the local availability, as well as the individual preference of the patient.

EXERCISE-BASED REHABILITATION DELIVERY MODELS FOR COPD-CHF PATIENTS

Although there is strong evidence supporting exercise-based rehabilitation as standard of care for people with COPD or CHF, there are only few RCTs demonstrating the models and effects of rehabilitation specifically for mutually combined COPD-CHF diagnosis. In most of the studies included in the review we found that studies primarily focused on the COPD population whereas cardiovascular impairments had a secondary emphasis.

Regardless of basic cardiac or pulmonary rehabilitation approaches, COPD and CHF have similar systemic manifestations such as limitation in exercise capacity, skeletal muscle dysfunction, dyspnea, deconditioning, reduced level of activities of daily living, and quality of life (23). To the best of our knowledge until now, there are only two studies focusing on rehabilitation specifically in patients with coexisting COPD-CHF (24, 25). Smyrnova et al. (23) carried out hospital based yogic breathing as an adjuvant therapy in PR to enhance the effects on the intervention group and found a significant difference compared with the control group. Bernocchi et al. (24) carried out a telerehabilitation home-based program with an individually tailored exercise program for each participant who were primarily having COPD-CHF diagnosis and found that home-based intervention was feasible and effective in improving exercise capacity. Most of the included studies which were performed with interventions in rehabilitation centers found improvements in objective measures such as exercise capacity, muscle strength, and subjective measures such as a sensation of dyspnea and quality of (QoL) assessed by Minnesota and saint George. Whereas, the home-based program with regular follow-up and counseling also demonstrated similar improvements, **Table 1** provides information on rehabilitation exercise-based delivered models and their effects on patients with coexisting COPD-CHF (24, 25) or COPD-cardiovascular comorbidities (26–32). The main approach to rehabilitation delivery was undertaken in an outpatient setting, center-based or/and home-based, and almost all programs were comprehensive

TABLE 1 | Exercise-base rehabilitation models and their effects on the population with COPD-CHF or COPD-Cardiovascular comorbidities.

References	Study design	Sample size	Participants and average age	Setting	Type of care	Interventions	Components	Effect of intervention	Risk of bias*
Smyrnova et al. (23)	Unclear	$n = 102$	COPD+CHF Average age: CG:67 ± 6 IG: 69 ± 6 years CHF type: not reported Average EF: not reported	Inpatient	Hospital based	CG: SC IG: SC + full yogic breathing	CG: PR program IG: PR and yogic breathing	Full yogic breathing + SC is associated with more pronounced ↑ exercise tolerance (6MWD), ↓ dyspnea (Borg scale), ↓ length of hospital stay, ↓ functional class	4
Bernocchi et al. (24)	RCT	$n = 112$	COPD+CHF Average age: IG: 71 ± 9 CG: 70 ± 9 years CHF type: not reported. Average EF: IG: 44.5 ± 12.4% CG: 43.3 ± 13.2%	Outpatient	Home based	CG: SC IG: tele rehabilitation educational intervention + personalized exercise program	CG: Educational program, medications and oxygen IG: Aerobic and resistance exercises + reinforcement on lifestyle changes	Rehabilitation was feasible and effective in ↑exercise capacity (6MWD), ↑ physical activity profile (PASE), ↑QoL (MLHFQ and CAT) and ↓disability (Barthel), ↓ dyspnea (MRC) and ↓time to hospitalisation/death	5
Berry et al. (25)	RCT	$n = 140$	COPD + HD comorbid ($n = 51$) Average age: 1st group = 67, 2nd group = 68 years HF type: not reported Average EF: not reported	Outpatient	Centre/Home based or community based	3 months supervised and then divided into: Short-Term (unmonitored) Or Long-Term Care (Supervised)	Aerobic exercise and upper-extremity resistance exercise training	Long term supervised care is more beneficial in ↑exercise capacity (6MWD), ↓disability (self-reported), ↓time to climb steps and overhead task	5
Berry et al. (26)	RCT	$n = 176$	COPD + HD comorbid ($n = 79$) Average age: TET: 66 ± 10/LAP: 66 ± 10 years HF type: not reported Average EF: not reported	Outpatient	Centre based	TET: Traditional exercises program or LAP: Behavioral Lifestyle program	TET: walking exercises + warm-up and cool down, LAP: education and self-reliance of exercise	Both were effective in increasing and maintaining moderate levels of physical activity (moderate physical activity—kcal/week)	6
Coultas et al. (27)	RCT	$n = 325$	COPD+CV comorbid ($n = 198$) Average age: 70 ± 9 years HF type: not reported Average EF: not reported	Outpatient	Centre based/Home based	SC or Moderate intensity lifestyle physical activity with a structured workbook	SC or Group workbook: telephone health coaching tailored to each participant	Home-based coaching intervention may ↓sedentary behavior and ↑physical activity levels (RAPA questionnaire), ↓rate of previous lung-related health care utilization	5

(Continued)

TABLE 1 | Continued

References	Study design	Sample size	Participants and average age	Setting	Type of care	Interventions	Components	Effect of intervention	Risk of bias*
Charikiopoulou et al. (28)	RCT	$n = 32$	COPD+CV comorbid ($n = 22$) Average age: G1:64 ± 5 G2:67 ± 6 years HF type: not reported Average EF: not reported	Outpatient	Centre based	Individualized rehabilitation program Two groups, according to comorbidities	Exercises: aerobic, resistance and respiratory muscle training; breathing retraining, education, diet, and psychological support	PR seems to be beneficial for all patients in ↓dyspnea (MRC), ↑QoL (SGRQ and CAT), ↑exercise capacity (6MWD), independently of the presence, the number or the nature of their comorbidities	3
Lenferink et al. (29)	RCT	$n = 201$	COPD+HD comorbid SM: 69 ± 9 years UC: 68 ± 9 years HF type: not reported Average EF: not reported	Outpatient	Centre based/Home based	Patient-tailored self-management intervention (Individual and group sessions + phone call) or SC (group session and phone call)	SM: Educational program (disease, self-treatment, importance of physical fitness and exercise, diet and lifestyles behaviors, exacerbation actions) or SC: Educational symptom level and diaries	Patient-tailored action plans for COPD patients with comorbidities, ↓duration per COPD exacerbation and ↓risk of respiratory-related hospitalization during follow-up	7
Foy et al. (30)	RCT	$n = 140$	COPD + HD comorbid ($n = 51$) Groups average age: G1:67 ± 6 G2:68 ± 6 years HF type: not reported Average EF: not reported	Outpatient	Centre/Home based	3 months supervised and then divided into: Short Term (unmonitored) Or Long-Term Care (Supervised)	Walking and strength training. Short term therapy mainly home based, long term structured regime	↑ CRQ after 3 months and ↓dyspnea, fatigue, emotional function and mastery after long term Men derive significant benefits from extended training	4
Vasilopoulou et al. (31)	RCT	$n = 150$	COPD + CV comorbid ($n = 42$) Average age: GA:67 ± 10 GB:67 ± 7 GC:64 ± 8 years HF type: not reported Average EF: not reported	Outpatient	Centre/Home based	Home-based maintenance tele rehabilitation in an individualized action plan Hospital-based: Outpatient maintenance rehabilitation or SC treatment	Home-based: exercise, psychological support; dietary and SM advice Hospital-based: exercise, physiotherapy, dietary and psychological advice SC: vaccination pharmacotherapy, oxygen	Home-based maintenance tele-rehabilitation is equally effective as hospital-based outpatient in ↓ risk for acute COPD exacerbation and hospitalizations and; in preserving exercise capacity (6MWD), peak work rate, QoL (dyspnea and mMRC)	5

*CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; CAT, COPD Assessment Test; CV, cardiovascular; EF, Ejection fraction; HD, heart disease; CG, Control Group; IG, Interventional Group; SC, standard care; MLHFQ, Minnesota Living with Heart Failure; MRC, Medical Research Council; QoL, Quality of life; PASE, physical activity profile; PR, Pulmonary rehabilitation; 6MWD, six-minute walking distance; TET, Traditional exercises program; LAP, Behavioral Lifestyle program; CRQ, Chronic Disease Respiratory Questionnaire; SM, self-management; RAPA, Rapid Assessment of Physical Activity. *Risk of Bias was assessed by PEDro Scale Tool.*

including exercises, education, and lifestyle change support. The program provided both supervised or unmonitored sessions and the exercise training was usually offered in an individually tailored manner.

Exercise Training Programs in Patients With COPD-CHF

Although statements have suggested exercise-based rehabilitation as a standard of care for people with COPD or CHF, there are few RCT studies that demonstrate the models provided specifically for the COPD-CHF overlap syndrome. A specific analysis of exercise-based rehabilitation, in both isolated conditions, shows a similarity in the specific type of interventions and training prescription, such as aerobic, resistance, and inspiratory muscle training. We carried out an analysis of the articles mentioned in **Table 1**, in a total of nine studies covered, we selected five RCTs that presented a better methodological description of the applied rehabilitation protocols (24, 25, 30–32). Only two studies (23, 24) evaluated the effect of rehabilitation on the coexistence of diseases. **Table 2** presents a summary of the three main types of exercise adopted, with intensity, duration, frequency, and supervision according to current evidence on an exercise-based rehabilitation program. In addition, the analysis described in the following paragraphs highlights the main forms of exercise prescription in this population and, at the same time, demonstrates the similarity between them in these three types of exercise-based therapy **(Table 2)**.

One of these modalities is aerobic training aiming to condition the muscles involved in walking and improving cardiorespiratory fitness (34). Exercises with an intensity >60% of the peak work rate in an incremental or constant test, performed for 30–60 min, are necessary to achieve these objectives (34). Interval training is proposed as an alternative to continuous training, especially for individuals who are unable to tolerate continuous high-intensity aerobic training due to intolerable symptoms and, therefore, shorter sessions should be advised in order to accumulate at least 30 min of exercise. Aerobic training per session (35). The training intensity can also be defined and/ or titrated according to Borg's dyspnea scores (4–6, moderate to intense) (32). A frequency of 3–5 sessions per week is recommended (35). Walking and the cycle ergometer are considered the best training modalities (32).

Aerobic exercise aims to minimize limiting symptoms such as skeletal and respiratory muscle dysfunction, dyspnea, and fatigue in these patients. These symptoms reduce patients' ability to exercise and compromise cardiac fitness, which further limits their exercise tolerance, creating a vicious downward spiral that can eventually lead to generalized debility and immobility. However, in some cases aerobic exercise is contraindicated. Patients with unstable heart and lung disease, locomotor difficulties that preclude patient exercise, significant cognitive, or psychiatric impairment that could lead to an inability to follow simple commands in a group setting should not be referred for rehabilitation (24, 25, 35).

Another modality is skeletal muscle resistance training (36). Evidence shows that resistance training alone or combined

TABLE 2 | Summary of exercise components and prescription (intensity, duration, frequency, and supervision) according to current evidence of exercise-based rehabilitation program to COPD-CHF or COPD cardiovascular comorbidities.

Exercise	Intensity	Duration	Frequency and duration	Supervision/control	Safety	Care to be taken
Aerobic exercise (24, 25, 30)	Initially (45–55% of VO_{2peak}) moderate level (?60% of VO_{2peak}) and intense (80% of VO_{2peak}) 60–85% of the maximum HR Borg dyspnea score of 4–6 (moderate to severe)	30–60 min	2–5 times a week 6–12 weeks	Borg dyspnea and fatigue score of 4–6 (moderate to severe), SpO_2 > 88% and HR should be below the maximum HR predicted by age	Exercise-based rehabilitation is safe, and it has no hemodynamic, respiratory, and/or musculoskeletal complications during the execution of exercise protocols (23, 24)	Patient education to perform the exercises and recognize the symptoms of dyspnea and fatigue (23, 24, 31)
Resistance Exercise (24, 25, 31)	From 20 to 85% of MR by muscle group Increment 5–10% of MR per week	3 sets of 10–15 repetitions of 1MR	2–3 times a week 6–24 weeks	Borg dyspnea and fatigue score of 4–6 (moderate to severe)		
Inspiratory muscle training (33)	30–80% of MIP	30 min	5 times a week 4–12 weeks.	Borg dyspnea and fatigue score of 4–6 (moderate to severe)		

VO_{2peak}, oxygen consumption; HR, heart rate; MR, maximum repetition; MIP, maximum inspiratory pressure; SpO_2, Peripheral oxygen saturation.

with aerobic training improves peak VO_2, QoL, and walking performance in patients with isolated heart failure (37, 38). While recognizing that the ideal prescription for resistance training for people with COPD-CHF has not been determined, the statement refers to the British Thoracic Society guidelines for prescribing resistance exercises (35). Most evidence recommends a prescription based on the maximum repetition test (1MR) (36). The overload principle is emphasized, which involves increasing the dosage of exercise over time to maximize gains in muscle strength and endurance. This can occur by increasing the weight, increasing the number of repetitions per set, increasing the number of sets of each exercise and/or decreasing the rest period between sets or exercises (36).

The exercise modality that is also performed in both pathologies is inspiratory muscle strength training (IMT) (39). IMT tries to improve the strength and resistance of the respiratory muscles by means of devices that allow inhalation against resistance within a certain limit (39). IMT can reduce dyspnea by favorably altering the relationship between the current inspiratory pressure generated and the maximum inspiratory pressure (34) and reducing the impairment of dynamic hyperinflation (37). The prescription of this modality includes a minimum load ranging from 30 to 80% of MIP assessed by manovacuometry. Most studies include prescriptions that vary with daily training (5–7 times a week) for a considerable period (around 30 min daily), some studies emphasize the division of this time (2 sets of 15 min each), and some studies include the number of repetitions in each set (12–15 repetitions) in their protocols (39).

In the absence of a clear protocol to guide the practice, physical therapists should use clinical assessment and provide carefully monitored and supervised exercises and a multidisciplinary and collaborative team approach for training, prescription and progression of individualized exercises (35). An initial and continuous assessment that includes the severity of the disease and symptoms, the comorbidities and the patient's goals should be emphasized. This should be combined with individual and aggregate measurement and analysis of patient-centered results and exercise capacity (35). Finally, rehabilitation must emphasize sustainable exercise that translates into increased physical activity in the long term through safe and effective interventions.

The study provides evidence that it is safe and feasible to apply early (40) pulmonary rehabilitation in patients with acute exacerbation of COPD. Most studies do not report care needs during exercise sessions. The current evidence demonstrates that continued supervised maintenance exercise compared to usual care following pulmonary rehabilitation reduces health care use in COPD (41). Similarly in heart failure, the exercise training was associated with modest significant reductions for both all-cause mortality or hospitalization and cardiovascular mortality or heart failure hospitalization (42). Cardiac rehabilitation may improve all-cause mortality in the long term (>12 months follow up; RR = 0.88, 95% CI: 0.75–1.02). Moreover, the CR probably reduces overall hospital admissions in the short term (up to 1 year of follow-up and may reduce HF-specific hospitalization) (20).

Adjuncts to Exercise Training Programs to Optimize Cardiac Rehab in COPD-CHF Patients

Several adjuncts associated with physical exercise have been applied in these patient populations, in their isolated or associated form in order to improve exercise capacity, reducing the overloaded respiratory muscles and consequently the breathlessness and increase muscle O_2 availability. Noninvasive positive pressure ventilation (NiPPV) as an adjunct during exercise is able to acutely relieve the ventilatory muscles and improve the supply of peripheral O_2 in these patients.

Previous studies have proven the positive effect of NiPPV on exercise tolerance, increase oxygen uptake and counterbalance mechanical ventilator changes in both COPD (43) and HF (44). A potential mechanism that could explain these benefits is the pulmonary mechanical effect that may improve cardiac function and regional vascular distribution (45, 46). In addition, recent evidence has demonstrated that NiPPV can also positively modulate heart rate variability during high-intensity exercise in COPD-CHF patients (47). The use of non-invasive ventilation during high intensity exercise (HIT) is thus recommended when the objective is to quickly emphasize peripheral muscle gains in a rehabilitation program when dyspnea symptoms can be the potential limiting factor for tasks that require greater efforts in these patients. Unfortunately, few studies have evaluated the effect of NiPPV during long-term rehabilitation programs in patients with COPD-CHF. Additionally, da Luz Goulart et al. (47) demonstrated that NiPPV applied through two pressure levels (Bilevel) 8–12 cmH_2O to inspiratory pressure and 4–6 cmH_2O for positive end-expiratory pressure produced a marked acute benefit on endothelial function associated with improved exercise tolerance during a bout of high-intensity aerobic exercise in patients with coexisting COPD-HF. The NiPPV improving peripheral oxygenation may also have influenced the local metabolic activity, causing an acute "restoration" of endothelial function in COPD-CHF patients (47).

Previously, Mazzuco et al. (48) have applied proportional assist ventilation mode of NiPPV (volume assist = 12–16 cmH_2O = and flow volume assist = 4–8 cmH_2O) and demonstrated an accelerated VO_2 recovery kinetics following high-intensity exercise in COPD-CHF. Therefore, the NiPPV was proved to be an interesting adjunct in CR programs to sustain higher levels of exercise intensity, reducing the work of breathing and beneficially modulate vascular reactivity and exercise tolerance during a single bout high-intensity exercise.

The risk of bias of the included studies in this mini-review was performed using the PEDro Scale Tool (0–10) (49) was demonstrated in **Table 1** and highlighted the need for more quality in RCT studies in this field of research. In the quality assessment, we observed that 100% of the studies meet the criteria of between-group comparison, 88% eligibility criteria and point estimates and variability, 77% random allocation and baseline comparability, 44% blinding assessors, adequate follow-up and intention-to-treat analysis, 11% concealed allocation, and 0% meet the criteria of blinding subjects and therapists.

CONCLUSION

Patients with coexistence of COPD-CHF present a further impaired exercise capacity, daily life activities and health status. Cardiopulmonary rehabilitation, involving a multifaceted program and professionals prepared and attentive to multimorbidity, aimed at improving aerobic capacity, respiratory and peripheral muscle strength, and endurance, appear to be safe, and effective in improving symptoms, exercise capacity and functionality. However, further randomized clinical trials deserve to be conducted to investigate in a higher level of quality the exercise-based rehabilitation in COPD-CHF overlap in a more systematically way in terms of criteria of inclusion, types of CHF (preserved or reduced), components and outcomes as exacerbation rates, morbidity, and mortality.

AUTHOR CONTRIBUTIONS

RGM, AG-A, DB-D, and SD: conceptualization and writing—original draft. EW, FRC, CLG, and GDB: literature collection and visualization. AB-S: conceptualization, writing—review, and editing. All authors contributed to the article and approved the submitted version.

FUNDING

This mini-review was sponsored by the Fundação de Amparo à Pesquisa do Estado de São Paulo, São Paulo, Brazil (FAPESP N° 2015/26501-1 and 2018/03233-0). AB-S is an Established Investigator (Level 1B) of the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq N° 443687/2018-8), Brazil.

REFERENCES

1. *Noncommunicable Diseases Progress Monitor*. (2020). Geneva: World Health Organization (2020).
2. Veltrano DL, Palmer K, Marengoni A, Marzetti E, Lattanzio F, Roller-Wirnsberger R, et al. Frailty and multimorbidity: a systematic review and meta-analysis. *J Gerontol A Biol Sci Med Sci.* (2019) 74:659–66. doi: 10.1093/gerona/gly110
3. Rutten FH, Cramer M-JM, Lammers J-WJ, Grobbee DE, Hoes AW. Heart failure and chronic obstructive pulmonary disease: an ignored combination? *Eur J Heart Fail.* (2006) 8:706–11. doi: 10.1016/j.ejheart.2006.01.010
4. Pirina P, Martinetti M, Spada C, Zinellu E, Pes R, Chessa E, et al. Prevalence and management of COPD and heart failure comorbidity in the general practitioner setting. *Repir Med.* (2017) 131:1–5. doi: 10.1016/j.rmed.2017.07.059
5. Barnes PJ. Chronic obstructive pulmonary disease. *N Engl J Med.* (2000) 343:269–80. doi: 10.1056/NEJM200007273430407
6. Savarese G, Lund LH. Global public health burden of heart failure. *Cardiac Fail Rev.* (2017) 3:7–11. doi: 10.15420/cfr.2016:25:2
7. De Miguel Díez J, Morgan JC, García RJ. The association between COPD and heart failure risk: a review. *Int J Chron Obstruct Pulmon Dis.* (2013) 8:305–12. doi: 10.2147/COPD.S31236
8. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of cardiology. Developed in collaboration with the heart failure association (HFA) of the ESC. *Eur J Heart Fail.* (2012) 14:803–69. doi: 10.1093/eurheartj/ehs104
9. Neder JA, Rocha A, Berton DC, O'Donnell DE. Clinical and physiologic implications of negative cardiopulmonary interactions in coexisting chronic obstructive pulmonary disease-heart failure. *Clin Chest Med.* (2019) 40:421–38. doi: 10.1016/j.ccm.2019.02.006
10. Gosker HR, Lencer NH, Franssen FM, van der Vusse GJ, Wouters EF, Schols AM. Striking similarities in systemic factors contributing to decreased exercise capacity in patients with severe chronic heart failure or COPD. *Chest.* (2003) 123:1416–24. doi: 10.1378/chest.123.5.1416
11. Poole DC, Hirai DM, Copp SW, Musch TI. Muscle oxygen transport and utilization in heart failure: implications for exercise (in)tolerance. *Am J Physiol Heart Circ Physiol.* (2012) 302:H1050–H63. doi: 10.1152/ajpheart.00943.2011
12. Guazzi M, Myers J, Vicenzi M, Bensimhon D, Chase P, Pinkstaff S, et al. Cardiopulmonary exercise testing characteristics in heart failure patients with and without concomitant chronic obstructive pulmonary disease. *Am Heart J.* (2010) 160:900–5. doi: 10.1016/j.ahj.2010.07.014
13. Goulart CL, Caruso FR, Arêas GPT, Santos PBD, Camargo PF, Carvalho LCS, et al. Impact of chronic obstructive pulmonary disease on linear and nonlinear dynamics of heart rate variability in patients with heart failure. *Braz J Med Biol Res.* (2020) 54:e10084. doi: 10.1590/1414-431x202010084
14. Oliveira MF, Alencar MC, Arbex F, Souza A, Sperandio P, Medina L, et al. Effects of heart failure on cerebral blood flow in COPD: rest and exercise. *Respir Physiol Neurobiol.* (2016) 221:41–48. doi: 10.1016/j.resp.2015.10.005
15. Neder JA, Rocha A, Alencar MCN, Arbex F, Berton DC, Oliveira MF, et al. Current challenges in managing comorbid heart failure and COPD. *Expert Rev Cardiovasc Ther.* (2018) 16:653–73. doi: 10.1080/14779072.2018.1510319
16. O'Donnell DE, Elbehairy AF, Faisal A, Webb KA, Neder JA, Mahler DA. Exertional dyspnoea in COPD: the clinical utility of cardiopulmonary exercise testing. *Eur Respir Rev.* (2016) 25:333–47. doi: 10.1183/16000617.0054-2016
17. Man WD, Chowdhury F, Taylor RS, Evans RA, Doherty P, Singh SJ, et al. Building consensus for provision of breathlessness rehabilitation for patients with chronic obstructive pulmonary disease and chronic heart failure. *Chron Respir Dis.* (2016) 13:229–39. doi: 10.1177/1479972316642363
18. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American thoracic society/European respiratory society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med.* (2013) 188:e13–e64.
19. Piña IL, Apstein CS, Balady GJ, Belardinelli R, Chaitman BR, Duscha BD, et al. Exercise and heart failure: a statement from the American Heart Association Committee on exercise, rehabilitation, and prevention. *Circulation.* (2003) 107:1210–25. doi: 10.1161/01.CIR.0000055013.92097.40
20. Long L, Mordi IR, Bridges C, Sagar VA, Davies EJ, Coats AJ, et al. Exercise-based cardiac rehabilitation for adults with heart failure. *Cochrane Database Syst Rev.* (2019) 1:CD003331. doi: 10.1002/14651858.CD003331.pub5
21. Desveaux L, Harrison S, Lee A, Mathur S, Goldstein R, Brooks D. "We are all there for the same purpose": support for an integrated community exercise program for older adults with HF COPD. *Heart Lung.* (2017) 46:308–12. doi: 10.1016/j.hrtlng.2017.04.008
22. Anderson L, Sharp GA, Norton RJ, Dalal H, Dean SG, Jolly K, et al. Home-based versus centre-based cardiac rehabilitation. *Cochrane Database Syst Rev.* (2017) 6:CD007130. doi: 10.1002/14651858.CD007130.pub4
23. Smyrnova GS, Babkina TM, Taradin GG, Vatutin M. Influence of pulmonary rehabilitation on clinical characteristics in patients with chronic heart failure and chronic obstructive pulmonary disease. *Int J Cardiovasc Sci.* (2018) 30:499–504. doi: 10.5935/2359-4802.20180051
24. Bernocchi P, Vitacca M, La Rovere MT, Volterrani M, Galli T, Baratti D, et al. Home-based telerehabilitation in older patients with chronic obstructive pulmonary disease and heart failure: a randomised controlled trial. *Age Ageing.* (2018) 47:82–8. doi: 10.1093/ageing/afx146
25. Berry MJ, Rejeski WJ, Adair NE, Ettinger WH Jr, Zaccaro DJ, Sevick MA. A randomized, controlled trial comparing long-term and short-term exercise in patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil.* (2003) 23:60–8. doi: 10.1097/00008483-200301000-00011
26. Berry MJ, Rejeski WJ, Miller ME, Adair NE, Lang W, Foy CG, et al. A lifestyle activity intervention in patients with chronic obstructive pulmonary disease. *Respir Med.* (2010) 104:829–39. doi: 10.1016/j.rmed.2010.02.015

27. Coultas DB, Jackson BE, Russo R, Peoples J, Singh KP, Sloan J, et al. Home-based physical activity coaching, physical activity, and health care utilization in chronic obstructive pulmonary disease. Chronic obstructive pulmonary disease self-management activation research trial secondary outcomes. *Ann Am Thorac Soc.* (2018) 15:470–8. doi: 10.1513/AnnalsATS.201704-308OC
28. Charikiopoulou M, Nikolaidis PT, Knechtle B, Rosemann T, Rapti A, Trakada G. Subjective and objective outcomes in patients with copd after pulmonary rehabilitation-the impact of comorbidities. *Front Physiol.* (2019) 10:286. doi: 10.3389/fphys.2019.00286
29. Lenferink A, van der Palen J, van der Valk PDLPM, Cafarella P, van Veen A, Quinn S, et al. Exacerbation action plans for patients with COPD and comorbidities: a randomised controlled trial. *Eur Respir J.* (2019) 54:1802134. doi: 10.1183/13993003.02134-2018
30. Foy CG, Rejeski WJ, Berry MJ, Zaccaro D, Woodard CM. Gender moderates the effects of exercise therapy on health-related quality of life among COPD patients. *Chest.* (2001) 119:70–6. doi: 10.1378/chest.119.1.70
31. Vasilopoulou M, Papaioannou AI, Kaltsakas G, Louvaris Z, Chynkiamis N, Spetsioti S, et al. Home-based maintenance tele-rehabilitation reduces the risk for acute exacerbations of COPD, hospitalisations and emergency department visits. *Eur Respir J.* (2017) 49:1602129. doi: 10.1183/13993003.02129-2016
32. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* (2015) 23:CD003793. doi: 10.1002/14651858.CD003793.pub3
33. Beaumont M, Forget P, Couturaud F, Reychler G. Effects of inspiratory muscle training in COPD patients: a systematic review and meta-analysis. *Clin Respir J.* (2018) 12:2178–88. doi: 10.1111/crj.12905
34. Woods JA, Keylock KT, Lowder T, Vieira VJ, Zelkovich W, Dumich S, et al. Cardiovascular exercise training extends influenza vaccine seroprotection in sedentary older adults: the immune function intervention trial. *J Am Geriatr Soc.* (2009) 57:2183–91. doi: 10.1111/j.1532-5415.2009.02563.x
35. Bolton CE, Bevan-Smith EF, Blakey JD, Crowe P, Elkin SL, Garrod R, et al. British Thoracic Society guideline on pulmonary rehabilitation in adults: accredited by NICE. *Thorax.* (2013) 68(Suppl. 2): ii1–ii30. doi: 10.1136/thoraxjnl-2013-203808
36. Higashimoto Y, Ando M, Sano A, Saeki S, Nishikawa Y, Fukuda K, et al. Effect of pulmonary rehabilitation programs including lower limb endurance training on dyspnea in stable COPD: a systematic review and meta-analysis. *Respir Investig.* (2020) 58:355–66. doi: 10.1016/j.resinv.2020.05.010
37. Jewiss F, Ostman C, Smart NA. The effect of resistence trauning on clinical outcomes in heart failure: a systematic review and meta-analysis. *Int J Cardiol.* (2016) 221:674–81. doi: 10.1016/j.ijcard.2016.07.046
38. Liao WH, Chen JW, Chen X, Lin L, Yan HY, Zhou YQ, et al. Impact of resistance training in subjects with COPD: a systematic review and meta-analysis. *Respir Care.* (2015) 60:1130–45. doi: 10.4187/respcare.03598
39. Giuliano C, Karahalios A, Neil C, Allen J, Levinger I. The effects of resistance training on muscle strength, quality of life and aerobic capacity in patients with chronic heart failure - a meta-analysis. *Int J Cardiol.* (2017) 227:413–23. doi: 10.1016/j.ijcard.2016.11.023
40. He M, Wang L, Lv H, Qiu Z. Efficiency and safety of pulmonary rehabilitation in acute exacerbation of chronic obstructive pulmonary disease. *Med Sci Monit.* (2015) 21:806–12. doi: 10.12659/MSM.892769
41. Jenkins AR, Gowler H, Curtis F, Holden N, Bridle C, Jones AW. Efficacy of supervised maintenance exercise following pulmonary rehabilitation on health care use: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis.* (2018) 13:257–73. doi: 10.2147/COPD.S150650
42. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA.* (2009) 301:1439–50. doi: 10.1001/jama.2009.454
43. Borghi-Silva A, Oliveira CC, Carrascosa C, Maia J, Berton DC, Queiroga F, et al. Respiratory muscle unloading improves leg muscle oxygenation during exercise in patients with COPD. *Thorax.* (2008) 63:910–5. doi: 10.1136/thx.2007.090167
44. Borghi-Silva A, Carrascosa C, Oliveira CC, Barroco AC, Berton DC, Vilaça D, et al. Effects of respiratory muscle unloading on leg muscle oxygenation and blood volume during high-intensity exercise in chronic heart failure. *Am J Physiol Heart Circ Physiol.* (2008) 294:2465–72. doi: 10.1152/ajpheart.91520.2007
45. Reis MS, Sampaio LMM, Lacerda D, De Oliveira LVF, Pereira GB, Pantoni CBF, et al. Acute effects of different levels of continuous positive airway pressure on cardiac autonomic modulation in chronic heart failure and chronic obstructive pulmonary disease. *Arch Med Sci.* (2010) 6:719–27. doi: 10.5114/aoms.2010.17087
46. Baffa GS, Goulart CL, Caruso F, Araujo ASG, Roscani MG, Prone FR, et al. Noninvasive ventilation can modulate heart rate variability during high-intensity exercise in COPD-CHF patients. *Heart Lung.* (2021) 50:609–14. doi: 10.1016/j.hrtlng.2021.04.004
47. da Luz Goulart C, Caruso FR, Garcia de Araújo AS, Tinoco Arêas GP, Garcia de Moura SC, Catai AM, et al. Non-invasive ventilation improves exercise tolerance and peripheral vascular function after high-intensity exercise in COPD-HF patients. *Respir Med.* (2020) 173:106173. doi: 10.1016/j.rmed.2020.106173
48. Mazzuco A, Souza AS, Goulart CL, Medeiros WM, Sperandio PA, Alencar MCN, et al. Noninvasive ventilation accelerates oxygen uptake recovery kinetics in patients with combined heart failure and chronic obstructive pulmonary disease. *J Cardiopulm Rehabil Prev.* (2020) 40:414–20. doi: 10.1097/HCR.0000000000000499
49. *PEDro: Physiotherapy Evidence Database*. Available online at: https://pedro.org.au/wp-content/uploads/PEDro_scale_portuguese(brasil).pdf (accessed September 05, 2021).

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 03 November 2021
doi: 10.3389/fcvm.2021.752640

Augmented Cardiac Mitochondrial Capacity in High Capacity Aerobic Running "Disease-Resistant" Phenotype at Rest Is Lost Following Ischemia Reperfusion

Musaad B. Alsahly[1,2], *Madaniah O. Zakari*[1,3], *Lauren G. Koch*[4], *Steven Britton*[5], *Laxmansa C. Katwa*[1], *Kelsey Fisher-Wellman*[1,6] *and Robert M. Lust*[1,6*]

[1] Department of Physiology, Brody School of Medicine, East Carolina University, Greenville, NC, United States, [2] East Carolina Diabetes and Obesity Center, East Carolina University, Greenville, NC, United States, [3] Department of Physiology, College of Medicine, King Saud University, Riyadh, Saudi Arabia, [4] Department of Physiology, College of Medicine, Taibah University, Medina, Saudi Arabia, [5] Department of Physiology and Pharmacology, University of Toledo, Toledo, OH, United States, [6] Departments of Anesthesiology and Molecular and Integrative Medicine, University of Michigan, Ann Arbor, MI, United States

OPEN ACCESS

Edited by:
Jian Yang,
Fudan University, China

Reviewed by:
Gentaro Ikeda,
Stanford University, United States
Pongpan Tanajak,
Apinop Wetchakham Hospital (Keang Khoi Medical Center), Thailand
Krekwit Shinlapawittayatorn,
Chiang Mai University, Thailand

***Correspondence:**
Robert M. Lust
lustr@ecu.edu

Specialty section:
This article was submitted to General Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

Received: 03 August 2021
Accepted: 30 September 2021
Published: 03 November 2021

Citation:
Alsahly MB, Zakari MO, Koch LG, Britton S, Katwa LC, Fisher-Wellman K and Lust RM (2021) Augmented Cardiac Mitochondrial Capacity in High Capacity Aerobic Running "Disease-Resistant" Phenotype at Rest Is Lost Following Ischemia Reperfusion. Front. Cardiovasc. Med. 8:752640. doi: 10.3389/fcvm.2021.752640

Rationale: Regular active exercise is considered therapeutic for cardiovascular disease, in part by increasing mitochondrial respiratory capacity, but a significant amount of exercise capacity is determined genetically. Animal models, demonstrating either high capacity aerobic running (HCR) or low capacity aerobic running (LCR) phenotypes, have been developed to study the intrinsic contribution, with HCR rats subsequently characterized as "disease resistant" and the LCRs as "disease prone." Enhanced cardioprotection in HCRs has been variable and mutifactoral, but likely includes a metabolic component. These studies were conducted to determine the influence of intrinsic aerobic phenotype on cardiac mitochondrial function before and after ischemia and reperfusion.

Methods: A total of 34 HCR and LCR rats were obtained from the parent colony at the University of Toledo, housed under sedentary conditions, and fed normal chow. LCR and HCR animals were randomly assigned to either control or ischemia-reperfusion (IR). On each study day, one HCR/LCR pair was anesthetized, and hearts were rapidly excised. In IR animals, the hearts were immediately flushed with iced hyperkalemic, hyperosmotic, cardioplegia solution, and subjected to global hypothermic ischemic arrest (80 min). Following the arrest, the hearts underwent warm reperfusion (120 min) using a Langendorff perfusion system. Following reperfusion, the heart was weighed and the left ventricle (LV) was isolated. A midventricular ring was obtained to estimate infarction size [triphenyltetrazolium chloride (TTC)] and part of the remaining tissue (~150 mg) was transferred to a homogenation buffer on ice. Isolated mitochondria (MITO) samples were prepared and used to determine respiratory capacity under different metabolic conditions. In control animals, MITO were obtained and prepared similarly immediately following anesthesia and heart removal, but without IR.

Results: In the control rats, both resting and maximally stimulated respiratory rates were higher (32 and 40%, respectively; $p < 0.05$) in HCR mitochondria compared to LCR. After IR, resting MITO respiratory rates were decreased to about 10% of control in both strains, and the augmented capacity in HCRs was absent. Maximally stimulated rates also were decreased more than 50% from control and were no longer different between phenotypes. Ca^{++} retention capacity and infarct size were not significantly different between HCR and LCR (49.2 ± 5.6 vs. 53.7 ± 4.9%), nor was average coronary flow during reperfusion or arrhythmogenesis. There was a significant loss of mitochondria following IR, which was coupled with decreased function in the remaining mitochondria in both strains.

Conclusion: Cardiac mitochondrial capacity from HCR was significantly higher than LCR in the controls under each condition. After IR insult, the cardiac mitochondrial respiratory rates were similar between phenotypes, as was Ca^{++} retention capacity, infarct size, and arrhythmogenicity, despite the increased mitochondrial capacity in the HCRs before ischemia. Relatively, the loss of respiratory capacity was actually greater in HCR than LCR. These data could suggest limits in the extent to which the HCR phenotype might be "protective" against acute tissue stressors. The extent to which any of these deficits could be "rescued" by adding an active exercise component to the intrinsic phenotype is unknown.

Keywords: aerobic capacity, HCR, LCR, intrinsic, coronary occlusion, mitochondria, energetics

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality in developed countries (1). The most common cause of cardiac injury is ischemic heart disease secondary to progressive coronary occlusion and is complicated frequently by complications such as ventricular arrhythmias and congestive heart failure (2). The most effective therapy, thus, far for limiting ischemic injury is early reperfusion, but reperfusion in itself has risks (3–5) to the extent that acute coronary occlusion and therapeutic intervention are collectively considered to produce an aggregate phenomenon recognized as ischemia-reperfusion (IR) injury (6–9).

Continuing research is aimed to explore the therapeutic interventions against IR injury. Although numerous pharmacological and preconditioning approaches to cardioprotection have been explored, regular exercise participation is recognized as an important, cost-effective, and safer lifestyle intervention in the prevention and treatment of IR injury (10–14). Redundant protective effects are evident in the exercised heart, namely, increased levels of heat shock proteins (15), altered nitric oxide (NO) signaling (16–18), enhanced Ca^{2+} handling proteins (19), improved ATP-sensitive potassium channels (20), and enhanced endogenous antioxidant (13, 21).

As an important site for ATP production *via* oxidative phosphorylation, mitochondria are critical in regulating normal cardiac metabolism and play a key role in the susceptibility of the heart to IR injury (22–28). The heart is an organ with high metabolic demand. Providing the myocardium with adequate coronary perfusion and oxygen delivery is crucial, but enhanced mitochondrial capacity also is essential. Mitochondrial respiratory rate and enzyme activities are the major elements that drive the oxidative phosphorylation process and structural integrity of the mitochondria. Myocardial IR can cause severe effects on mitochondrial homeostasis which dramatically affects mitochondrial function and survival (29–32). In addition to the detrimental effects of impaired mitochondrial energy production, mitochondrial ionic imbalance, and cell stress signaling can cause mitochondrial-mediated cell death (33–37).

Myocardial IR injury is an important cause of impaired heart function in the early postoperative period after cardiac surgery and acute myocardial ischemia. Growing evidence has become available supporting a crucial role of mitochondrial dysfunction in myocardial IR injury. Mitochondrial dysfunction during ischemia is a major mechanism that contributes to cardiomyocytes damage during IR (24, 26–31). Increased reactive oxygen species (ROS) generation, defects in electron transport chain activity and oxidative phosphorylation process, impaired respiratory chain complexes activity, opening of the mitochondrial permeability transition pore (mPTP), and release of cytochrome care considered contributing factors in mitochondrial dysfunction associated with heart IR (30–36).

Stunned (reversibly injured and nonfunctioning) myocardium displays relatively excess oxygen consumption for a specified rate of contractile work and, therefore, has a declined mechanical efficiency, which may be due to a rapid recovery of the intracellular pH during reperfusion (6). Once perfusion is restored, the intracellular increased accumulation of H^+ during ischemia is transported into the extracellular space to

normalize the pH in exchange for Na^+ *via* Na^+/H^+ exchanger, while ATP depletion inactivates Na^+/K^+-ATPase. The combined effect results in an increase in intracellular Na^+ which, in turn, activates the sarcolemmal $2Na^+/Ca^{2+}$ exchanger, resulting in the exchange of intracellular Na^+ with extracellular Ca^{2+}. A high rate of $2Na^+/Ca^{2+}$exchange can finally lead to Ca^{2+} overload which, in turn, induce arrhythmogenesis, myocardial stunning, contracture, and ultimately apoptotic or autophagic cell death. Fluctuations in $Ca^{2+}$from the sarcoplasmic reticulum during reperfusion stimulate the opening of the mPTP (29, 30). Opening of the mPTP leads to rapid dissipation of the membrane potential gradient which is essential for the synthesis of ATP, water enters through the open pore causing mitochondrial swelling and lysis triggering apoptosis and cell death (28–30).

The proposed mechanisms underlying exercise-induced cardioprotection in IR are numerous. Some are systemic (12), some are vascular (12–14, 21), some are neural (38, 39), some are structural (9), and some are energetic/metabolic (40, 41) including expression of selected mitochondrial proteins resulting in a mitochondrial phenotype that is resistant to IR-induced injury (13, 19). While these studies generally support exercise-induced adaptations that produce resistance to injury, few address the mitochondrial functional consequences following an injury.

Although regular exercise training is recognized as an important lifestyle intervention in the prevention and treatment of CVD and IR injury, not all the individuals experience the same benefits from participating in the exercise. There is a paradox that some individuals with many modifiable risk factors (hypertension, diabetes, and obesity), and who do not exercise, also do not get CVD, while others who have no risk factors, and exercise regularly, and still experience adverse cardiac outcomes, suggesting a significant intrinsic component to the exercise effect. It has been estimated that up to 70% of the variation in exercise capacity is due to the intrinsic genetic component (42). Thus, studying the differential impacts of intrinsic aerobic exercise capacity after cardiac IR injury using intrinsic aerobic phenotype rats bred for low and high aerobic running capacity would provide a better platform for understanding the influences of intrinsic aerobic capacity on cardiac metabolic capacity and mitochondrial adaptive response pre- and post-IR injury in these phenotypes.

Koch and Britton used phenotypic selection based on treadmill running time at 11 weeks of age in an outbred rat strain (NIN:N) to create divergent strains that have become known as high capacity aerobic running (HCR) and low capacity aerobic running (LCR) rats (43–47). The HCR animals generally are characterized as "disease resistant," while the LCR animals are characterized as disease prone. Interestingly, the HCR/LCR strains demonstrate many of the same traits related to CVD that had been previously associated with active exercise (48–52) including some mitochondrial/metabolic effects (53, 54). Still, cardioprotection in the HCRs is not always observed (55–57), and while LCR did associate with a higher incidence of pump failure, it did not associate with multiorgan system failure in hemorrhagic shock (58). We have previously reported that cardioprotection in HCRs was present but limited, was likely intrinsic to the tissue, and could be overwhelmed by IR severity (57). Given the consistent metabolic differences that characterized HCR and LCR, the current studies were designed to identify the relative influence of aerobic phenotype on the impact of IR on subsequent mitochondrial function.

MATERIALS AND METHODS

Animal Strains

A total of 34 HCR and LCR female rats from generation 32 were obtained from the parent colony at the University of Toledo. The protocol for generating the animal model has been described in detail previously (43–46). Briefly, starting with an outbred founder population (N: NIH stock), two-way selective breeding using run time until exhaustion on a graded treadmill exercise test as selection criteria, was used to create low capacity runner (LCR) and high capacity runner (HCR) strains. A total of 13 animals of each sex with the shortest run times and 13 animals of each sex with the highest run times were used as the founding population of LCR and HCR cohorts. Well-managed breeding strategies within each cohort were used to create subsequent generations that were increasingly divergent in total running capacity. Upon arrival at this location, animals were maintained in quarantine under standard husbandry conditions. Animal procedures were conducted following the American Physiological Society guidelines for the humans and safe use of animals and all the protocols involving animals in these experiments were approved by the East Carolina University Animal Care and Use Committee.

Cardiac Ischemic-Reperfusion Injury

Rats were anesthetized with an intraperitoneal injection of ketamine/xylazine (90/10 mg/kg ip, Patterson Veterinary Supply, Greeley, Colorado, USA). Once appropriate anesthetic depth was achieved, the thorax was opened and the heart was excised rapidly. The aortic root was cannulated and the coronary circulation was flushed immediately with warm saline. After the saline flush, the control hearts were flushed again with cold saline and transferred to buffer to being mitochondrial isolation. The IR hearts were immediately arrested with 10 ml of iced St Thomas' cardioplegic solution (NaCl 110.0 mM, $NaHCO_3$ 10.0 mM, KCl 16.0 mM, $MgCl_2$ 16.0 mM, $CaCl_2$ 1.2 mM, and pH 7.8) at 4°C and the hearts were then stored in this solution at the same temperature for 80 min. After 80 min of cold global ischemic arrest, the aorta was cannulated and the heart was immediately perfused retrogradely on a Langendorff perfusion apparatus with Krebs–Henseleit buffer (KHB) for 120 min at 37°C (KHB composition (mM): NaCl 118; KCl 4.7; $MgSO_4$ 1.2; KH_2PO_4 1.2; $NaHCO_3$ 25; $CaCl_2$ 1.4; glucose 11; and pH 7.3–7.4). Perfusion was gravity-fed constant pressure maintained at 80 mm Hg, established by the appropriate height of the perfusion reservoir above the heart. Coronary flow and heart rhythm were monitored throughout the reperfusion period. The Langendorff system is widely used because of the ability to control a large number of performance variables (preload, rate, and afterload), but it also has the disadvantage of not actively pumping a volume. In addition, since the system is crystalloid perfused typically, any

circulating agents like pro- or anti-inflammatory cytokines are not present, nor are hormones or autonomic nervous influences. In this case, that can be an asset, since any of those can be changed by exercise and would not be confounding aspects of the study.

Tissue Isolation and Infarct Size Quantification

Following reperfusion, the IR hearts were taken off the cannula and weighed. The right ventricle and atrial tissue were removed and a midventricular ring was obtained from the left ventricle (LV) for infarct size quantification, while the balance of the LV was prepared for mitochondrial isolation, or for −80°C storage and future analysis. The midventricular ring was placed in a 0.1% triphenyltetrazolium chloride solution and incubated at 37°C for 10 min in a shaking water bath. Following incubation, both sides of the slice were photographed with a digital camera attached to a dissecting microscope. Images were quantified using Image J software where total area, lumen area, and infarcted area were measured and quantified as described previously (21, 30, 57).

Mitochondria Isolation

Left ventricular mitochondria were isolated as described in Fisher-Wellman et al. (68). Briefly, one portion of isolated LV (∼40 mg) was immediately placed in ice-cold buffer A [phosphate-buffered saline (pH = 7.4), supplemented with EDTA (10 mM)]. All the tissues were minced and resuspended in buffer C (MOPS (4-Morpholinepropanesulfonic acid, 50 mM; pH = 7.1), KCl (100 mM), EGTA (egtazic acid, 1 mM), and $MgSO_4$ (5 mM) supplemented with bovine serum albumin (BSA; 2 g/l)) and then homogenized *via* a Teflon pestle and borosilicate glass vessel. Tissue homogenates were centrifuged at 500 × g for 10 min at 4°C. Supernatant from each tissue was then filtered through thin layers of gauze and subjected to additional centrifugation at 10,000 × g for 10 min at 4°C. Mitochondrial pellets were washed in 1.4 ml of buffer B [MOPS (50 mM; pH = 7.1), KCl (100 mM), EGTA (1 mM), and $MgSO_4$ (5 mM)], transferred to microcentrifuge tubes, and centrifuged at 10,000× g for 10 min at 4°C. Buffer B was aspirated from each tube and final mitochondrial pellets were suspended in 100–200 μl of buffer B. Protein content was determined *via* the Pierce BCA protein assay. Functional assays involving isolated mitochondria were carried out in the following buffers: buffer D-potassium-MES (105 mM; pH = 7.2), KCl (30 mM), KH_2PO_4 (10 mM), $MgCl_2$ (5 mM), EGTA (1 mM), BSA (2.5 g/l); buffer E-HEPES (20 mM; pH = 8.0), KCl (100 mM), KH_2PO_4 (2.5 mM), $MgCl_2$ (2.5 mM), and glycerol (1%).

Mitochondrial Respiratory Control (JO_2)

High-resolution O_2 consumption measurements were conducted at 37°C in 2 ml of assay buffer by using the Oroboros Oxygraph-2K (Oroboros Instruments, Innsbruck, Austria), as previously described (67). Briefly, isolated mitochondria (0.025 mg/ml) were added to assay buffer, supplemented with creatine (Cr; 5 mM), phosphocreatine (PCr; 1 mM), and creatine kinase (CK; 20 U/ml), followed by the addition of respiratory substrates then ATP (5 mM). Respiratory control was assessed through the sequential additions of PCr to final concentrations of 6 mM, 12 mM, 15 mM, and 21 mM before additions of 5 μM fluorocarbonyl cyanide phenylhydrazone (FCCP). Calculation of ATP free energy of hydrolysis (ΔG_{ATP}) was determined for each PCR concentration as previously described (68) using an online tool (Bioenergetic Calculators (dmpio.github.io)).

Citrate Synthase Activity

Citrate synthase activity was measured using a standard, commercially available kit (Sigma, St Louis, Missouri, USA), according to the instructions of the manufacturer. The assay generates a colorimetric signal in proportion to the rate of conversion between acetyl-CoA and oxaloacetic acid and is read on a spectrophotometer.

Ca^{2+} Retention Capacity

Calcium retention protocols were modified from Sloan et al. (30) where 0.5 mg mitochondria were suspended in an assay buffer containing: 125 mM KCl, 5 mM HEPES, 2 mM KH_2PO_4, and 1 mM $MgCl_2$ (25°C, pH = 7.3). The fluorescent Ca^{2+} indicator, calcium green 5 N salt, was utilized to track changes in extramitochondrial calcium levels. Extramitochondrial calcium fluorescence was measured using a fluorescence spectrophotometer (Photon Technology International, Birmingham, New Jersey, USA), with excitation and emission wavelengths set to 506/532 nm, respectively. Calcium-induced mPTP opening experiments were performed under state 2 respiration conditions (5 mM glutamate/5 mM malate). Mitochondrial PTP opening was induced by subjecting mitochondria to sequential 50 nmol $CaCl_2$ pulses every 3 min, which causes a repeated decrease in the fluorescent signal as Ca^{2+} is taken up by the mitochondria. Induction of mPTP was denoted by a sharp increase in extramitochondrial Ca^{2+}fluorescence, representing the release of the accumulated Ca^{2+} from the mitochondrial matrix. Calcium-retention capacity was quantified as the amount of calcium needed to induce PTP opening (nmol $CaCl_2$/mg mitochondria).

Statistical Analysis

Statistical analysis was performed by using commercial software (GraphPad Prism, San Diego, California, USA). Data are expressed as means ± SD and a $p < 0.05$ was considered as statistically significant.

RESULTS

Myocardial Infarct Size

Infarctions were somewhat larger than expected despite the relatively long ischemic times, considering the use of the cold cardioplegic solution. About 80 min of cold global ischemic arrest and 120 min of warm reperfusion, myocardial infarct size was not significantly different between LCRs and HCRs (47.2 ± 4.8 vs. 42.9 ± 5.2, respectively). Hearts from HCR and LCR animals showed different patterns of infarction, with HCR being more contiguous and LCR more diffuse, but relatively similar in the overall amount of tissue involved (**Figure 1**).

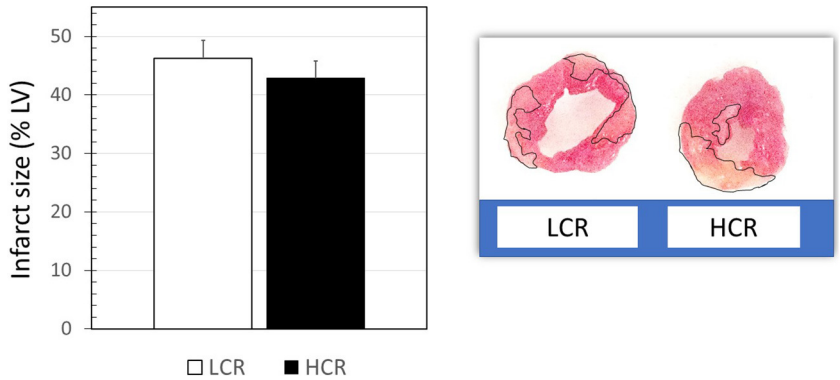


FIGURE 1 | Examples of triphenyltetrazolium chloride (TTC)-stained myocardial sections, and graphical summary of group data for infarct size results ($n = 9$ per group).

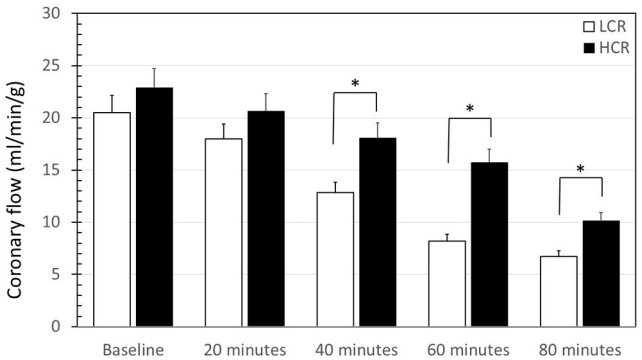


FIGURE 2 | Summary of coronary flow results during reperfusion of low capacity aerobic running (LCR) and high capacity aerobic running (HCR) hearts. Data are expressed as mean ± SD. $n = 9$ per group. *$p < 0.05$ in designated comparison.

Coronary Artery Flow

When normalized to heart weight, baseline coronary flow at the onset of reperfusion was not different between LCR and HCR hearts (20.5 ± 3.2 vs. 23.6 ± 2.8, respectively). However, coronary flow decreased by 68% in LCRs and by 56% in HCRs over the 2 h of reperfusion and coronary flow decreased more quickly in the LCRs compared to the HCRs, becoming significantly different at 40 min of reperfusion (**Figure 2**). In a constant pressure system, the decreasing flow is consistent with an increased coronary vascular resistance. Still, there was a substantial drop in coronary flow in both groups, and the relatively higher/less diminished flow, was not enough to produce any difference in overall infarction size.

Reperfusion Arrhythmia

Upon harvest, the hearts were placed immediately into the cold storage solution, so there were no baseline rhythm measurements. The first perfusion on the column constituted the onset of rewarming and reperfusion. Arrhythmia was evaluated followed by the guidelines established by the Lambeth Conventions and graded by using a numerical scoring system as described previously (30). Fibrillation was a uniform finding early in reperfusion with similar frequency and severity in both LCR and HCR hearts (**Figure 3**).

Mitochondrial Respiratory Capacity

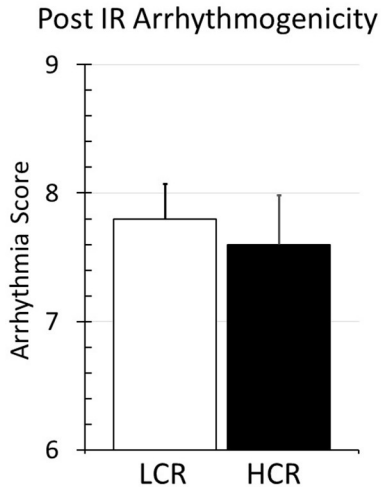
Control Comparisons

Cardiac mitochondria respiratory rates were 32% higher at rest in HCR and more than 40% higher under maximally stimulated conditions, compared to LCR (both $p < 0.05$). Generally, HCR mitochondria showed significantly higher mitochondria respiration with all substrates compared to LCR. The addition of the uncoupling agent, carbonyl cyanide 4-(trifluoromethoxy) phenylhydrazone (FCCP) (1 μM), at the end of the respirometry experiments rescued absolute rates of oxygen consumption (**Figure 4**).

Post-ir Injury Comparisons

In contrast to control experiments, HCR mitochondria no longer showed relatively increased respiratory capacity compared to LCR (**Figure 5**). Comparing control to post-I/R under pyruvate/malate conditions, respiratory rates were reduced in both phenotypes to levels <10% of baseline (**Figure 6**). There was recruitable respiratory capacity in both HCR and LCR postischemic mitochondria, but the differences between phenotypes that been observed across the spectrum of substrate conditions were no longer present after ischemia. In fact, HCRs showed a greater loss of respiratory capacity in response to FCCP than the LCR (**Figure 6**).

The amount of mitochondrial protein harvested from LV tissue samples (w/w) was not different between HCR and LCR under control conditions (**Figure 7A**). Following cold storage ischemia and rewarming/reperfusion, there was a significant decrease in mitochondrial protein in both strains ($p < 0.05$), consistent with a loss of mitochondria. However, the decrease was similar in both groups (**Figure 7A**). Interestingly, the citrate synthase activity of the remaining mitochondria following reperfusion also was reduced comparably in both groups, consistent with possible functional impairment in surviving mitochondria (**Figure 7B**).



Arrhythmia scoring system

0	0–49 PVCs
1	50–499 PVCs
2	>499 PVCs and/or 1 episode of SVT or VF
3	>1 episode of VT or VF or both (<60 sec combined duration)
4	VT or VF or both (60–119 sec total combined duration)
5	VT or VF or both (>119 sec total combined duration)
6	Fatal VF starting at >15 min after occlusion
7	Fatal VF starting between 4 and 14 min 59 s after occlusion
8	Fatal VF starting between 1 min and 3 min 59 s after occlusion
9	Fatal VF starting < 1 min after occlusion

FIGURE 3 | Summary of arrhythmia results during reperfusion of LCR and HCR hearts (left panel), and the arrhythmia scoring system that was used (right panel) to generate the data. Data are expressed as mean ± SD. $n = 9$ per group. $^*p < 0.05$ in designated comparison.

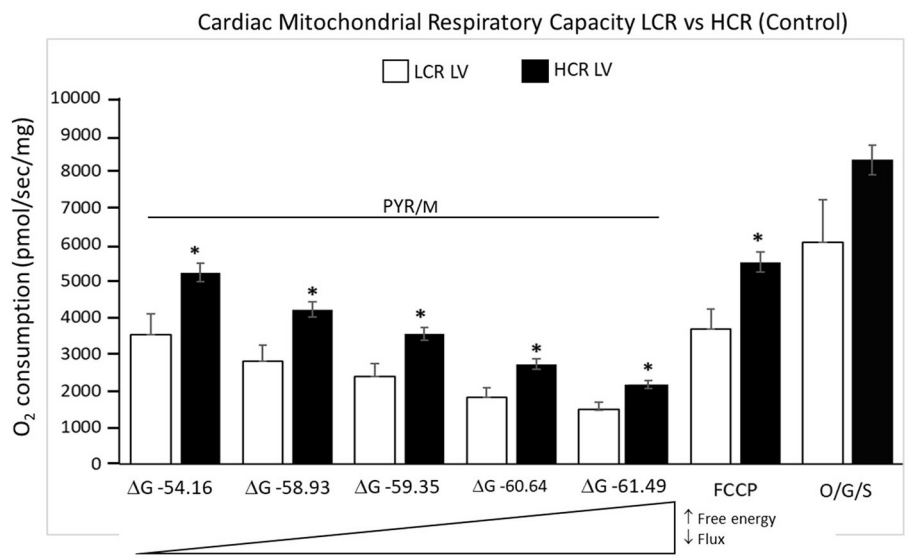


FIGURE 4 | Summary of mitochondrial respiration results in samples isolated from HCR and LCR control ventricles. The top inset shows representative tracing, while the graphic summarizes group results. Data are expressed as mean ± SD. $n = 8$ per group. $^*p < 0.05$ in designated comparison.

Ca^{2+} Retention Capacity

There were no differences in baseline mitochondrial calcium retention. Similar to the respiratory deficits that occurred in mitochondria after I/R, the ability to retain calcium was also reduced significantly following ischemia. On average, the permeability transition pore (PTP) opened with about 75% less calcium than it did before the I/R insult but the impairments were similar in both the phenotypes (**Figure 8**).

DISCUSSION

The results of this study showed that while there was increased mitochondrial capacity in HCRs compared to LCRs, the increased cellular respiratory capacity did not translate to reduced injury from ischemic arrest and reperfusion even with the benefit of supplemental cardioprotection by using established cardioplegia regimens. Moreover, there was accelerated relative loss of mitochondrial respiratory capacity in the HCRs compared to the LCRs, even though coronary blood flow was better preserved during reperfusion in the HCRs compared to the LCRs. The lack of benefit despite better flow was a bit unexpected, as dynamic exercise has generally associated cardioprotection with improved perfusion. A decrease in infarct size after training was seen in rats subjected to a swim training regimen after permanent occlusion which the authors attributed to increased myocardial vascularity (59). In a much-cited paper, Brown et

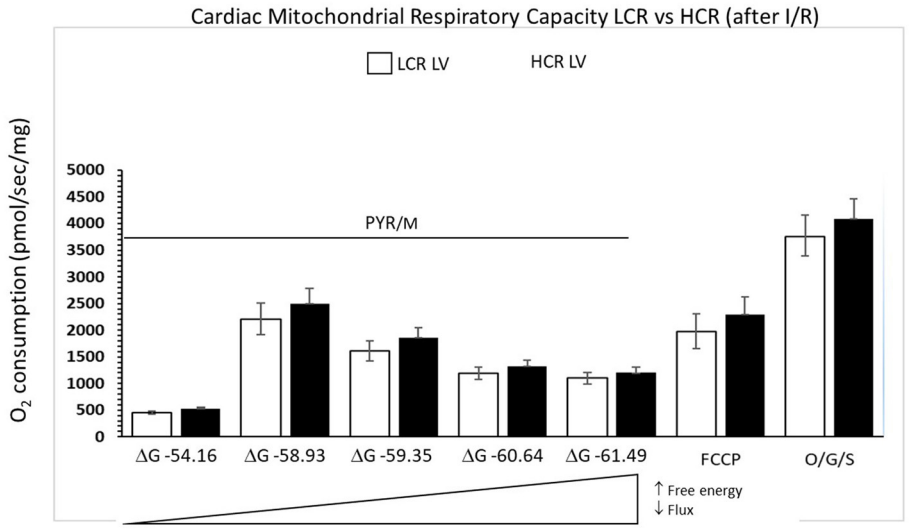


FIGURE 5 | Summary of mitochondrial respiration results in samples isolated from HCR and LCR ventricles following IR. The top inset shows representative tracing, while the graphic summarizes group results. Data are expressed as mean ± SD. $n = 9$ per group. $^{*}p < 0.05$ in designated comparison.

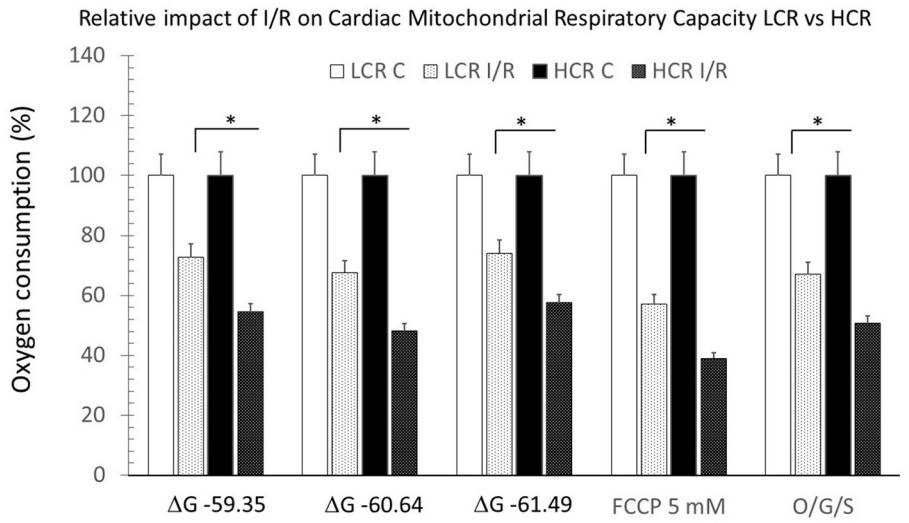


FIGURE 6 | Summary of mitochondrial respiration, comparing results within and between phenotypes, under control and post-ischemia-reperfusion (IR) conditions. Data are expressed as mean ± SD. $n = 8$ per group for controls and 9 per group for IR. $^{*}p < 0.05$ in designated comparison.

al. demonstrated that prolonged endurance training confers a cardioprotective effect against infarction in myocardium subjected to severe ischemia and subsequent reperfusion (21). In addition, they observed that during severe ischemia, coronary flow to regions of the myocardium outside the ischemic area at risk was better maintained in hearts isolated from endurance-trained rats. Furthermore, on reperfusion of the area at risk, the increase in flow to the previously ischemic region of the heart was markedly higher in hearts isolated from trained rats (21).

We have demonstrated that the cardioprotection associated with the HCR phenotype may be limited (57). We did not have sufficient animals available to complete a preliminary dose response study to determine the optimal cold storage time, and it is possible that despite the cardioplegia, the ischemic time was simply too long and overwhelmed and benefit the HCR phenotype might have conferred. However, the results are consistent with those reported by others working with the model (55, 56). Still, there are important differences worth noting. In particular, active exercise training programs produce improvements to ischemic tolerance *via* a host of mechanisms (5, 6, 9, 10, 14, 15), notably including increased mitochondrial functional capacity (19, 24, 59). Gallego-Selles et al. described experiments in humans subjects indicating that, at least in skeletal muscle, nrf2 is activated rapidly by exercise to exhaustion

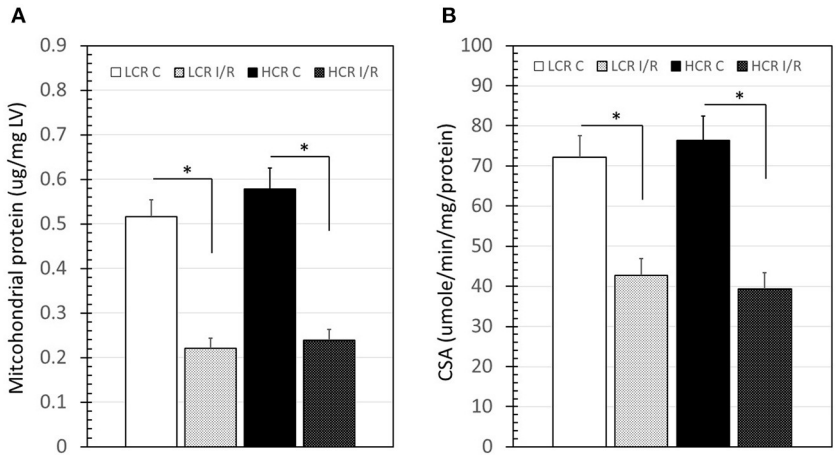


FIGURE 7 | Summary of mitochondrial protein "yield" from left ventricle (LV) samples (left panel) and citrate synthase activity (CSA, right panel) before and after IR. Data are expressed as mean ± SD. $n = 8$ per group for controls and 9 per group for IR. $^{*}p < 0.05$ in designated comparison.

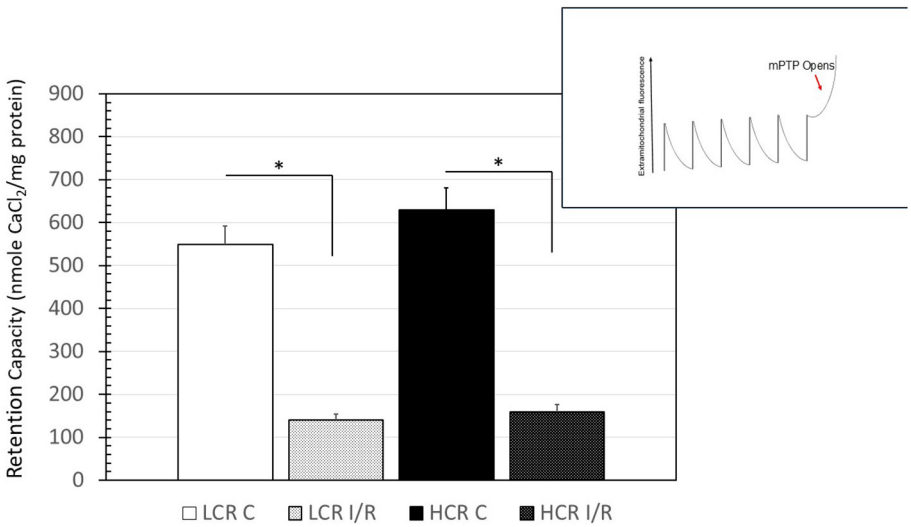


FIGURE 8 | Summary of results for the calcium-retention experiments. Inset is a representation of the tracings obtained, while the chart is a graphical summary of the group data. Arrow in inset indicates the change in calcium uptake that occurs when the transition pore opens. Data are expressed as mean ± SD. $n = 8$ per group for controls and 9 per group for IR. $^{*}p < 0.05$ in designated comparison.

and can dynamically modulate ROS and mitochondrial-sourced proteins such as catalase (61). Flockhart demonstrated, also in human subjects, that participating in an intense, active exercise program produced functional impairment in the mitochondria that also was associated with at least a transient decrease in glucose tolerance (62). In our hands, despite an increased resting mitochondrial capacity in the HCRs, there was no protection against the ischemic insult. Together, it seems clear that there can be substantial differences in the role of mitochondria in the response to ischemia that can be influenced by the nature and duration of the exercise training and confounded by differences dictated by the intrinsic capacity for exercise, independent of actual active exercise. The importance and role of pathways such as nrf2/keap1/catalase and others in bridging the components of an exercise effect (intrinsic vs. active) remain to be determined.

Several previous experimental studies of myocardial ischemia generally have indicated a good correlation between disruption of complex I through a variety of mechanisms (16–18, 33, 41), as well as opening of the permeability transition pore, with outcomes in cardiac ischemia and reperfusion (23, 26, 28–30). Some have suggested that complex I is considered the main site of damage to the respiratory chain in IR, while downstream electron transport chains are relatively resistant to IR injury (60, 63, 64). Furthermore, Veitch and his colleagues (63) found a major decline in complex I activity in perfused rat hearts subjected to 20 min of global ischemia, and Cairns and his group (64) demonstrated that this damage was exacerbated by reperfusion.

In contrast to these studies, our results suggest a more generalized loss of mitochondrial respiratory capacity following IR. Perhaps that should not be surprising. Animals that have been selectively inbred using aerobic running capacity as the selection criteria create a strain optimized for performance when aerobic conditions exist. Ischemia certainly is not an aerobic condition. While it is possible that the HCR phenotype augments several factors that could delay the onset of ischemia and which would be protective (57), they may be maladapted if the transition to anaerobic conditions still occurs. Structural adaptations like increased capillary density or increased vasodilator capacity, which might have been beneficial in delaying the onset of ischemia, would also be factors that could aggravate the potential for reperfusion injury once perfusion was reestablished after an acute ischemic episode. When ample oxygen is present, cardiac mitochondria have greater substrate flexibility than many other tissues, meaning that cardiac mitochondria can respire effectively using a wide variety of substrates (67). Tolerance for IR may not be related so much to the capacity to respire using a given substrate, but more to the ability to switch from one substrate to another. With the newest approaches that have been developed (68), and the energy hypothesis that is being advanced by the HCR LCR work (46, 53), the HCR LCR phenotypes could provide interesting and valuable perspective on factors contributing to substrate preference. To the extent that HCR complex I respiratory capacity was impacted strongly by IR, and that there was a similarity between PTP function and infraction size in HCR and LCR, suggest that a more complex assessment of specific mitochondria adaptations in these strains might be warranted.

Mitochondria comprise a large fraction of the heart mass and are critical for the normal mechanical and electrophysiological function of the cardiomyocyte, playing roles that extend beyond bioenergetics and metabolism. Proper function is required to meet the high energetic demand of the cardiomyocyte and playing an essential role in controlling oxidative stress and Ca^{2+} handling (34). Ischemia-reperfusion injury increases the production of ROS and induces calcium overload into mitochondria (35) which can interact together to induce opening of the mPTP and, therefore, triggering apoptosis by promoting the release of proapoptotic proteins (i.e., cytochromec) and subsequent activation of the programmed cell (65, 66).

Our results indicate that intrinsic aerobic capacity must be tied to mitochondrial performance at a subcellular level. It also is clear that the dynamic role of mitochondria in cardiac ischemia, perfusion, and heart failure is only now beginning to be appreciated, but remains confused, perhaps in part because the underlying intrinsic elements have not been adequately considered in the assessment of the active exercise response. Models such as these HCR and LCR phenotypes should provide a unique window on how that background influences the extent to which inducible adaptive responses can be accomplished best using an active exercise regimen.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by Institutional Animal Care and Use Committee (IACUC) East Carolina University.

AUTHOR CONTRIBUTIONS

RL participated in designing, conducting, analyzing, and writing. MA and MZ participated in conducting, analyzing, and writing. KF-W participated in designing, conducting, and analyzing. LCK participated in conducting and analyzing. LGK and SB provided animals and insight on study design. All authors contributed to the article and approved the submitted version.

REFERENCES

1. American Heart Association/American Stroke Association. Cardiovascular disease: a costly burden for america projections through 2035. Available online at: https://healthmetrics.heart.org/wp-content/uploads/2017/10/Cardiovascular-Disease-ACostly-Burden.pdf
2. Burke AP, Virmani R. Pathophysiology of acute myocardial infarction. *Med Clinics North America.* (2007) 91:553–72. doi: 10.1016/j.mcna.2007.03.005
3. Buja LM, Weerasinghe P. Unresolved issues in myocardial reperfusion injury. *Cardiovascular Pathology*. (2010) 19:29–35. doi: 10.1016/j.carpath.2008.10.001
4. Vetterlein F, Schrader C, Volkmann R, Neckel M, Ochs M, Schmidt G, et al. Extent of damage in ischemic, nonreperfused, and reperfused myocardium of anesthetized rats. *Am J Physiol Circ Physiol.* (2003) 285:H755–65. doi: 10.1152/ajpheart.00269.2002
5. Frank A, Bonney M, Bonney S, Weitzel L, Koeppen M, Eckle T. Myocardial ischemia reperfusion injury: From basic science to clinical bedside. *Sem in Cardiothor Vasc Anes.* (2012) (16):123–32. doi: 10.1177/1089253211436350
6. Yellon DM, Hausenloy DJ. Myocardial reperfusion injury. *N Eng J Med.* (2007) 357:1121. doi: 10.1056/NEJMra071667
7. Moens AL, Claeys MJ, Timmermans JP, Vrints CJ. Myocardial ischemia/reperfusion-injury, a clinical view on a complex pathophysiological process. *Int J Cardiol.* (2005) 100:179–90. doi: 10.1016/j.ijcard.2004.04.013
8. Kalogeris T, Baines CP, Krenz M, Korthuis RJ. Cell Biology of Ischemia/Reperfusion Injury. *Int Rev Cell Mol Biol.* (2012) 229–317. doi: 10.1016/B978-0-12-394309-5.00006-7
9. Hausenloy DJ, Yellon DM. Myocardial ischemia-reperfusion injury: A neglected therapeutic target. *J Clin Invest.* (2013) 123:92–100. doi: 10.1172/JCI62874
10. Quindry J, Hamilton K. Exercise and cardiac preconditioning against ischemia reperfusion injury. *Curr Cardiol Rev.* (2013) 9:220–9. doi: 10.2174/1573403X113099990033
11. Borges JP, da Silva Verdoorn K. Cardiac ischemia/reperfusion injury: The beneficial effects of exercise. In: Advances in Experimental Medicine and Biology. New York LLC: Springer (2017). pp. 155–79. doi: 10.1007/978-981-10-4307-9_10
12. Kavazis AN. Exercise preconditioning of the myocardium. *Sports Med.* (2009) 39:923–35. doi: 10.2165/11317870-000000000-00000
13. Powers SK, Quindry JC, Kavazis AN. Exercise-induced cardioprotection against myocardial ischemia-reperfusion injury. *Free Radic Biol Med.* (2008) 44:193–201. doi: 10.1016/j.freeradbiomed.2007.02.006

14. Frasier CR, Moore RL, Brown DA. Exercise-induced cardiac preconditioning: How exercise protects your achy-breaky heart. *J Appl Physiol.* (2011) 111:905–15. doi: 10.1152/japplphysiol.00004.2011
15. Hamilton KL, Staib JL, Phillips T, Hess A, Lennon SL, Powers SK. Exercise, antioxidants, and HSP72: protection against myocardial ischemia/reperfusion. *Free Radic Biol Med.* (2003) 34:800–9. doi: 10.1016/S0891-5849(02)01431-4
16. Abe K, Hayashi N, Terada H. Effect of endogenous nitric oxide on energy metabolism of rat heart mitochondria during ischemia and reperfusion. *Free Radic Biol Med.* (1999) 26:379–87. doi: 10.1016/S0891-5849(98)00222-6
17. Riobó NA, Clementi E, Melani M, Boveris A, Cadenas E, Moncada S, et al. Nitric oxide inhibits mitochondrial NADH:ubiquinone reductase activity through peroxynitrite formation. *Biochem J.* (2001) 359:139–45. doi: 10.1042/bj3590139
18. Jekabsone A, Ivanoviene L, Brown GC, Borutaite V. Nitric oxide and calcium together inactivate mitochondrial complex I and induce cytochrome c release. *J Mol Cell Cardiol.* (2003) 35:803–9. doi: 10.1016/S0022-2828(03)00137-8
19. Kavazis AN, Alvarez S, Talbert E, Lee Y, Powers SK. Exercise training induces a cardioprotective phenotype and alterations in cardiac subsarcolemmal and intermyofibrillar mitochondrial proteins. *Am J Physiol - Hear Circ Physiol.* (2009) 297:H144–52. doi: 10.1152/ajpheart.01278.2008
20. Hausenloy DJ, Tsang A, Yellon DM. The Reperfusion Injury Salvage Kinase Pathway: A Common Target for Both Ischemic Preconditioning and Postconditioning. *Trends Cardiovasc Med.* (2005) 15:69–75. doi: 10.1016/j.tcm.2005.03.001
21. Brown DA, Jew KN, Sparagna GC, Musch TI, Moore RL. Exercise training preserves coronary flow and reduces infarct size after ischemia-reperfusion in rat heart. *J Appl Physiol.* (2003) 95:2510–8. doi: 10.1152/japplphysiol.00487.2003
22. Pell VR, Chouchani ET, Murphy MP, Brookes PS, Krieg T. Moving forwards by blocking back-flow the yin and yang of MI therapy. *Circ Res.* (2016) 118:898–906. doi: 10.1161/CIRCRESAHA.115.306569
23. Halestrap AP, Pasdois P. The role of the mitochondrial permeability transition pore in heart disease. *Biochimica et Biophysica Acta - Bioenergetics.* (2009) 1787:1402–15. doi: 10.1016/j.bbabio.2008.12.017
24. Machado NG, Alves MG, Carvalho RA, Oliveira PJ. Mitochondrial involvement in cardiac apoptosis during ischemia and reperfusion: Can we close the box? *Cardiovasc Toxicol.* (2009) 9:211–27. doi: 10.1007/s12012-009-9055-1
25. Chen YR, Zweier JL. Cardiac mitochondria and reactive oxygen species generation. *Circ Res.* (2014) 114:524–37. doi: 10.1161/CIRCRESAHA.114.300559
26. Honda HM, Ping P. Mitochondrial permeability transition in cardiac cell injury and death. *Cardiovasc Drugs Ther.* (2006) 20:425–32. doi: 10.1007/s10557-006-0642-0
27. Paradies G, Paradies V, Ruggiero FM, Petrodillo G. Mitochondrial bioenergetics and cardiolipin alterations in myocardial ischemia-reperfusion injury: implications for pharmacological cardioprotection. *Am J Physiol Heart Circ Physiol.* (2018) 315:H1341–52. doi: 10.1152/ajpheart.00028.2018
28. Di Lisa F, Menabò R, Canton M, Barile M, Bernardi P. Opening of the mitochondrial permeability transition pore causes depletion of mitochondrial and cytosolic NAD+ and Is a causative event in the death of myocytes in postischemic reperfusion of the heart. *J Biol Chem.* (2001) 276:2571–5. doi: 10.1074/jbc.M006825200
29. Abdallah Y, Kasseckert SA, Iraqi W, Said M, Shahzad T, Erdogan A, et al. Interplay between Ca 2+ cycling and mitochondrial permeability transition pores promotes reperfusion-induced injury of cardiac myocytes. *J Cell Mol Med.* (2011) 15:2478–85. doi: 10.1111/j.1582-4934.2010.01249.x
30. Sloan RC, Moukdar F, Frasier CR, Patel HD, Bostian PA, Lust RM, et al. Mitochondrial permeability transition in the diabetic heart: Contributions of thiol redox state and mitochondrial calcium to augmented reperfusion injury. *J Mol Cell Cardiol.* (2012) 52:1009–18. doi: 10.1016/j.yjmcc.2012.02.009
31. Heather LC, Carr CA, Stuckey DJ, Pope S, Morten KJ, Carter EE, et al. Critical role of complex III in the early metabolic changes following myocardial infarction. *Cardiovasc Res.* (2010) 85:127–36. doi: 10.1093/cvr/cvp276
32. Halestrap AP, Richardson AP. The mitochondrial permeability transition: A current perspective on its identity and role in ischaemia/reperfusion injury. *J Mol and Cell Cardiol.* (2015) 78:129–41. doi: 10.1016/j.yjmcc.2014.08.018
33. Paradies G, Petrosillo G, Pistolese M, Ruggiero FM. Reactive oxygen species affect mitochondrial electron transport complex I activity through oxidative cardiolipin damage. *Gene.* (2002) 286:135–41. doi: 10.1016/S0378-1119(01)00814-9
34. Dedkova EN, Blatter LA. Calcium signaling in cardiac mitochondria. *J Mol Cell Cardiol.* (2013) 58:125–33. doi: 10.1016/j.yjmcc.2012.12.021
35. Vercesi AE, Kowaltowski AJ, Oliveira HCF, Castilho RF. Mitochondrial Ca2+ transport, permeability transition and oxidative stress in cell death: Implications in cardiotoxicity, neurodegeneration and dyslipidemias. *Frontiers Biosci.* (2006) 11:2554–64. doi: 10.2741/1990
36. Raedschelders K, Ansley DM, Chen DDY. The cellular and molecular origin of reactive oxygen species generation during myocardial ischemia and reperfusion. *Pharmacol Therapeut.* (2012) 133:230–55. doi: 10.1016/j.pharmthera.2011.11.004
37. Paradies G, Petrosillo G, Pistolese M, Di Venosa N, Serena D, Ruggiero FM. Lipid peroxidation and alterations to oxidative metabolism in mitochondria isolated from rat heart subjected to ischemia and reperfusion. *Free Radic Biol Med.* (1999) 27:42–50. doi: 10.1016/S0891-5849(99)00032-5
38. Dickson EW, Hogrefe CP, Ludwig PS, Ackermann LW, Stoll LL, Denning GM. Exercise enhances myocardial ischemic tolerance via an opioid receptor-dependent mechanism. *Am J Physiol - Hear Circ Physiol.* (2008) 294:H402–8. doi: 10.1152/ajpheart.00280.2007
39. La Rovere MT, Bersano C, Gnemmi M, Specchia G, Schwartz PJ. Exercise-induced increase in baroreflex sensitivity predicts improved prognosis after myocardial infarction. *Circulation.* (2002) 106:945–9. doi: 10.1161/01.CIR.0000027565.12764.E1
40. Demirel HA, Powers SK, Caillaud C, Coombes JS, Naito H, Fletcher LA, et al. Exercise training reduces myocardial lipid peroxidation following short- term ischemia-reperfusion. *Med Sci Sports Exerc.* (1998) 30:1211–6. doi: 10.1097/00005768-199808000-00005
41. Paradies G, Paradies V, De Benedictis V, Ruggiero FM, Petrosillo G. Functional role of cardiolipin in mitochondrial bioenergetics. *Biochimica et Biophysica Acta - Bioenergetics.* (2014) 1837:408–17. doi: 10.1016/j.bbabio.2013.10.006
42. Bouchard C, Lesage R, Lortie G, Simoneau JA, Hamel P, Boulay MR, et al. Aerobic performance in brothers, dizygotic and monozygotic twins. Med Sci Sports Exerc. 10.
43. Koch LG. Britton Sl. Artificial selection for intrinsic aerobic endurance running capacity in rats. *Physiol Genomics.* (2001) 5:45–52. doi: 10.1152/physiolgenomics.2001.5.1.45
44. Britton SL, Koch LG. Animal genetic models for complex traits of physical capacity. *Exerc Sport Sci Rev.* (2001) 29:7–14. doi: 10.1097/00003677-200101000-00003
45. Koch LG, Britton SL, Wisløff U, A. rat model system to study complex disease risks, fitness, aging, and longevity. *Trends Cardiovasc Med.* (2012) 22:29–34. doi: 10.1016/j.tcm.2012.06.007
46. Koch LG, Britton SL. Theoretical and Biological Evaluation of the Link between Low Exercise Capacity and Disease Risk. *Cold Spring Harb Perspect Med.* (2018) 8:639–46. doi: 10.1101/cshperspect.a029868
47. Koch LG, Britton SL. Aerobic metabolism underlies complexity and capacity. *J Physiol.* (2008) 586:83–95. doi: 10.1113/jphysiol.2007.144709
48. Wisloff U, Najjar SM, Ellingsen O, Haram PM, Swoap S, Al-Share Q, et al. Cardiovascular risk factors emerge after artificial selection for low aerobic capacity. *Science.* (2005) 307:418–20. doi: 10.1126/science.1108177
49. de Godoy MRC, Padilla J, Swanson KS, Vieira-Potter VJ. Soy improves cardiometabolic health and cecal microbiota in female low-fit rats. *Sci Rep.* (2017) 7:9261. doi: 10.1038/s41598-017-08965-0
50. Rosenblat M, Volkova N, Abassi Z, Britton SL, Koch LG, Aviram M. High intrinsic aerobic capacity and pomegranate juice are protective against macrophage atherogenecity: studies in high- vs. *low-capacity runner (HCR vs LCR) rats J Nutr Biochem.* (2015) 26:1015–21. doi: 10.1016/j.jnutbio.2015.04.001
51. Høydal MA, Stølen TO, Johnsen AB, Alvez M, Catalucci D, Condorelli G, et al. Reduced aerobic capacity causes leaky ryanodine receptors that trigger arrhythmia in a rat strain artificially selected and bred for low aerobic running capacity. *Acta Physiol (Oxf).* (2014) 210:854–64. doi: 10.1111/apha.12238
52. Hussain SO, Barbato JC, Koch LG, Metting PJ, Britton SL. Cardiac function in rats selectively bred for low- and high-capacity running. *Am J Physiol Regul*

Integr Comp Physiol. (2001) 281:R1787–91. doi: 10.1152/ajpregu.2001.281.6.R1787
53. Aon MA, Cortassa S, Juhaszova M, González-Reyes JA, Calvo-Rubio M, Villalba JM, et al. Mitochondrial health is enhanced in rats with higher vs. lower intrinsic exercise capacity and extended lifespan. *NPJ Aging Mech Dis.* (2021) 7:1. doi: 10.1038/s41514-020-00054-3
54. Johnsen VL, Belke DD, Hughey CC, Hittel DS, Hepple RT, Koch LG, et al. Enhanced cardiac protein glycosylation (O-GlcNAc) of selected mitochondrial proteins in rats artificially selected for low running capacity. *Physiol Genomics.* (2013) 45:17–25. doi: 10.1152/physiolgenomics.00111.2012
55. Hjortbak MV, Grønnebæk TS, Jespersen NR, Lassen TR, Seefeldt JM, Tonnesen PT, et al. Differences in intrinsic aerobic capacity alters sensitivity to ischemia-reperfusion injury but not cardioprotective capacity by ischemic preconditioning in rats. *PLoS ONE.* (2020) 15:e0240866. doi: 10.1371/journal.pone.0240866
56. Høydal MA, Kaurstad G, Rolim NP, Johnsen AB, Alves M, Koch LG, et al. High inborn aerobic capacity does not protect the heart following myocardial infarction. *J Appl Physiol.* (1985) 115:1788–95. doi: 10.1152/japplphysiol.00312.2013
57. Alsahly MB, Zakari, MO, Koch, LG, Britton S, Katwa LC, Lust RM. Influence of intrinsic aerobic capacity and sex on cardiac injury following acute myocardial ischemia and reperfusion. *Front Cardiovasc Med*. (in press).
58. Palpant NJ, Szatkowski ML, Wang W, Townsend D, Bedada FB, Koch LG, et al. Artificial selection for whole animal low intrinsic aerobic capacity co-segregates with hypoxia-induced cardiac pump failure. *PLoS ONE.* (2009) 4:e6117. doi: 10.1371/journal.pone.0006117
59. McElroy CL, Gissen SA, Fishbein MC. Exercise-induced reduction in myocardial infarct size after coronary artery occlusion in the rat. *Circulation.* (1978) 57:958–62. doi: 10.1161/01.CIR.57.5.958
60. Solaini G, Harris DA. Biochemical dysfunction in heart mitochondria exposed to ischaemia and reperfusion. *Biochem J.* (2005) 390:377–94. doi: 10.1042/BJ20042006
61. Gallego-Selles A, Martin-Rincon M, Martinez-Canton M, Perez-Valera M, Martín-Rodríguez S, Gelabert-Rebato M, et al. Regulation of Nrf2/Keap1 signalling in human skeletal muscle during exercise to exhaustion in normoxia, severe acute hypoxia and post-exercise ischaemia: Influence of metabolite accumulation and oxygenation. *Redox Biol.* (2020) 36:101627. doi: 10.1016/j.redox.2020.101627
62. Flockhart M, Nilsson LC, Tais S, Ekblom B, Apró W, Larsen FJ. Excessive exercise training causes mitochondrial functional impairment and decreases glucose tolerance in healthy volunteers. *Cell Metab.* (2021) 33:957–70. doi: 10.1016/j.cmet.2021.02.017
63. Veitch K, Hombroeckx A, Caucheteux D, Pouleur H, Hue L. Global ischaemia induces a biphasic response of the mitochondrial respiratory chain: Anoxic pre-perfusion protects against ischaemic damage. *Biochem J.* (1992) 281:709–15. doi: 10.1042/bj2810709
64. Cairns CB, Ferroggiaro AA, Walther JM, Harken AH, Banerjee A. Postischemic administration of succinate reverses the impairment of oxidative phosphorylation after cardiac ischemia and reperfusion injury. *Circ.* (1997) 96:260–5.
65. Daugas E, Susin SA, Zamzami N, Ferri KF, Irinopoulou T, Larochette N, et al. Mitochondrio-nuclear translocation of AIF in apoptosis and necrosis. *FASEB J.* (2000) 14:729–39. doi: 10.1096/fasebj.14.5.729
66. Li P, Nijhawan D, Budihardjo I, Srinivasula SM, Ahmad M, Alnemri ES, et al. Cytochrome c and dATP-dependent formation of Apaf-1/caspase-9 complex initiates an apoptotic protease cascade. *Cell.* (1997) 91:479–89. doi: 10.1016/S0092-8674(00)80434-1
67. McLaughlin KL, Hagen JT, Coalson HS, Nelson MAM, Kew KA, Wooten AR, Fisher-Wellman KH. Novel approach to quantify mitochondrial content and intrinsic bioenergetic efficiency across organs. *Sci Rep.* (2020) 10:17599.
68. Fisher-Wellman KH, Davidsom MT, Narowski TM, Lin, CT, Koves TR, Muoio DM. Mitochondrial diagnostics: a multiplexed assay platform for comprehensive assessment of mitochondrial energy fluxes. *Cell Reports.* (2018) 24:3593–606. doi: 10.1016/j.celrep.2018.08.091

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 12 November 2021
doi: 10.3389/fcvm.2021.721140

Acute Hemodynamic Responses to Enhanced External Counterpulsation in Patients With Coronary Artery Disease

Yahui Zhang[1,2,3], *Ziqi Chen*[1,2], *Zhouming Mai*[4], *Wenjuan Zhou*[1], *Hui Wang*[5], *Xiaodong Zhang*[6], *Wenbin Wei*[1], *Jianhang Du*[1,2,3]* and *Guifu Wu*[1,2,3]*

[1] Department of Cardiology, The Eighth Affiliated Hospital, Sun Yat-sen University, Shenzhen, China, [2] National Health Commission (NHC) Key Laboratory of Assisted Circulation, Sun Yat-sen University, Guangzhou, China, [3] Guangdong Innovative Engineering and Technology Research Center for Assisted Circulation, Shenzhen, China, [4] Department of Cardiology, Huizhou Third People's Hospital, Huizhou, China, [5] Department of Cardiac Ultrasound, The Eighth Affiliated Hospital, Sun Yat-sen University, Shenzhen, China, [6] Department of Physical Education, Nanjing University of Finance and Economics, Nanjing, China

OPEN ACCESS

Edited by:
Richard Yang Cao,
Shanghai Xuhui Central Hospital, China

Reviewed by:
Valdo Jose Dias Da Silva,
Universidade Federal do Triângulo Mineiro, Brazil
Ricardo Armentano,
Universidad de la República, Uruguay

***Correspondence:**
Guifu Wu
wuguifu@mail.sysu.edu.cn
Jianhang Du
dujh8@mail.sysu.edu.cn

Specialty section:
This article was submitted to General Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

Received: 06 June 2021
Accepted: 12 October 2021
Published: 12 November 2021

Citation:
Zhang Y, Chen Z, Mai Z, Zhou W, Wang H, Zhang X, Wei W, Du J and Wu G (2021) Acute Hemodynamic Responses to Enhanced External Counterpulsation in Patients With Coronary Artery Disease. Front. Cardiovasc. Med. 8:721140. doi: 10.3389/fcvm.2021.721140

Purpose: Enhanced external counterpulsation is a non-invasive treatment that increases coronary flow in patients with coronary artery disease (CAD). However, the acute responses of vascular and blood flow characteristics in the conduit arteries during and immediately after enhanced external counterpulsation (EECP) need to be verified.

Methods: Forty-two patients with CAD and 21 healthy controls were recruited into this study to receive 45 min-EECP. Both common carotid arteries (CCAs), namely, the left carotid (LC) and right carotid (RC), the right brachial (RB), and right femoral (RF) artery were imaged using a Color Doppler ultrasound. The peak systolic velocity (PSV), end-diastolic velocity (EDV), mean inner diameter (ID), resistance index (RI), and mean flow rate (FR) were measured and calculated before, during, and after the 45 min-EECP treatment.

Results: During EECP, in the CCAs, the EDV was significantly decreased, while the RI was markedly increased in the two groups (both $P < 0.01$). However, immediately after EECP, the RI in the RC was significantly lower than that at the baseline in the patients with CAD ($P = 0.039$). The FR of the LC was markedly increased during EECP only in the CAD patients ($P = 0.004$). The PSV of the patients with CAD was also significantly reduced during EECP ($P = 0.015$) and immediately after EECP ($P = 0.005$) compared with the baseline. Moreover, the ID of the LC, RB, and RF was significantly higher immediately after EECP than that at the baseline (all $P < 0.05$) in the patients with CAD. In addition, they were also higher than that in the control groups (all $P < 0.05$). Furthermore, by the subgroup analysis, there were significant differences in the FR, PSV, and RI between females and males during and immediately after EECP (all $P < 0.05$).

Conclusions: Enhanced external counterpulsation creates different responses of vascular and blood flow characteristics in carotid and peripheral arteries, with more

significant effects in both the carotid arteries. Additionally, the beneficial effects in ID, blood flow velocity, RI, and FR after 45 min-EECP were shown only in the patients with CAD. More importantly, acute improvement of EECP in the FR of the brachial artery was showed in males, while the FR and RI of the carotid arteries changed in females.

Keywords: enhanced external counterpulsation, carotid arteries, peripheral hemodynamics, coronary artery disease, acute response

INTRODUCTION

Enhanced external counterpulsation is a non-invasive treatment for patients with stable coronary artery disease (CAD), who are not amenable to standard revascularization procedures, such as percutaneous coronary intervention (1, 2). Several studies have demonstrated that enhanced external counterpulsation (EECP) alleviates symptoms of angina and reduces myocardial ischemia (3, 4). Enhanced external counterpulsation also significantly increased myocardial perfusion and coronary collateral flow in patients with CAD (5, 6). In addition, EECP has been previously shown to increase coronary artery flow velocity (7). However, little is known about whether it can affect vascular and blood flow characteristic variables in conduit arteries such as the carotid and those of the limbs, as the pathogenesis and progression of CAD are influenced not only by the behavior of the coronary arteries but also by other more peripheral systemic vessels (8).

These alterations of peripheral vascular and blood flow characteristics play a key role in the modulation of central arterial function, cardiac load, and myocardial perfusion (9). For instance, lower peak systolic velocity (PSV), higher resistance index (RI), and lower end-diastolic velocity (EDV) in the common carotid artery (CCA) are related to adverse cardiovascular events (10–12). Studies showed that the left and right CCA may exhibit different prognostic values in the investigated population (13, 14). Due to the different anatomical origins of the left and the right CCA, it was speculated that hemodynamics would have different effects depending on whether the left carotid (LC) or right carotid (RC) artery was considered (15). Brachial artery blood flow velocities are associated with carotid atherosclerosis (16). More importantly, the presence of atherosclerotic plaques and altered vascular function in the aorta, femoral, and carotid arteries are strong predictors of CAD (17).

Nevertheless, there have been few studies on the effects of EECP on conduit artery vascular and blood flow characteristics, and the controversy remains even in patients with CAD. It has been reported that EECP can increase the peak limb blood flow and improve the endothelium-dependent vasodilation in the resistance arteries (18). A similar improvement has been shown in the femoral and brachial arteries (19). Enhanced external counterpulsation can also reduce carotid vascular resistance (9). Whereas, others have found that EECP does not affect the central and peripheral arterial stiffness (20). It has also been reported that the cerebral mean flow velocities increased in patients with stroke during EECP, while it remained unchanged in the elderly controls (21).

Given the controversial reports of the effects of EECP on systemic circulation, this study aimed to investigate the acute effects of EECP on the vascular and blood flow characteristics in the carotid, brachial, and femoral arteries in patients with CAD. Meanwhile, to further explore the mechanisms of these effects, we also aimed to compare the responses to those of the controls at the baseline, during, and immediately after 45 min-EECP.

MATERIALS AND METHODS

Participants

We enrolled patients with CAD to EECP treatment, diagnosed by angiographically proven stenosis ≥50% in at least one major coronary artery. They were admitted to the Department of Cardiovascular Medicine of the Eighth Affiliated Hospital of Sun Yat-sen University. The exclusion criteria were contraindications for EECP, including uncontrolled hypertension (SBP ≥180 mmHg and/or DBP ≥100 mmHg), carotid dissection, and deep vein thrombosis at lower extremities. In addition, we recruited healthy people as the control through the Health Examination Center of the Eighth Affiliated Hospital of Sun Yat-sen University. After explaining the purpose of this study and the potential risks, all the participants provided written informed consent. This study was conducted in accordance with the Declaration of Helsinki and was approved by the medical ethics committee of the Eighth Affiliated Hospital of Sun Yat-sen University.

Procedures

All participants received a single, 45-min session of EECP treatment. They lay supine on the EECP treatment bed with their legs and buttocks wrapped in cuffs, which were sequentially inflated from the lower to the upper thigh and buttocks at the beginning of the diastolic phase, followed by a quick, simultaneous deflation of all the cuffs just before the onset of systole. The EECP was conducted using an Oxygen Saturation Monitoring Enhanced External Counterpulsation Instrument (PSK P-ECP/TM, Chongqing, China). The pressure generated by the device was 0.028–0.033 MPa (212.8–250.8 mmHg).

Measurement of Peripheral Vascular and Blood Flow Characteristics

A Color Doppler Ultrasound (GE logic E) examination was performed 10 min before the start of the EECP at 15–25 min after its start and 30 s−1 min immediately after the end of the session. The measurement time for each part was about 2 min and the measurements were performed in the order: RC, LC, right brachial (RB), and right femoral (RF) arteries (19, 22). The

right and left CCAs were scanned 1.5 cm proximal to the internal-external carotid bifurcation. The RB and RF measurement sites were fixed approximately 5 cm above the antecubital fossa and 2 cm below the inguinal ligament, respectively. The RF artery was not measured during the EECP because the legs and buttocks on this side were wrapped in the cuffs.

Variables Calculation

The variables, PSV, RI, peak diastolic velocity (VD), PSV/VD (VS/VD), and velocity-time integral (VTI) in the CCAs were continuously recorded for 10 s and then were tracked and calculated.

The mean inner diameters (ID) of all the arteries were calculated as

$$\bar{ID} = (ID_{dia} + ID_{sys})/2, \quad (1)$$

where ID_{sys} and ID_{dia} are the systolic and diastolic diameters, respectively.

The *RI* was analyzed only in the carotid arteries because, as a measure of cerebral resistance, it is closely associated with cardiovascular risk. It was calculated as

$$RI = (V_{peak} - V_{end-dia})/V_{peak}, \quad (2)$$

where V_{peak} is the PSV and $V_{end-dia}$ is the EDV.

The mean flow rate (FR) was calculated from the vessel diameter, cardiac period, and velocity-time integral as

$$\bar{FR} = (\frac{1}{4}\pi(\bar{ID}) \times VTI)/t \quad (3)$$

where VTI is the averaged velocity-time integral, and t is the averaged cardiac cycle time.

Statistical Analysis

The results are expressed as means ± SE. The normal distribution for all the vascular and blood flow characteristic variables was evaluated by a Kolmogorov–Smirnov test. The basic characteristics of the two groups were compared by an independent *t*-test. A Chi-square test was also used for the analysis of the gender and risk factors in the two groups. The dependent variables before, during, and after the 45-min EECP, and between the patients with CAD and controls were analyzed by two repeated measures-ANOVA. Gender was regarded as a covariate in the two-way ANOVA of the inter and intra groups. In addition, the hemodynamic variables in each artery were also performed by subgroup analysis of gender. The *post hoc* analysis was conducted using Fisher's least significant difference. The software SPSS version 20.0 (IBM SPSS Statistics, Armonk, New York, United States) was used for all the statistical tests, and $P < 0.05$ was taken as a measure of statistical significance.

RESULTS

The basic information of the two groups is listed are **Table 1**. There were 42 patients with CAD and 21 healthy controls in the study. There were no significant differences between them in number, age, height, weight, and body mass index (BMI) ($p > 0.05$), while significant differences appeared in gender and risk factors in this study ($P < 0.05$).

TABLE 1 | Base information and major cardiovascular risk factors in the two groups.

Variables	CAD	Control	*P*-value
Number	42	21	
Age (year)	57.52 ± 9.24	53.95 ± 8.44	0.142
Female (percentage/*n*)	33.3 (14)	66.67 (14)	0.012
Height (cm)	164.90 ± 8.37	161.25 ± 9.47	0.129
Weight (kg)	69.21 ± 11.60	65.30 ± 13.31	0.234
BMI (kg/m^2)	25.34 ± 2.95	24.36 ± 3.08	0.245
Hypertension (percentage/*n*)	64.29 (27)	0(0)	0.000
Hyperlipidemia (percentage/*n*)	47.62 (20)	0(0)	0.000
Hyperglycemia (percentage/*n*)	40.48 (17)	0(0)	0.000
Smoking (percentage/*n*)	28.57 (12)	0(0)	0.000

The ultrasound picture and Doppler spectrum of carotid and brachial arteries during EECP are presented in **Figures 1**, **2**, respectively. The effect of EECP on the measured variables varied in each artery as did the differences between the patients with CAD and controls are illustrated in **Figures 3**–**7**. In addition, the significant differences in the hemodynamic parameters in females and males of both groups were analyzed by subgroup analysis. These results are shown in **Table 2**.

Mean ID

During EECP, the ID of the LC was significantly increased compared with the baseline in the patients with CAD ($P = 0.013$, **Figure 3B**). Immediately after EECP, the ID of the LC, RB, and RF was significantly higher than that at the baseline (all $P < 0.05$) in the patients with CAD. In addition, the ID of the patients with CAD in the carotid, brachial and femoral arteries was also higher than that in the control groups (all $P < 0.05$, **Figure 3**). However, there was no significant difference in the ID of the controls during and immediately after EECP (all $P > 0.05$).

PSV

The PSV of the LC was significantly reduced during ($P = 0.015$) and after EECP ($P = 0.005$) compared with the baseline in the patients with CAD. However, in the control group, the PSV in the RC and RB was significantly decreased after and during EECP, respectively. These results are illustrated in **Figure 4**. Based on the subgroup analysis of gender, there was a different pattern in the PSV of the LC and RB between males and females immediately after EECP (both $P < 0.05$, **Table 2**).

EDV

The EDV in the CCAs significantly decreased in the two groups during EECP, and then markedly increased following the 45 min-EECP (all $P < 0.01$, **Figure 5**). Additionally, during EECP, the EDV of the RC was lower in the patients with CAD than in the controls ($P = 0.000$, **Figure 5A**). The EDV in the RB was significantly reduced compared with the baseline only in the

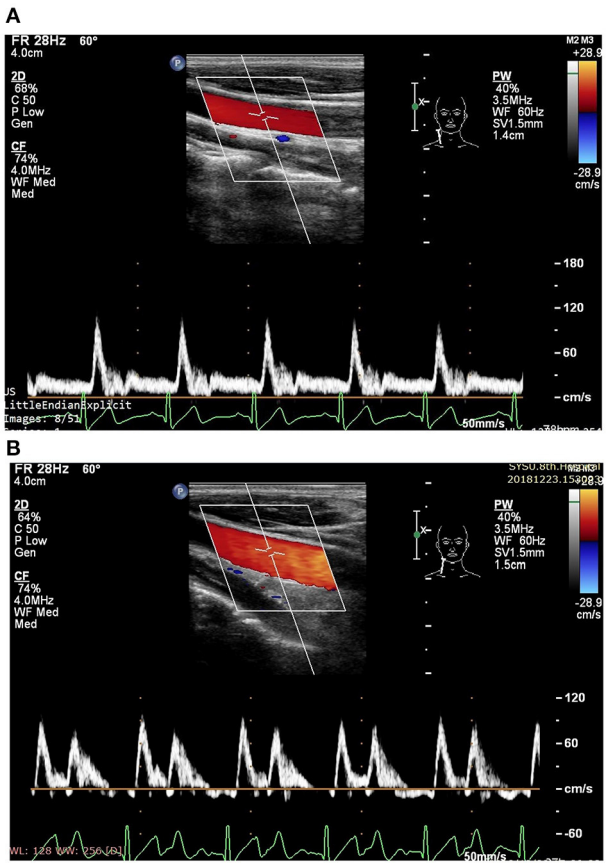


FIGURE 1 | Measurement of blood flow velocity spectrum in the right common carotid artery (CCA) [**A** before enhanced external counterpulsation (EECP) and **B** during EECP].

FIGURE 2 | Measurement of blood flow velocity spectrum in the right brachial (RB) artery (**A** before EECP and **B** during EECP).

patients with CAD ($P = 0.000$, **Figure 5C**). However, there was no significant difference in the EDV of the RF immediately after EECP in the two groups ($P > 0.05$, **Figure 5D**).

RI

In the carotid arteries, there was a significant increase in the RI during EECP both in the patients and controls (**Figure 6**). However, in the RC, the effect was maintained when measured at the end of the treatment period only in the patients with CAD ($P = 0.039$, **Figure 6A**). Moreover, the baseline values of the patients were not significantly higher than those of the controls but differ in the RC during ($P = 0.002$) and immediately after EECP ($P = 0.036$, **Figure 6A**). Furthermore, by the subgroup analysis of gender, the RI in the RC was significantly lower immediately after EECP compared with the baseline only in females with CAD (0.703 ± 0.016 vs. 0.731 ± 0.014, $P = 0.002$, **Table 2**), while the same change in the RI of the LC was shown only in healthy men (0.723 ± 0.013 vs. 0.682 ± 0.009, $P = 0.044$, **Table 2**).

Mean FR

The FR of the LC was significantly increased during EECP, and then markedly recovered to the baseline in the patients with CAD (both $P < 0.01$, **Figure 7B**). It led to a significant difference in the FR between the patients with CAD and controls during EECP ($P = 0.029$). The FR in the RC was significantly reduced immediately after EECP compared with during EECP only in the controls. Contralaterally, the FR in the RB was markedly higher immediately after EECP than that during EECP in both groups (all $P < 0.01$, **Figure 7C**). By the subgroup analysis, the FR of the LC was markedly elevated during EECP in the females with CAD (879.522 ± 60.419 vs. 779.718 ± 50.483, $P = 0.021$). By contrast, the FR of the RB was significantly increased in the healthy males and those with CAD during and immediately after EECP (all $P < 0.05$, **Table 2**).

DISCUSSION

This study was designed to investigate the responses of the carotid and peripheral artery vascular and blood flow characteristics to EECP, both during and after a 45 min-session EECP. During EECP, there were different responses of ID, PSV, and FR in the CCAs and RB. Additionally, immediately after EECP, the ID of the LC, RB, and RF was significantly higher, while the PSV of the LC and the RI of the RC were significantly lower than those at the baseline only in the patients with CAD.

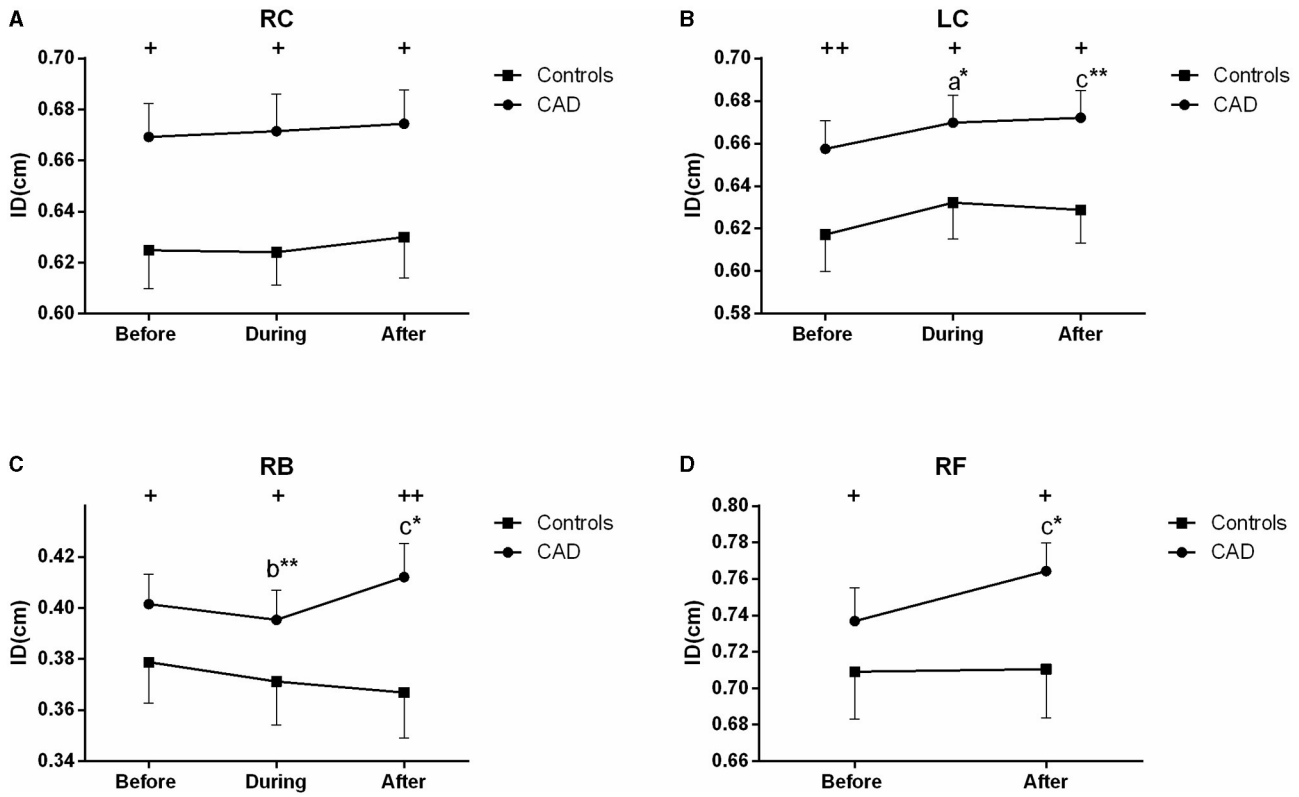


FIGURE 3 | Effect of EECP on the mean inner diameters (ID) of the left and right carotid artery (RC/LC) **(A,B)**, RB **(C)**, and right femoral (RF) artery **(D)** in the patients with coronary artery disease (CAD) and controls before, during, and after a 45 min-EECP. a indicates significant differences in measurements obtained during EECP vs. pre-EECP; b indicates differences between post-EECP vs. during-EECP, and c refers to comparisons between post-EECP vs. pre-EECP. "*" and "**" denote $p <$ 0.5 and < 0.01 respectively. "+" and "++" denote p-values of the difference between groups < 0.5 and < 0.01, respectively.

Moreover, the RI and FR of the carotid arteries were changed in females, while a significant difference in the FR of the RB was shown in males.

In this study, a significant effect on the ID in the LC was observed in the patients with CAD. Additionally, immediately after EECP, the ID of the carotid and peripheral arteries was significantly higher than that at the baseline only in the patients with CAD. Importantly, they were also higher than those in the control groups. Previous large-scale studies have reported that carotid artery response is closely associated with coronary heart disease (23, 24). In addition, a study supported the present findings that EECP had arterial effects on large and small vessels of the carotid circulation in patients with CAD (9). One possible mechanism is by decreasing arterial pressure (25), the other mechanism is EECP, as well as physical training, may also activate the catecholamines and/or metabolic vasodilator pathways (9). A study also demonstrated that femoral artery diameter and vascular shear stress were significantly increased after supervised exercise training (26). Studies have also shown that changes in shear rate led by femoral artery vascular tone elicit an increased femoral baseline diameter after EECP intervention (19). More importantly, studies have demonstrated that endothelial functional changes induced by the shear rate in the peripheral circulations were modestly correlated with changes in the coronary flow reserve (27). The acute increase of ID in the patients with CAD may be related to the effects of peripheral function on the coronary circulation in this study (28).

There were some controversies in the changes of ID in the RB and RF during and immediately after EECP. Zhang et al. found that EECP did not cause an increase in the internal diameter of the RB (29). Gurovich et al. reported that peak diameter was also not increased, while absolute change (mm) of the brachial and femoral arteries significantly increased immediately after EECP (19). They found that the change of the brachial artery diameter affected the improvement of the brachial flow-mediated dilation (FMD), which was closely related to an increase in the brachial artery shear stress (19). Studies have suggested that both flow- and pressure-induced forces played an important role in vessel wall diameter (30–32). Inflation of the EECP cuffs can produce high-pressure retrograde blood flow in the femoral arteries and simultaneous moderate-pressure antegrade flow in the brachial arteries (29, 33). The brachial blood flow velocity in the diastole increased by 132% and led to the increase of the brachial artery wall shear stress (29). Cai et al. observed a 1.2-fold increase in femoral artery retrograde blood flow velocity (34). In this study, the PSV of the patients with CAD was significantly reduced during and after EECP compared with the baseline. In addition, the PSV of the RB and EDV of the carotid and peripheral arteries also significantly decreased in the patients with CAD.

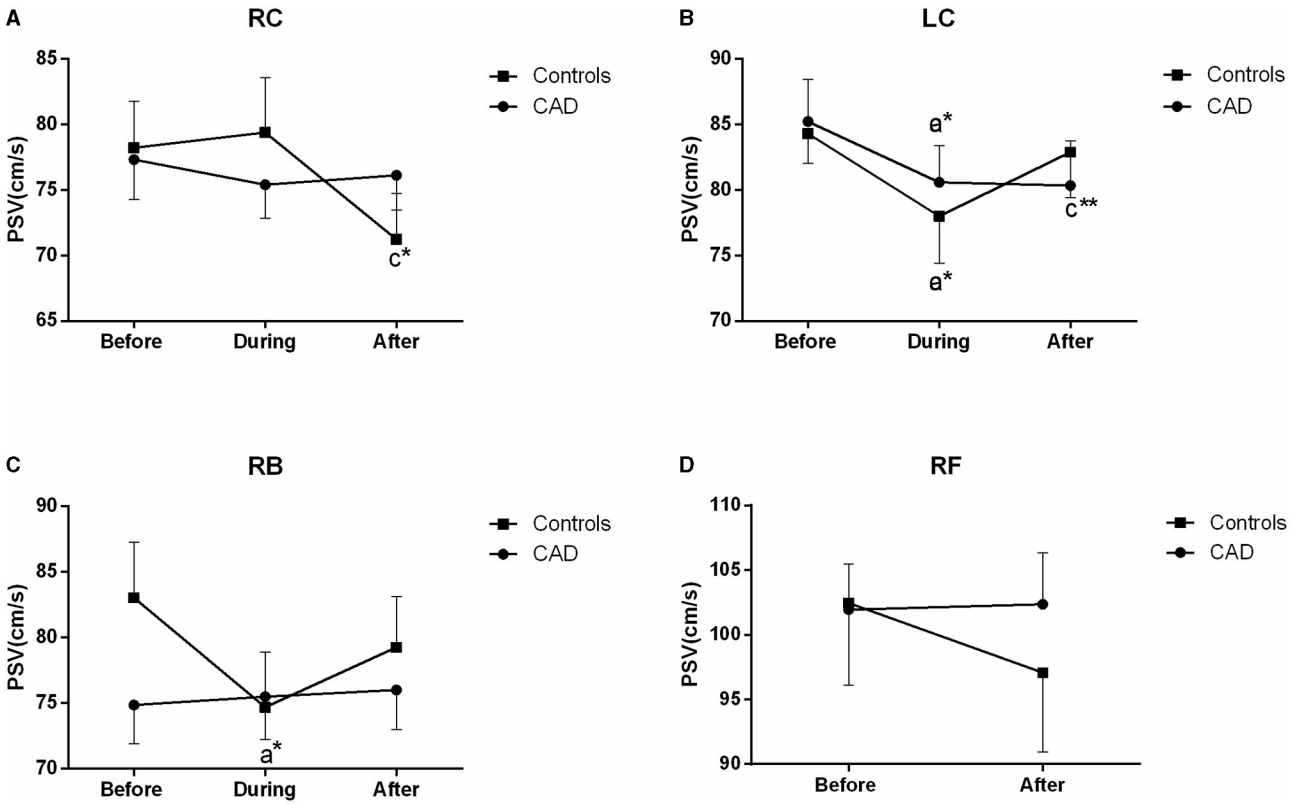


FIGURE 4 | Effect of EECP on the peak systolic velocity (PSV) of the RC and LC **(A,B)**, RB **(C)**, and RF **(D)** in the patients with CAD and controls before, during, and after a 45 min-EECP. a indicates significant differences in measurements obtained during EECPvs. pre-EECP; c refers to comparisons between post-EECP vs. pre-EECP. * and ** denote $p < 0.5$ and < 0.01 respectively.

TABLE 2 | Significant differences of the hemodynamic variables for the patients with CAD and controls by subgroup analysis.

CAD		**Female ($n = 14$)**			**Male ($n = 28$)**		
Artery	**Variable**	***Before***	***During***	***After***	***Before***	***During***	***After***
RC	RI	0.731 ± 0.014*	0.798 ± 0.023**	0.703 ± 0.016**	0.740 ± 0.010**	0.915 ± 0.017**	0.732 ± 0.010
LC	PSV (cm/s)	89.285 ± 4.446**	83.541 ± 4.060	86.018 ± 5.565	83.170 ± 4.243	79.083 ± 3.722	77.490 ± 4.217**
	FR (ml/min)	779.718 ± 50.483*	879.522 ± 60.419	824.476 ± 57.001	756.306 ± 34.921	790.222 ± 43.359	747.223 ± 33.274
RB	PSV (cm/s)	76.444 ± 6.871	71.140 ± 6.978*	81.191 ± 7.256	74.062 ± 2.838	77.663 ± 3.456	73.416 ± 2.736
	FR (ml/min)	138.667 ± 18.659	136.900 ± 26.098	165.519 ± 24.443	152.599 ± 12.840	140.961 ± 12.700*	162.473 ± 16.322
Control		**Female ($n = 14$)**			**Male ($n = 7$)**		
Artery	**Variable**	***Before***	***During***	***After***	***Before***	***During***	***After***
RB	FR (ml/min)	129.891 ± 11.601	100.755 ± 9.515	101.260 ± 11.246	179.977 ± 21.346	184.630 ± 18.061*	263.706 ± 21.276*
LC	RI	0.696 ± 0.007**	0.854 ± 0.030**	0.683 ± 0.014	0.682 ± 0.009*	0.887 ± 0.064*	0.723 ± 0.013*

*RC, LC, RB, and RF are the right carotid, left carotid, brachial and femoral arteries, respectively. PSV, peak systolic velocity; ID, mean inner diameter; FR, mean flow rate; EDV, end-diastolic velocity; RI, resistance index. * and ** denote p < 0.5 and < 0.01 respectively.*

Although few studies have focused on blood flow velocity during EECP, the use of an intra-aortic balloon pump, which has some similar mechanisms of action to EECP, induced a decrease of carotid PSV, and an increase in mean blood flow velocity (35) which supports the findings that cerebral flow velocity in the systole is significantly decreased during EECP both in the patients and controls (36). This was attributed to the decreased systolic blood pressure and enhanced cerebral vascular autoregulation (36). Furthermore, decreased systolic blood pressure reduces cardiac afterload after deflation, resulting

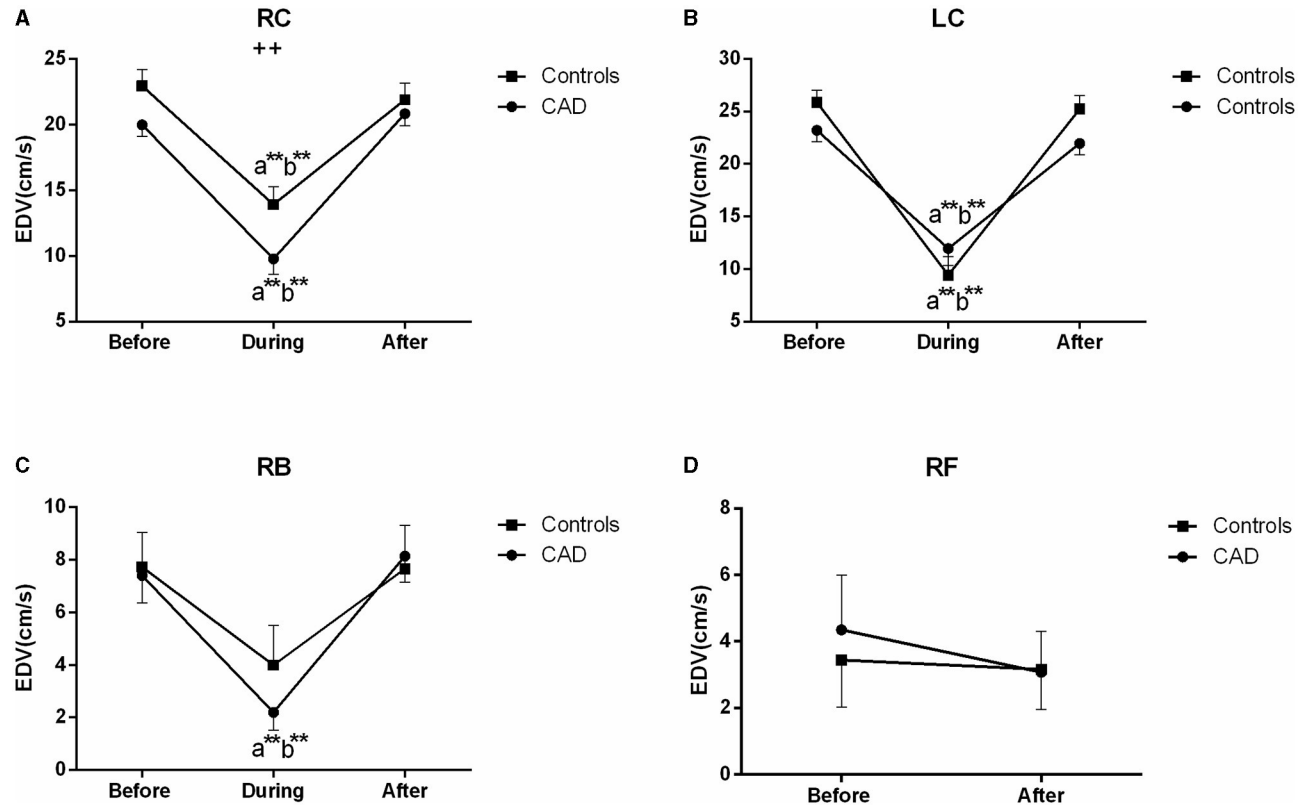


FIGURE 5 | Effect of EECP on the end-diastolic velocity (EDV) of RC and LC **(A,B)**, RB **(C)**, and RF **(D)** in the patients with CAD and controls before, during, and after a 45 min-EECP. a indicates significant differences in measurements obtained during EECP vs. pre-EECP; b indicates differences between post-EECP vs. during-EECP. ** and $^{++}$ denote p-values < 0.01 of the difference between groups.

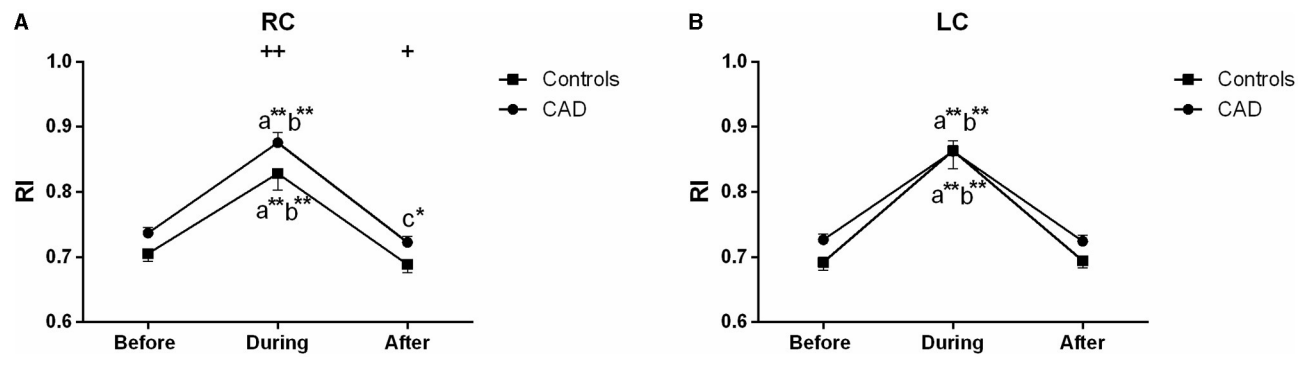


FIGURE 6 | Effect of EECP on the resistance index (RI) of RC **(A)** and LC **(B)** in the patients with CAD and controls before, during, and after a 45 min-EECP. a indicates significant differences in measurements obtained during EECP vs. pre-EECP; b indicates differences between post-EECP vs. during-EECP, and c refers to comparisons between post-EECP vs. pre-EECP. * and ** denote $p < 0.5$ and < 0.01 respectively. $^{+}$ and $^{++}$ denote p-values of the difference between groups < 0.5 and < 0.01, respectively.

in decreased PSV. Immediately after EECP, there was no significant difference in the systolic flow velocity in both the patients and controls (36). By contrast, we found that the PSV and EDV of the LC and the RI of the RC were significantly lower than those at the baseline immediately after EECP. Some studies consisted of our findings that EECP increased the cerebral peak velocity in diastole both in the patients and controls (21, 36). It has been shown that improved carotid flow following EECP is associated with decreased arterial stiffness and resistance, dependent upon arterial pressure, modulation of smooth muscle activity, and shear stress (9). More importantly, other investigations suggested that a better coronary vasodilatory response was associated with well-functioning endothelium and blood flow velocity (28).

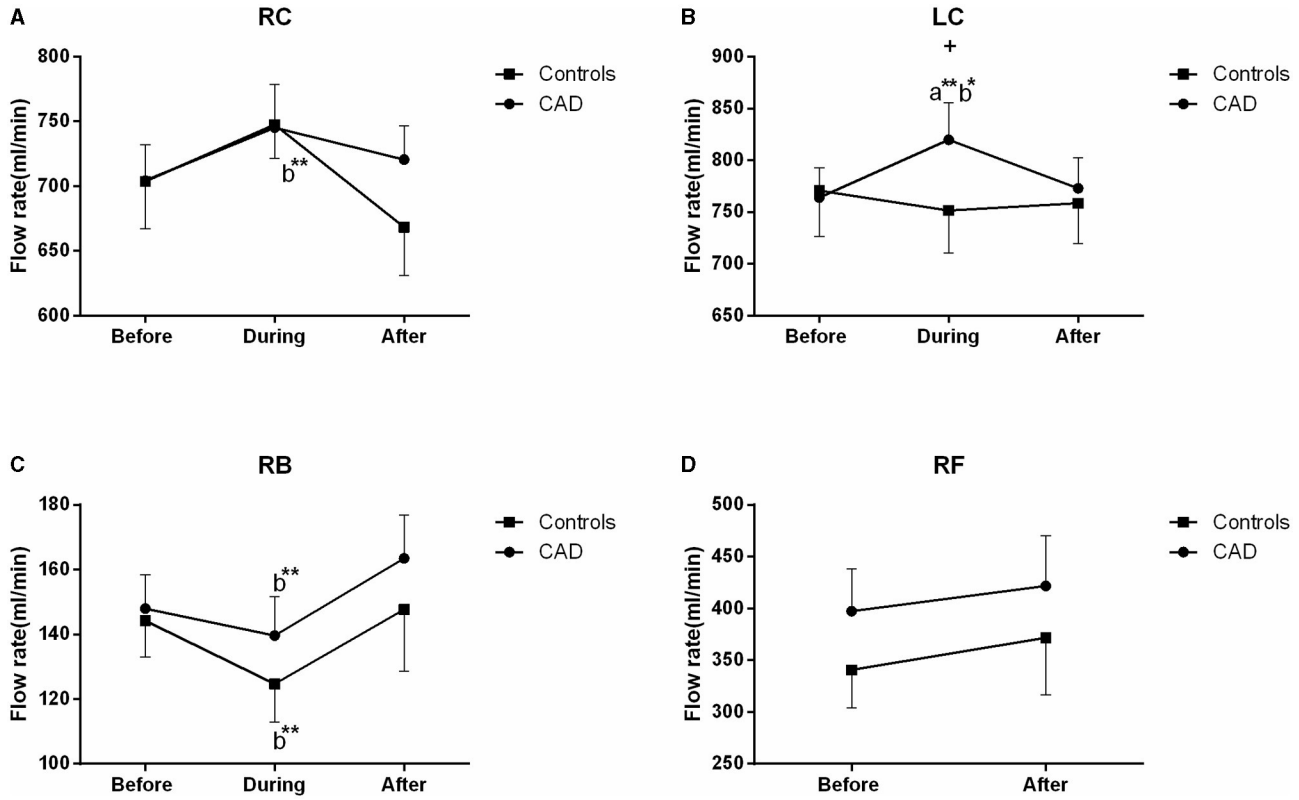


FIGURE 7 | Effect of EECP on the flow rate (FR) of RC and LC **(A,B)**, RB **(C)**, and RF **(D)** in the patients with CAD and controls before, during, and after a 45 min-EECP. a indicates significant differences in measurements obtained during EECP vs. pre-EECP; b indicates differences between post-EECP vs. during-EECP. * and ** denote $p < 0.5$ and < 0.01 respectively. $^{+}$ denotes p-values of the difference between groups < 0.5.

Some studies have found that blood flow velocity is a parameter related to the arterial diameter, RI, and blood flow (37). More importantly, studies also reported that the regulation of steady blood flow is associated with carotid diameters and blood flow velocity (38). In the present study, there were different responses from the vascular and blood flow characteristics in the CCAs and RB during and immediately after EECP. The FR of the LC was significantly increased during EECP in the patients with CAD. It led to a significant difference in the FR between the patients with CAD and controls during EECP. The FR in the RC was significantly reduced immediately after EECP compared with during EECP only in the controls. Contralaterally, the FR in the RB was markedly higher immediately after EECP than during EECP in both groups. There were some controversial results in the FR during and immediately after EECP. Levenson et al. (9) found that in patients with CAD, the mean carotid blood flow was significantly increased during EECP. Lin et al. found that the cerebral blood flow of patients with ischemic stroke increased during EECP, but there was no change in the elderly subjects (21). Werner et al. found that EECP induced an augmentation in the cerebral blood flow both in the patients and controls (36). Cerebral autoregulation plays an important role in guaranteeing the constancy of cerebral perfusion during EECP (39). The increased FR in the RB after EECP may be related to the increase of the brachial artery wall shear stress (29).

We also found that the FR in the LC was higher than in the RC during and after the 45 min-EECP. This result was consistent with previous findings that the prognostic power of the altered vascular and blood flow characteristics for cardiovascular events is greater in the right CCA than the left (13, 14). Furthermore, the FR of the LC was markedly elevated during EECP in females with CAD. By contrast, the FR in the RB was significantly increased in healthy males and those with CAD during and immediately after EECP. Studies found that cardiovascular function during exercise is also affected by gender (40, 41). Meanwhile, the blood pressure and total peripheral resistance during exercise are higher in women than in men. They thought that the vasodilatory capacity of active muscle groups plays an important role in the cardiovascular differences between women and men (42).

In the study, the RI of the RC was also significantly lower immediately after EECP compared with the baseline only in females with CAD. The decrease of the RI which is strongly associated with cerebrovascular resistance can predict the degree of atherosclerosis and is also beneficial to the increase of blood flow (42, 43). Although the RI significantly increased during EECP, it recovered quickly after the treatment stopped. More importantly, the RI of the right CCA was lower after treatment than the pre-EECP values in the patients with CAD. Our results support those of a previous study that short-term EECP reduces the β-stiffness index and carotid vascular resistance

in patients with CAD (9). In addition, studies reported that EECP can reduce distal brain resistance and increase cerebral perfusion (21). It suggests that the benefits of EECP may be attributable to the global improvement of cerebral perfusion (44). Moreover, cerebral autoregulation confirms the constancy of cerebral blood flow under fluctuant cerebral perfusion pressure (39). Furthermore, decreased RI elevates peripheral vascular function, which may, in turn, induce an improvement of the diastolic flow pattern in the coronary arteries (45). Indeed, reduced RI is an important reason for the improvement of carotid hemodynamics in patients with CAD.

Limitations

Some limitations of the present study should be emphasized. Firstly, the sample size was relatively small. Secondly, the order of the measurements after the EECP was femoral, brachial, RC, and LC artery to firstly observe the blood flow from the legs which was directly pressurized during and after EECP. Therefore, at the end of the treatment, the recovery time was minimal for the femoral and increased by 30 s−1 min for each subsequent measurement site. Thirdly, we did not continuously measure these arteries at 1–2 min after EECP. Further study is needed to investigate the duration of the effect on these muscular arteries.

CONCLUSIONS

Enhanced external counterpulsation creates different acute responses from the inner diameters, blood flow velocity, and FR between the carotid and peripheral arteries, with more obvious effects in both carotid arteries. Additionally, after the 45-min EECP, the more sustained effects in the inner diameters, RI, blood flow velocity, and FR were shown only in the patients with CAD. Moreover, an acute improvement brought by EECP to the FR of the brachial artery and blood flow velocity of the carotid artery showed in men, while the FR and RI of carotid arteries changed in females. This indicated that EECP should be conducted with different counterpulsation modes, separately intervening carotid arteries and peripheral arteries. More importantly, these findings suggest that EECP can regulate the vascular and blood flow characteristics of conduit arteries, and further improve the carotid and peripheral function in patients with CAD.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethics Committee of the Eighth Affiliated Hospital of Sun Yat-sen University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YZ and GW proposed the scientific problems. YZ, GW, and JD designed the experiments. YZ, ZM, ZC, WZ, and HW collected the experimental data. YZ and XZ processed and calculated the data. YZ conducted the statistical analysis and wrote the draft manuscript. WW and GW contributed to the revision and final version of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was, in part, supported by the National Natural Science Foundation of China (Grant No. 819770367 and 81670417) and the National Key Research and Development Program of China (No. 2020YFC2004400).

REFERENCES

1. Bonetti PO, Holmes DR, Lerman A, Barsness GW. Enhanced external counterpulsation for ischemic heart disease. *J Am Coll Cardiol.* (2003) 41:1918–25. doi: 10.1016/S0735-1097(03)00428-5
2. Members TF, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J.* (2013) 34:2949–3003. doi: 10.1093/eurheartj/eht296
3. Lawson WE, Hui JC, Soroff HS, Zheng ZS, Kayden DS, Sasvary D, et al. Efficacy of enhanced external counterpulsation in the treatment of angina pectoris. *Am J Cardiol.* (1992) 70:859–62. doi: 10.1016/0002-9149(92)90727-G
4. Kim MC, Kini A, Sharma SK. Refractory angina pectoris: mechanism and therapeutic options. *J Am Coll Cardiol.* (2002) 39:923–34. doi: 10.1016/S0735-1097(02)01716-3
5. Masuda D, Nohara R, Hirai T, Kataoka K, Chen L, Hosokawa R, et al. Enhanced external counterpulsation improved myocardial perfusion and coronary flow reserve in patients with chronic stable angina. Evaluation by13N-ammonia positron emission tomography. *Eur Heart J.* (2001) 22:1451–8. doi: 10.1053/euhj.2000.2545
6. Gloekler S, Meier P, de Marchi SF, Rutz T, Traupe T, Rimoldi SF, et al. Coronary collateral growth by external counterpulsation: a randomised controlled trial. *Heart.* (2010) 96:202–7. doi: 10.1136/hrt.2009.184507
7. Michaels AD, Accad M, Ports TA, Grossman W. Left ventricular systolic unloading and augmentation of intracoronary pressure and doppler flow during enhanced external counterpulsation. *Circulation.* (2002) 106:1237–42. doi: 10.1161/01.CIR.0000028336.95629.B0
8. Hirai T, Sasayama S, Kawasaki T, Yagi S. Stiffness of systemic arteries in patients with myocardial infarction. A noninvasive method to predict severity of coronary atherosclerosis. *Circulation.* (1989) 80:78–86. doi: 10.1161/01.CIR.80.1.78
9. Levenson J, Simon A, Megnien JL, Chironi G, Gariepy J, Pernollet MG, et al. Effects of enhanced external counterpulsation on carotid circulation in patients with coronary artery disease. *Cardiology.* (2007) 108:104–10. doi: 10.1159/000095949
10. Bai CH, Chen JR, Chiu HC, Pan WH. Lower blood flow velocity, higher resistance index, and larger diameter of extracranial carotid arteries are associated with ischemic stroke independently of carotid atherosclerosis and cardiovascular risk factors. *J Clin Ultrasound.* (2007) 35:322–30. doi: 10.1002/jcu.20351

11. Ozari HO, Oktenli C, Celik S, Tangi F, Ipcioglu O, Terekeci HM, et al. Are increased carotid artery pulsatility and resistance indexes early signs of vascular abnormalities in young obese males? *J Clin Ultrasound.* (2012) 40:335–40. doi: 10.1002/jcu.21927
12. Chuang SY, Bai CH, Cheng HM, Chen JR, Yeh WT, Hsu PF, et al. Common carotid artery end-diastolic velocity is independently associated with future cardiovascular events. *Eur J Prev Cardiol.* (2016) 23:116–24. doi: 10.1177/2047487315571888
13. Lee SW, Hai JJ, Kong SL, Lam YM, Lam S, Chan PH, et al. Side differences of carotid intima-media thickness in predicting cardiovascular events among patients with coronary artery disease. *Angiology.* (2011) 62:231–6. doi: 10.1177/0003319710379109
14. Loizou CP, Nicolaides A, Kyriacou E, Georghiou N, Griffin M, Pattichis CS. A comparison of ultrasound intima-media thickness measurements of the left and right common carotid artery. *IEEE J Transl Eng Health Med.* (2015) 3:1900410. doi: 10.1109/JTEHM.2015.2450735
15. Luo X, Yang Y, Cao T, Li Z. Differences in left and right carotid intima-media thickness and the associated risk factors. *Clin Radiol.* (2011) 66:393–8. doi: 10.1016/j.crad.2010.12.002
16. Jarhult SJ, Sundstrom J, Lind L. Brachial artery hyperemic blood flow velocities are related to carotid atherosclerosis. *Clin Physiol Funct I.* (2009) 29:360–5. doi: 10.1111/j.1475-097X.2009.00879.x
17. Khoury Z, Schwartz R, Gottlieb S, Chenzbraun A, Stern S, Keren A. Relation of coronary artery disease to atherosclerotic disease in the aorta, carotid, and femoral arteries evaluated by ultrasound. *Am J Cardiol.* (1997) 80:1429–33. doi: 10.1016/S0002-9149(97)00701-7
18. Avery JC, Beck DT, Casey DP, Sardina PD, Braith RW. Enhanced external counterpulsation improves peripheral resistance artery blood flow in patients with coronary artery disease. *Appl Physiol Nutr Metab.* (2014) 39:405–8. doi: 10.1139/apnm-2013-0309
19. Gurovich AN, Braith RW. Enhanced external counterpulsation creates acute blood flow patterns responsible for improved flow-mediated dilation in humans. *Hypertens Res.* (2013) 36:297–305. doi: 10.1038/hr.2012.169
20. Dockery F, Rajkumar C, Bulpitt CJ, Hall RJ, Bagger JP. Enhanced external counterpulsation does not alter arterial stiffness in patients with angina. *Clin Cardiol.* (2004) 27:689–92. doi: 10.1002/clc.4960271206
21. Lin W, Xiong L, Han J, Leung TW, Soo YO, Chen X, et al. External counterpulsation augments blood pressure and cerebral flow velocities in ischemic stroke patients with cerebral intracranial large artery occlusive disease. *Stroke.* (2012) 43:3007–11. doi: 10.1161/STROKEAHA.112.659144
22. Zheng ZS, Li TM, Kambic H, Chen GH, Yu LQ, Cai SR, et al. Sequential external counterpulsation (SECP) in China. *Trans Am Soc Artif Intern Organs.* (1983) 29:599–603.
23. Kallikazaros I, Tsioufis C, Sideris S, Stefanadis C, Toutouzas P. Carotid artery disease as a marker for the presence of severe coronary artery disease in patients evaluated for chest pain. *Stroke.* (1999) 30:1002–7. doi: 10.1161/01.STR.30.5.1002
24. Sedaghat S, van Sloten TT, Laurent S, London GM, Pannier B, Kavousi M, et al. Common carotid artery diameter and risk of cardiovascular events and mortality: pooled analyses of four cohort studies. *Hypertension.* (2018) 72:85–92. doi: 10.1161/HYPERTENSIONAHA.118.11253
25. Armentano R, Simon A, Levenson J, Chau NP, Megnien JL, Pichel R. Mechanical pressure versus intrinsic effects of hypertension on large arteries in humans. *Hypertension.* (1991) 18:657–64. doi: 10.1161/01.HYP.18.5.657
26. Dopheide JF, Rubrech J, Trumpp A, Geissler P, Zeller GC, Schnorbus B, et al. Supervised exercise training in peripheral arterial disease increases vascular shear stress and profunda femoral artery diameter. *Eur J Prev Cardiol.* (2017) 24:178–91. doi: 10.1177/2047487316665231
27. Hägg U, Wandt B, Bergström G, Volkmann R, Gan LM. Physical exercise capacity is associated with coronary and peripheral vascular function in healthy young adults. *Am J Physiol Heart Circ Physiol.* (2005) 289:H1627–34. doi: 10.1152/ajpheart.00135.2005
28. Al-Badri A, Kim JH, Liu C, Mehta PK, Quyyumi AA. Peripheral microvascular function reflects coronary vascular function. *Arterioscler Thromb Vasc Biol.* (2019) 39:1492–500. doi: 10.1161/ATVBAHA.119.312378
29. Zhang Y, He X, Chen X, Ma H, Liu D, Luo J, et al. Enhanced external counterpulsation inhibits intimal hyperplasia by modifying shear stress responsive gene expression in hypercholesterolemic pigs. *Circulation.* (2007) 116:526–34. doi: 10.1161/CIRCULATIONAHA.106.647248
30. Helisch A, Schaper W. Arteriogenesis: the development and growth of collateral arteries. *Microcirculation.* (2003) 10:83–97. doi: 10.1080/mic.10.1.83.97
31. Heil M, Schaper W. Influence of mechanical, cellular, and molecular factors on collateral artery growth (arteriogenesis). *Circ Res.* (2004) 95:449–58. doi: 10.1161/01.RES.0000141145.78900.44
32. Schaper W, Scholz D. Factors regulating arteriogenesis. *Arterioscler Thromb Vasc Biol.* (2003) 23:1143–51. doi: 10.1161/01.ATV.0000069625.11230.96
33. Ozawa ET, Bottom KE, Xiao X, Kamm RD. Numerical simulation of enhanced external counterpulsation. *Ann Biomed Eng.* (2001) 29:284–97. doi: 10.1114/1.1359448
34. Cai D, Wu R, Shao Y. Experimental study of the effect of external counterpulsation on blood circulation in the lower extremities. *Clin Invest Med.* (2000) 23:239–47. doi: 10.1038/sj.cgt.7700222
35. Applebaum RM, Wun HH, Katz ES, Tunick PA, Kronzon I. Effects of intraaortic balloon counterpulsation on carotid artery blood flow. *Am Heart J.* (1998) 135(Pt. 1):850–4. doi: 10.1016/S0002-8703(98)70045-6
36. Werner D, Marthol H, Brown CM, Daniel WG, Hilz MJ. Changes of cerebral blood flow velocities during enhanced external counterpulsation. *Acta Neurol Scand.* (2003) 107:405–11. doi: 10.1034/j.1600-0404.2003.00074.x
37. Schmidt-Trucksass A, Grathwohl D, Schmid A, Boragk R, Upmeier C, Keul J, et al. Structural, functional, and hemodynamic changes of the common carotid artery with age in male subjects. *Arterioscler Thromb Vasc Biol.* (1999) 19:1091–7. doi: 10.1161/01.ATV.19.4.1091
38. Levenson JA, Simon AC, Safar ME. Vasodilatation of small and large arteries in hypertension. *J Cardiovasc Pharmacol.* (1985) 7(Suppl. 2):S115–120. doi: 10.1097/00005344-198507002-00022
39. Markus HS. Cerebral perfusion and stroke. *J Neurol Neurosurg Psychiatry.* (2004) 75:353–61. doi: 10.1136/jnnp.2003.025825
40. Hossack KF, Bruce RA. Maximal cardiac function in sedentary normal men and women: comparison of age-related changes. *J Appl Physiol Respir Environ Exerc Physiol.* (1982) 53:799–804. doi: 10.1152/jappl.1982.53.4.799
41. Higginbotham MB, Morris KG, Coleman RE, Cobb FR. Sex-related differences in the normal cardiac response to upright exercise. *Circulation.* (1984) 70:357–66. doi: 10.1161/01.CIR.70.3.357
42. Martin WHIII, Ogawa T, Kohrt WM, Malley MT, Korte E, Kieffer PS, et al. Effects of aging, gender, and physical training on peripheral vascular function. *Circulation.* (1991) 84:654–64. doi: 10.1161/01.CIR.84.2.654
43. Frauchiger B, Schmid HP, Roedel C, Moosmann P, Staub D. Comparison of carotid arterial resistive indices with intima-media thickness as sonographic markers of atherosclerosis. *Stroke.* (2001) 32:836–41. doi: 10.1161/01.STR.32.4.836
44. Liebeskind DS. Collateral circulation. *Stroke.* (2003) 34:2279–84. doi: 10.1161/01.STR.0000086465.41263.06
45. Tanaka H, Dinenno FA, Monahan KD, Clevenger CM, DeSouza CA, Seals DR. Aging, habitual exercise, and dynamic arterial compliance. *Circulation.* (2000) 102:1270–5. doi: 10.1161/01.CIR.102.11.1270

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Cardiovascular Medicine

CLINICAL TRIAL
published: 18 November 2021
doi: 10.3389/fcvm.2021.736208

The Role of 6-Minute Walk Test Guided by Impedance Cardiography in the Rehabilitation Following Knee Arthroplasty: A Randomized Controlled Trial

Yangyang Lin[1†], Xingwei Hu[2†], Yalin Cao[3], Xing Wang[4], Yao Tong[4], Fengjuan Yao[5], Peihui Wu[6] and Huiling Huang[4,7*]*

[1] Department of Rehabilitation Medicine, The Sixth Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China, [2] Department of Cardiology, Affiliated Hospital of Zunyi Medical University, Zunyi, China, [3] Department of Cardiology, Guizhou Provincial People's Hospital, Guiyang, China, [4] Department of Cardiology, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China, [5] Department of Cardiac Ultrasound, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China, [6] Department of Articular Surgery, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China, [7] Key Laboratory on Assisted Circulation, Ministry of Health, Guangzhou, China

OPEN ACCESS

Edited by:
Jian Yang,
Fudan University, China

Reviewed by:
Paulo M. Dourado,
University of São Paulo, Brazil
Xuejuan Jin,
Fudan University, China

***Correspondence:**
Peihui Wu
wupeihui3@mail.sysu.edu.cn
Huiling Huang
hhling@mail.sysu.edu.cn

[†] These authors have contributed equally to this work

Specialty section:
This article was submitted to General Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

Received: 04 July 2021
Accepted: 19 October 2021
Published: 18 November 2021

Citation:
Lin Y, Hu X, Cao Y, Wang X, Tong Y, Yao F, Wu P and Huang H (2021) The Role of 6-Minute Walk Test Guided by Impedance Cardiography in the Rehabilitation Following Knee Arthroplasty: A Randomized Controlled Trial. Front. Cardiovasc. Med. 8:736208. doi: 10.3389/fcvm.2021.736208

Objective: To explore the effect of the 6-minute walk test (6MWT) guided by non-invasive cardiac output on the rehabilitation of patients with knee osteoarthritis following artificial total knee arthroplasty.

Methods: About 66 patients with knee osteoarthritis planned to undergo artificial total knee arthroplasty were included from March 2019 to October 2019, and randomly assigned to the intervention group or control group. Under the guidance of a clinical rehabilitation physician, orthopedic physician, and cardiologist, a home rehabilitation exercise program based on 6MWT and non-invasive cardiac output was formulated for patients with knee osteoarthritis. The participants of the intervention group conducted full rehabilitation training supervision and guidance through the WeChat platform to ensure their rehabilitation pieces of training were completed safely and effectively. As for the control group, patients were just given rehabilitation training manuals at the time of discharge and completed the training by themselves.

Results: At 6 months post-operatively, 6-minute walk distance (413.88 ± 44.61 vs. 375.00 ± 40.53 m, $P < 0.05$), active metabolic equivalent (4.13 ± 0.29 vs. 3.88 ± 0.27, $P < 0.05$), stroke volume after 6MWT (114.97 ± 12.05 vs. 98.38 ± 16.43 ml, $P < 0.05$), and cardiac output (11.92 ± 1.68 vs. 9.79 ± 1.82 l/min, $P < 0.05$) of the intervention group were significantly higher than those of the control group. The symptom evaluation scores of the intervention group were also better than those of the control group.

Conclusions: The multidisciplinary post-operative rehabilitation exercise training program is beneficial to the recovery of lower limb function and the improvement of exercise capacity after knee replacement, and it also helps to improve the non-invasive hemodynamic indicators related to the cardiac function of the patient.
Clinical Trial Registration: http://www.chictr.org.cn/index.aspx.

Keywords: rehabilitation training plan, knee arthroplasty, 6MWT, non-invasive cardiac output, ICG

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Ours was the first study to investigate the effect of the 6-minute walk test (6MWT) guided by the non-invasive cardiac output on the rehabilitation of patients with knee osteoarthritis undergoing artificial knee arthroplasty.
- We explored the feasibility and effectiveness of multidisciplinary post-operative rehabilitation guidance and follow-up based on the mobile Internet platform.
- A total of 36 patients were unable to return to the hospital to perform the assessment of 6MWT and the non-invasive cardiac output at 6 months due to the outbreak control of COVID-19, which may have led to bias.

INTRODUCTION

Knee osteoarthritis (KOA) commonly occurs in the aged population, and they are also the high-risk group of cardiovascular diseases such as hypertension and coronary heart disease. The 6-minute walk test (6MWT) has been acknowledged as one of the most important methods to evaluate the cardiopulmonary function, exercise capacity, and quality of life of patients with various cardiopulmonary diseases, because of its easy implementation, safety, and low cost (1, 2). The change of 6-minute walking distance (6MWD) has been confirmed by many studies to assess the effects of drug therapy and personalized cardiopulmonary rehabilitation training (3, 4). The main technical principle of non-invasive cardiac output (CO) is thoracic bioelectrical impedance analysis. Parameters, namely, stroke volume (SV), CO, myocardial contractility index (CTI), preload rate, and peripheral vascular resistance, can be obtained through the analysis of impedance cardiography. Therefore, the hemodynamics can be monitored dynamically (5). By synchronizing non-invasive CO with 6MWT, the hemodynamic changes were detected real-time, continuously, and dynamically, to formulate a precise rehabilitation training plan.

With the development of joint surgery, rehabilitation exercise is becoming more and more important in the early stage after the operation. As an auxiliary treatment manner, post-operative rehabilitation exercise can improve the knee joint function and relieve pain timely and effectively and reduce the occurrence of complications (6). However, the effect of exercise rehabilitation after total knee arthroplasty on cardiovascular function in patients with knee osteoarthritis remains unclear. In addition, the long-term compliance of some patients is poor in traditional family rehabilitation training. With the popularity of smartphones, a variety of mobile terminal software for the popularization of health science emerged. But there are few relevant studies on whether follow-up through mobile Internet platforms can improve compliance and the effect of rehabilitation.

METHODS

Study Design

The study was a prospective, randomized controlled trial with a follow-up of 6 months after the intervention with assessments performed to determine the role of 6MWT guided by impedance cardiography in the rehabilitation following knee arthroplasty. From March 2019 to October 2019, patients with knee osteoarthritis were screened for eligibility and invited to participate in the study before the operation in the Department of Articular Surgery of the First Affiliated Hospital of Sun Yat-sen University. Patients who met the following inclusion criteria and did not meet any of the exclusion criteria would be recruited. If the eligible patients consented to participation, they would be randomly allocated into two groups (the intervention group or the control group) in a 1:1 ratio. All participants would provide their written informed consent to participate in this study. In addition, we set up an independent outcome measurement committee to measure outcome variables and an intervener committee to implement the interventions. The study was approved by the Ethics Committees of the First Affiliated Hospital of Sun Yat-sen University, China. The study has been retrospectively registered on the Chinese Clinical Trial Registry, and the project is under approval.

Inclusion criteria (7):

(1) With advanced knee osteoarthritis needs surgical treatment;
(2) Between the ages of 50 and 80;
(3) New York Heart Association (NYHA) grades I–III;
(4) Not living alone;
(5) No obvious abnormality of vital signs before operation;
(6) No history of central nervous system diseases and mental disorders;
(7) Normal liver and kidney function; and
(8) Can communicate normally with medical staff.

Exclusion criteria:

(1) Secondary osteoarthritis: such as rheumatoid arthritis, traumatic arthritis, and Charko's joint;
(2) Mild joint lesion, the course <1 month, the pain visual analog scale (VAS) <4 when walking up and down stairs

or squatting, or serious joint pain, VAS more than 8 when walking on a flat road;
(3) Unable to walk due to severe joint disease, or suffering from other diseases that affect motor function, such as Parkinson's disease and cerebral infarction;
(4) Received intra-articular injection therapy within 6 months or oral glucocorticoids within 1 month;
(5) Case history of serious cardiocerebrovascular events, and/or NYHA grade worse than IV;
(6) With central nervous system disease and cannot communicate normally;
(7) Poorly controlled hypertension and respiratory dysfunction; and
(8) Received long-term drug treatment that affected the experimental results or a history of alcohol or drug abuse.

Central Randomization and Blinding

To avoid or reduce bias as much as possible, the randomization and allocation of intervention would be managed through a central computer network system. The random code list was generated by an independent statistician with SAS System Release 9.2 software, and which would be put into the interactive web response system (IWRS) before the experiment was applied. After eligible patients signed the informed consent form, the designated third party (a nurse) logged in to IWRS to obtain the intervention assignment. The interventions were implemented by the staff of the intervener committee. The staff of the outcome measurement committee and patients were all masked to the treatment assigned. Meanwhile, the researchers did not know which group the patients were allocated to neither did the surgeons who treated the patients during the hospital stay. As far as we knew the concealment was successful.

Sample Size Estimation

The primary outcome variable was assessed by the 6MWT. According to the data extracted from the previous study (8), a change of 50 m in the 6MWT was considered a meaningful change in older adults. We estimated the sample size with PASS software, version 15.0, to detect a difference of 50 m between the groups. With a standard deviation of 70, a statistical power of 80%, and a two-tailed significance level of 0.05, each group had to have 30 patients. With a lost follow-up of 5%, 32 patients at least would included in each group.

Intervention Programs

The included patients were randomly assigned into the intervention group and the control group. Unilateral artificial knee arthroplasty was performed and followed up 6 months after the operation. Under the multidisciplinary guidance of clinical rehabilitation physician, orthopedic physician, and cardiologist, a home rehabilitation exercise program that based on 6MWT and non-invasive CO was formulated for the patients with KOA (including three stages: 1–4, 4–8, and 8–24 weeks after surgery). To ensure the rehabilitation training plan was completed safely and effectively, in addition, to providing rehabilitation training manuals, the intervention group patients received full supervision and precise rehabilitation training guidance by the investigators through the Wechat platform. As for the control group, patients were just provided rehabilitation training manuals when they discharged and completed the training by themselves. The shape, color, size, and thickness of the rehabilitation training manuals were exactly the same.

Outcome Measure

Primary Outcome Measure

The 6MWT was used as the primary outcome measure, it was performed before surgery and at 6 months post-operation. The changes of 6MWD, activity metabolic equivalent (METs), and exercise energy consumption were monitored. No encouragement was given to the patients during the test.

Secondary Outcome Measure

(1) Non-invasive hemodynamic indexes: Before surgery and at 6 months post-operatively, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure were monitored under resting state, and heart rate, SV, CO, cardiac index (CI), CTI, left cardiac work index (LCWI), left ventricular ejection time, early diastolic filling rate (EDFR), systemic vascular resistance index (SVRI), and ejection fraction (EF) were also detected at rest and the end of the test.
(2) Symptom assessment: At admission and 6 months after the operation, the pain VAS and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) were compared, respectively, between the two groups to evaluate the effect of rehabilitation training.

Statistical Analyses

All statistical tests were performed using SPSS software, version 22.0. Descriptive statistics for continuous data were given as mean values with SDs (M ± SD). Normally distributed continuous data were analyzed using an independent sample *t*-test, the chi-squared test was used to analyze differences between groups for categorical data. Changes within the groups were analyzed by paired sample *t*-test. Abnormally distributed continuous data were analyzed by non-parametric Mann–Whitney U rank-sum test. Primary and secondary outcome variable analyses were conducted after the exclusion of those patients who were randomized but were found not to receive any allocated interventions or not any follow-up information (full analysis set, FAS). FAS is the main dataset of this study for the outcome evaluation. Due to the outbreak control of COVID-19, more than half of the participants were unable to return to the hospital to assess 6MWT and non-invasive cardiac output at 6 months, which would seriously affect the outcome evaluation. Thus we reported the result of 6MWT and non-invasive cardiac output based on a preprotocol analysis set. Differences were regarded as statistically significant when the two-tailed *P*-value was < 0.05.

RESULTS

Study Patients

A total of 127 patients were screened for eligibility and invited to participate in our study before surgery, of whom 66 were randomized in a 1:1 ratio. **Figure 1** outlines the reasons for non-recruitment. In addition to 40 patients who did not meet

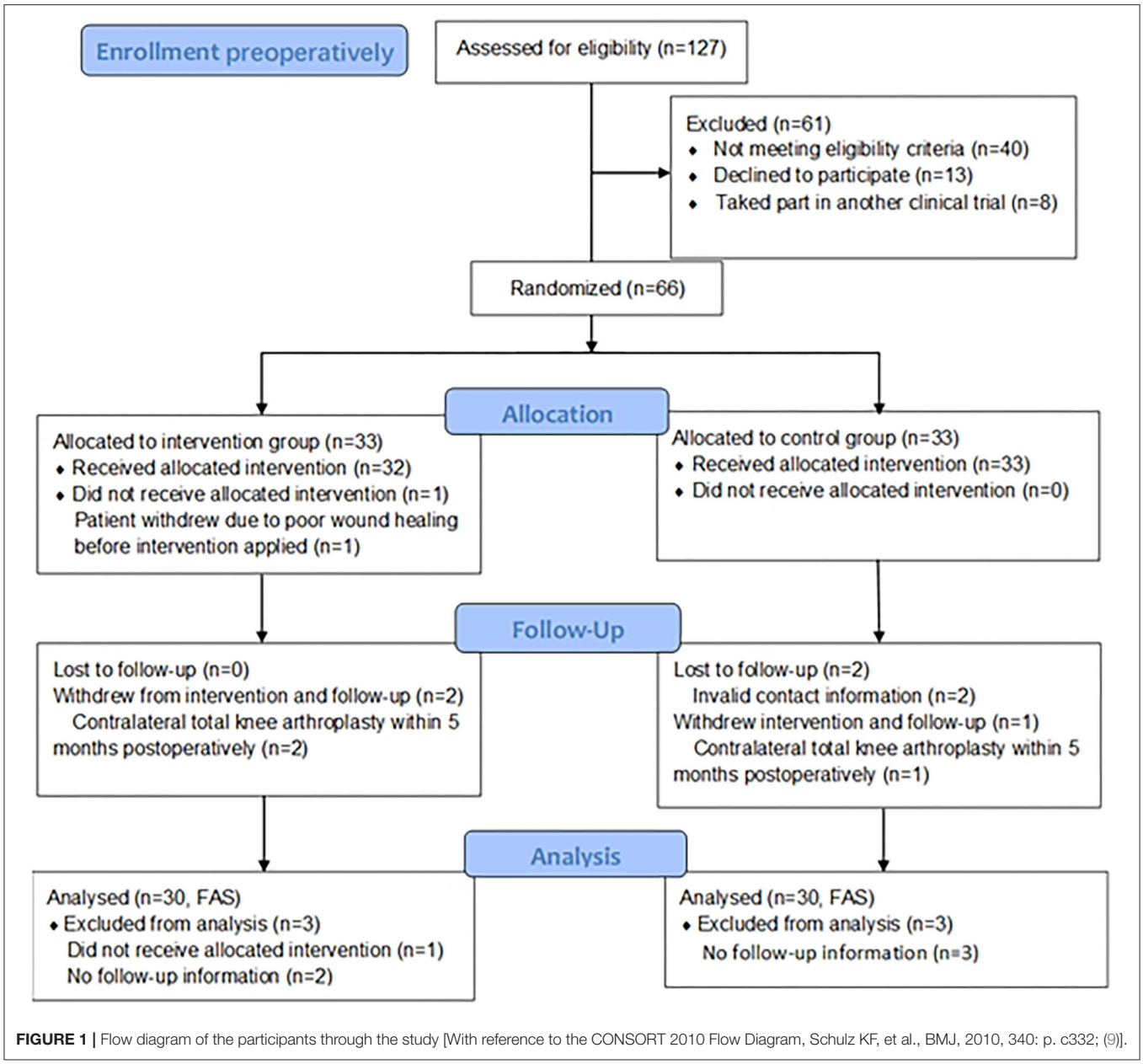


FIGURE 1 | Flow diagram of the participants through the study [With reference to the CONSORT 2010 Flow Diagram, Schulz KF, et al., BMJ, 2010, 340: p. c332; (9)].

eligibility criteria, 13 declined to participate, eight had been taking part in another clinical trial. One patient withdrew from the study due to poor wound healing before intervention was applied. Three participants withdrew from intervention and follow-up because of contralateral total knee arthroplasty within 5 months post-operatively [$n = 2$ (6.06%) the intervention group, $n = 1$ (3.03%) the control group]. Two lost to follow-up owing to invalid contact information in the control group. Ultimately, 60 participants completed the rehabilitation training plan and follow-up. Unfortunately, due to the outbreak control of COVID-19, 18 separately in both groups were unable to return to perform the assessment of 6MWT and non-invasive cardiac output at 6 months. However, we obtained the data of VAS score and WOMAC score through a telephone follow-up survey.

Characteristics of the Participants

General data of the included patients were collected, namely, gender, age, height, weight, body mass index (BMI), operative time, amount of blood loss, location of disease, and presence of hypertension, and there was no statistically significant difference in all above indicators ($P > 0.05$, **Table 1**).

Evaluation of Exercise Tolerance Between the Two Groups

At 6 months post-operatively, 6MWD, METs, and exercise energy consumption in the intervention group were significantly increased than those before surgery ($P < 0.05$), in which 6MWD and METs were better than the control group ($P < 0.05$). Moreover, the exercise energy consumption in the control group was higher after 6 months than that before operation ($P < 0.05$).

TABLE 1 | Characteristics of the study participants ($\bar{x} \pm s$).

	Intervention group ($n = 30$)	Control group ($n = 30$)	t/X^2	P
Sex				
Male	7	5	0.417□	0.519
Female	23	25		
Age (y)	66.16 ± 6.69	67.26 ± 7.99	−0.594Δ	0.555
Height (cm)	158.53 ± 6.03	157.32 ± 7.02	0.734Δ	0.466
Weight (Kg)	64.81 ± 9.71	61.81 ± 10.05	1.208Δ	0.232
BMI (kg/m^2)	25.76 ± 3.33	24.86 ± 2.88	1.145Δ	0.257
Operative time (min)	107.28 ± 7.14	108.81 ± 7.31	−0.838Δ	0.405
Blood loss (mL)	318.75 ± 73.78	316.13 ± 58.29	0.156Δ	0.876
Location of disease				
Left	12	13	0.069□	0.793
Right	18	17		
Hypertension				
Yes	13	11	0.278□	0.598
No	17	19		

Δ Indicates the value of t and □ indicates the value of chi-square.
BMI, body mass index.

TABLE 2 | 6MWT measures between the two groups ($\bar{x} \pm s$).

	Intervention group ($n = 12$)	Control group ($n = 12$)	t	P
6MWD (m)				
Pre-intervention	365.92 ± 73.41	348.92 ± 59.68	0.622	0.540
Post-intervention	413.88 ± 44.61**	375.00 ± 40.53	2.234	0.036*
METs				
Pre-intervention	3.81 ± 0.48	3.71 ± 0.39	0.622	0.540
Post-intervention	4.13 ± 0.29**	3.88 ± 0.27	2.243	0.035*
Exercise energy consumption (Kcal/min)				
Pre-intervention	4.21 ± 0.66	3.95 ± 0.75	0.901	0.378
Post-intervention	4.57 ± 0.63**	4.12 ± 0.67**	1.690	0.105

** Indicates $P < 0.05$ compared between groups and ** indicates within groups.*
METs, activity metabolic equivalent; 6MWD, 6-minute walking distance; 6MWT, 6-minute walking test.

Although 6MWD and METs in the control group were improved compared with pre-operation, there was no statistical difference ($P > 0.05$) (**Table 2**).

Non-invasive Cardiac Output Indexes Between the Two Groups

(1) At rest state

At 6 months after surgical operation, the parameters, namely, SV, CO, CI, CTI, LCWI, and EF increased and SVRI decreased compared with pre-operation in the intervention group ($P < 0.05$), and cardiac output and CI in the control group were also significantly improved ($P < 0.05$). Meanwhile, SV, CTI, and SVRI in the intervention group were better than all of them in the control group after 6 months ($P < 0.05$) (**Table 3**).

(2) At the end of 6MWT

At 6 months, the indexes, namely, SV, CO, CI, LCWI, and EF in the intervention group were significantly improved compared with those before operation ($P < 0.05$), while no significant changes were found in non-invasive cardiac output in the control group ($P > 0.05$). Furthermore, SV and CI in the intervention group were higher compared with the control group after 6 months, while SVRI was lower ($P < 0.05$) (**Table 4**).

TABLE 3 | Non-invasive cardiac output at rest ($\bar{x} \pm s$).

	Intervention group ($n = 12$)	Control group ($n = 12$)	t/Z	P
HR (min^{-1})				
Pre-intervention	73.17 ± 8.24	85.50 ± 23.20	−1.389□	0.097
Post-intervention	78.50 ± 11.53	80.50 ± 10.98	−0.435Δ	0.668
SV (ml)				
Pre-intervention	71.85 ± 14.21	67.53 ± 12.54	0.770Δ	0.450
Post-intervention	82.13 ± 10.06**	68.85 ± 10.91	3.100Δ	0.005*
CO (L/min)				
Pre-intervention	5.14 ± 1.39	5.08 ± 0.89	0.140Δ	0.890
Post-intervention	6.51 ± 1.56**	5.48 ± 0.78**	2.057Δ	0.052
CI [(L/(min^{-1}·m^{-2})]				
Pre-intervention	3.12 ± 0.85	3.15 ± 0.67	−0.107Δ	0.916
Post-intervention	3.89 ± 0.90**	3.38 ± 0.65**	−1.389□	0.165
CTI (dPmx)				
Pre-intervention	152.68 ± 55.25	163.38 ± 57.54	−0.465Δ	0.647
Post-intervention	193.55 ± 66.10**	138.52 ± 51.17	−2.194□	0.028*
LCWI (kg × m × m^{-2})				
Pre-intervention	4.20 ± 1.79	4.79 ± 1.36	−1.388Δ	0.165
Post-intervention	5.47 ± 1.63**	4.68 ± 1.22	1.164Δ	0.257
LVET (ms)				
Pre-intervention	400.91 ± 58.78	376.66 ± 57.78	−0.981□	0.326
Post-intervention	373.38 ± 63.90	361.22 ± 78.37	0.417Δ	0.681
EDFR (%)				
Pre-intervention	56.00 ± 5.80	54.77 ± 10.89	−1.790□	0.073
Post-intervention	62.97 ± 13.07	62.69 ± 12.70	0.052Δ	0.959
SVRI (D.S × cm^{-5} × m^{-2})				
Pre-intervention	2456.83 ± 435.38	2484.42 ± 334.83	−0.174Δ	0.863
Post-intervention	2041.58 ± 429.25**	2372.33 ± 337.18	−2.099Δ	0.048*
EF (%)				
Pre-intervention	55.07 ± 10.13	56.71 ± 9.18	−0.493□	0.488
Post-intervention	59.06 ± 10.58**	53.67 ± 10.80	−1.126□	0.260

*Δ Indicates the value of t, □ indicates Z value of Mann–Whitney U rank-sum test; * indicates $P < 0.05$ between-group comparison and ** indicates within-groups.*

Symptom Assessment

There were no significant differences in VAS score, total score, and each score of WOMAC between the two groups before surgery ($P > 0.05$). After 6 months post-operatively, the VAS score and WOMAC score within both groups were better than

TABLE 4 | Non-invasive cardiac output at the end of 6MWT ($\bar{x} \pm s$).

	Intervention group ($n = 12$)	Control group ($n = 12$)	t/Z	P
HR (min^{-1})				
Pre-intervention	111.08 ± 25.74	100.50 ± 21.475	1.094Δ	0.286
Post-intervention	104.08 ± 13.56	101.00 ± 11.74	0.595Δ	0.558
SV (ml)				
Pre-intervention	92.30 ± 19.67	90.98 ± 15.45	0.182Δ	0.857
Post-intervention	114.97 ± 12.05**	98.38 ± 16.43	2.820Δ	0.010*
CO (L/min)				
Pre-intervention	9.99 ± 3.25	9.68 ± 1.63	0.301Δ	0.766
Post-intervention	11.92 ± 1.68**	9.79 ± 1.82	2.978Δ	0.007
CI [($L/(min^{-1} \cdot m^{-2})$]				
Pre-intervention	5.98 ± 1.93	6.06 ± 1.18	−0.115Δ	0.910
Post-intervention	7.15 ± 1.04**	6.11 ± 1.17	2.299Δ	0.031*
CTI (dPmx)				
Pre-intervention	269.33 ± 124.11	294.18 ± 145.52	−0.450Δ	0.657
Post-intervention	353.63 ± 124.43	283.66 ± 105.78	1.484Δ	0.152
LCWI ($kg \times m \times m^{-2}$)				
Pre-intervention	8.03 ± 2.95	8.18 ± 2.55	−0.133Δ	0.895
Post-intervention	9.83 ± 2.08**	8.44 ± 2.39	1.515Δ	0.144
LVET (ms)				
Pre-intervention	274.28 ± 116.23	294.18 ± 63.43	0.594Δ	0.559
Post-intervention	235.63 ± 73.19	227.83 ± 81.16	0.247Δ	0.807
EDFR (%)				
Pre-intervention	75.89 ± 14.71	65.33 ± 21.50	1.404Δ	0.174
Post-intervention	67.93 ± 19.24	64.97 ± 22.18	−0.404□	0.686
SVRI ($D.S \times cm^{-5} \times m^{-2}$)				
Pre-intervention	1572.50 ± 685.65	1290.25 ± 205.57	1.366Δ	0.186
Post-intervention	1125.42 ± 245.45	1337.42 ± 228.479	−2.190Δ	0.039*
Ejection Fraction (EF) (%)				
Pre-intervention	62.36 ± 11.77	64.22 ± 11.75	−0.387Δ	0.702
Post-intervention	69.02 ± 9.26**	63.68 ± 12.94	1.163Δ	0.257

*Δ Indicates the value of t, □ indicates Z value of Mann–Whitney U rank-sum test; * indicates $P < 0.05$ compared between groups and ** indicates within groups.*
CO, cardiac output; CI, cardiac index; CTI, contractility index; EDFR, early diastolic filling rate; EF,; HR, heart rate; LCWI, left cardiac work index; LVET, left ventricular ejection time; SV, stroke volume; SVRI, systemic vascular resistance index.

TABLE 5 | VAS score between groups ($\bar{x} \pm s$).

	Intervention group ($n = 30$)	Control group ($n = 30$)	Z	P
VAS score				
Pre-intervention	6.10 ± 1.03	6.60 ± 1.25	−1.922	0.055
Post-intervention	1.73 ± 1.05	2.47 ± 1.33	−2.25	0.024*
Z	−4.825	−4.719	–	–
P	0.000**	0.000**	–	–

** Indicates $P < 0.05$ compared between groups and ** indicates within groups.*
VAS, visual analog scale.

TABLE 6 | WOMAC score measure between groups ($\bar{x} \pm s$).

	Intervention group ($n = 30$)	Control group ($n = 30$)	t/Z	P
WOMAC (Total score)				
Pre-intervention	56.90 ± 10.92	59.53 ± 12.42	−0.872Δ	0.387
Post-intervention	15.43 ± 8.42**	21.17 ± 8.88**	−2.566Δ	0.013*
Pain score				
Pre-intervention	12.90 ± 2.62	13.87 ± 2.96	−1.341Δ	0.185
Post-intervention	3.27 ± 1.95**	4.80 ± 2.78**	−2.472Δ	0.016*
Stiffness score				
Pre-intervention	1.33 ± 0.80	1.47 ± 0.90	−0.440□	0.660
Post-intervention	1.07 ± 0.91	1.20 ± 0.89	−0.529□	0.597
Physiological function score				
Pre-intervention	42.67 ± 10.52	44.20 ± 10.31	−0.570Δ	0.571
Post-intervention	11.10 ± 7.24**	15.17 ± 7.21**	−2.180□	0.033*

*Δ Indicates the value of t, □ indicates Z value of Mann–Whitney U rank-sum test; *indicates $P < 0.05$ compared between groups and **indicates within groups.*
WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

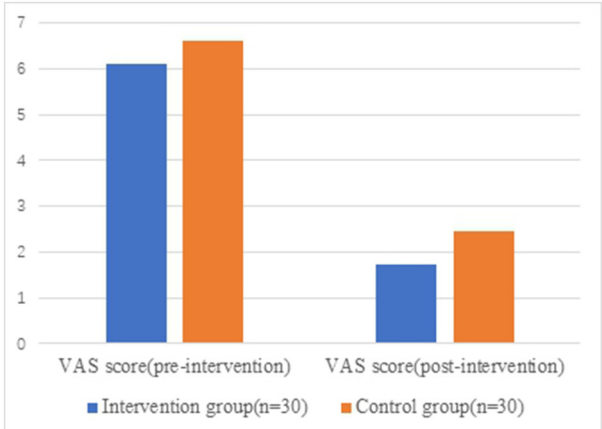


FIGURE 2 | VAS score between groups. VAS, visual analog scale.

those before surgical operation ($P < 0.05$), and all of VAS score, WOMAC score, namely, total score, pain score, and physiological function score in the intervention group significantly preceded the control group ($P < 0.05$) (**Tables 5**, **6** and **Figures 2**, **3**).

DISCUSSION

For patients undergoing knee arthroplasty, the purpose of post-operative rehabilitation exercise is mainly to adapt to the prosthesis, prevent joint stiffness, increase the range of motion, and promote the recovery of function. In addition, rehabilitation exercise also has a certain positive effect on cardiopulmonary function and systemic inflammatory response. In our study, under the multidisciplinary guidance of clinical rehabilitation physician, orthopedic physician, and cardiologist, a home rehabilitation exercise program that based on 6MWT synchronized with non-invasive cardiac output was formulated for the patients with KOA, and the influence of post-operative

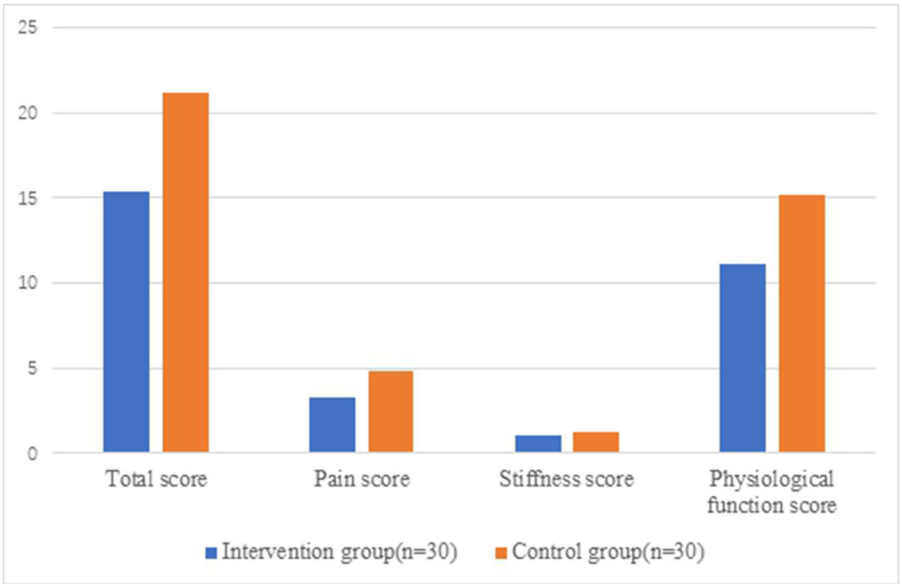


FIGURE 3 | WOMAC score measure between groups post-intervention. WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

rehabilitation exercise on cardiac and lower limb function of patients with KOA, and how to formulate an appropriate post-operative treatment, follow-up and rehabilitation training plan to make operation to achieve the best therapeutic effect were explored.

Assessment of Activity Tolerance

In addition to reflecting the cardiac function of patients under submaximal exercise, 6MWT is also used to evaluate the activity tolerance and lower limb function. A study suggests that low muscle strength and joint pain of the lower extremity may lead to slow walking speed and short 6MWD during 6MWT (10). Other studies have demonstrated that 6MWT has good reliability and validity in the assessment of motor function and activity tolerance in patients with lower limb arthritis and joint replacement (11, 12).

In this study, we found that 6MWD, METs, and exercise energy consumption of patients in the intervention group significantly increased compared with pre-intervention after 6 months of rehabilitation exercise ($P < 0.05$), and 6MWD and METs were better than the control group ($P < 0.05$).

Patients with knee osteoarthritis commonly tend to develop bad habits such as being sedentary and bedridden because of lower limb pain, and their daily activity was significantly lower than that of normal people (13). And patients who underwent artificial knee arthroplasty will be able to walk longer distances, have better exercise capacity, and can tolerate more activity through rehabilitation training. During the 6 months of post-operative rehabilitation training, the exercise tolerance and motor function were significantly improved, enabling the patients to do more and longer exercise, and obtain a virtuous cycle. In addition, the improvement of walking distances and METs in the intervention group were better than those in the control group, which indicates that rehabilitation exercise under professional guidance and supervision can help patients develop good training habits and maintain a certain amount of daily exercise, and contribute to complete the training plan on time, and improve their activity tolerance.

Evaluation of Non-invasive Cardiac Output

Patients with lower extremity joint disease may fail to reach the submaximal exercise state due to low limb pain during 6MWT, which will affect the evaluation of cardiac function. The post-operative 6MWD of the patients in the intervention group increased significantly, should this be attributed to the improvement of cardiac function or the recovery of lower limb function? Obviously, the traditional 6MWT has some limitations.

Non-invasive cardiac output detection technology, also known as non-invasive hemodynamic monitoring technology, which main technical principle is thoracic electrical bioimpedance. As the heart relaxes and contracts, the intravascular blood flow changes, and the impedance when the current passes the chest also change accordingly. Non-invasive hemodynamic monitoring by impedance cardiography is based on the principle of the impedance of the thorax, parameters, namely, SV, CO, CTI, EDFR, SVR, etc. could be obtained by processing impedance cardiogram, and these parameters could be detected dynamically and continuously. By synchronizing impedance cardiography, non-invasive hemodynamic monitoring with 6MWT, the changes in cardiac function can be more accurately reflected during 6MWT.

In our research, it was found that in addition to the increase of CO, CI, CTI, EF, and LCWI, SVRI was also significantly decreased at 6 months after operation in the intervention group.

We held the opinion that, with the improvement of lower limb function after the operation, patients gradually increased the amount of daily activity and carried out rehabilitation exercises as required, which was conducive to the improvement of physical fitness and cardiac function. Besides the improvement of the strength and coordination of lower limb muscles by the training exercise itself, deep breathing, abdominal and chest breathing training would contribute to enhancing the strength of respiratory muscles, expanding the range of thoracic movement, and increasing the distance of the diaphragm downward in the process of post-operative rehabilitation training, which could effectively expand the airway, reduce respiratory resistance. And then the circulating blood volume also increased when the ventilation-perfusion ratio remained constant, further improving cardiac function, consequently. Furthermore, rehabilitation exercise could promote venous blood reflux caused by muscle contraction, which increased circulating blood volume. It was basically consistent with the results of Wang et al. (14).

At the end of the trial, CI and CO in the intervention group were higher than those in the control group, while SVRI was lower. And EF and LCWI were also increased compared to pre-operation ($P < 0.05$). It suggested that multidisciplinary exercise prescription based on hemodynamics and post-operative rehabilitation guidance on the strength of mobile Internet platforms were helpful to the recovery of cardiac function. Some scholars have proposed that patients with hip or knee arthritis could not significantly improve their daily activities after joint replacement (15). In fact, the effect of traditional family rehabilitation training is limited by the own educational level, compliance, and understanding of rehabilitation training. And the effect of a post-operative rehabilitation training plan with professional supervision and guidance is better than the traditional family rehabilitation training.

In the control group, there was no significant difference in the changes of non-invasive cardiac output between pre-operation and post-operation, which may be associated with the lack of guidance in traditional family rehabilitation training. Although the daily activities of patients have improved after surgical operation, insufficient training time and intensity, lack of aerobic exercise training, and irregular functional training on the improvement of cardiac function are limited.

Improvement of Symptoms

VAS and WOMAC scores are commonly used to evaluate the subjective feelings of patients with osteoarthritis. VAS score is mainly used for the overall evaluation of pain symptoms of patients, and the WOMAC scale is divided into three dimensions, namely, pain, joint stiffness, and dysfunction (16, 17). Pain and limitation of physiological function are the main reasons for most patients with osteoarthritis to seek medical treatment. After joint functional exercise and moderate aerobic exercise, patients with osteoarthritis were evaluated by WOMAC, KOOS, and other rating scales again, and their scores were found to be improved (18). Domestic scholars have verified the effectiveness of using the WOMAC scale to evaluate the pathogenetic condition of Chinese patients with knee arthritis (19).

In this study, the subjective pain assessment of patients in both groups had been significantly improved after rehabilitation training ($P < 0.05$), and the VAS score of the intervention group was better than that of the control group, and the difference was statistically significant ($P < 0.05$). Meanwhile, the pain score and function score of WOMAC in the intervention group were better than those in the control group ($P < 0.05$), which was basically consistent with the results of previous studies.

Moreover, combined with the indexes of non-invasive cardiac output, this study showed that patients with knee osteoarthritis were treated with surgery and rehabilitation training, even though some patients had poor compliance and did not complete the rehabilitation training as planned, it is also possible to improve their exercise tolerance and cardiac function by increasing the amount of daily activity. And the score of rating scales given by the patients in the intervention group was better, which indicated that rehabilitation training under professional supervision could make patients obtain a better quality of life and be more satisfied with the surgical effect.

CONCLUSIONS

To formulate a precise rehabilitation training plan with 6MWT guided by non-invasive cardiac output is beneficial to the recovery of lower limb function and the increase of exercise tolerance after knee arthroplasty, and the improvement of cardiac function and quality of life. The accurate rehabilitation exercise prescription based on the guidance of clinical rehabilitation physician, orthopedic physician, and cardiologist is worth applying and popularizing for patients underwent knee arthroplasty.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committees of the First Affiliated Hospital of Sun Yat-Sen University, China, approved the study (No. [2019]259). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HH and PW conceived of the study. YL and XH performed the statistical analysis and drafted the manuscript. HH, PW, YL, XH, and YC developed the study protocol. XW, YT, and FY led the implementation of the study and collected data. YC, XW, and YT performed follow-up for all patients. All authors revised it critically for important intellectual content and approved the final manuscript.

FUNDING

This study was supported by the Open Project of State Key Laboratory of Organ Failure Research (Grant No. G820NF1024).

ACKNOWLEDGMENTS

The authors thank the patients and especially thank the nurses of the Department of Rehabilitation Medicine and the Department of Cardiology for their help on participant recruitment.

REFERENCES

1. Ferreira JP, Duarte K, Graves TL, Zile MR, Abraham WT, Weaver FA, et al. Natriuretic peptides, 6-min walk test, and quality-of-life questionnaires as clinically meaningful endpoints in HF trials. *J Am Coll Cardiol.* (2016) 68:2690–707. doi: 10.1016/j.jacc.2016.09.936
2. Olsson LG, Swedberg K, Clark AL, Witte KK, Cleland JG. Six minute corridor walk test as an outcome measure for the assessment of treatment in randomized, blinded intervention trials of chronic heart failure: a systematic review. *Eur Heart J.* (2005) 26:778–93. doi: 10.1093/eurheartj/ehi162
3. Ferreira JP, Metra M, Anker SD, Dickstein K, Lang CC, Ng L, et al. Clinical correlates and outcome associated with changes in 6-minute walking distance in patients with heart failure: findings from the BIOSTAT-CHF study. *Eur J Heart Fail.* (2019) 21:218–26. doi: 10.1002/ejhf.1380
4. Faggiano P, D'Aloia A, Gualeni A, Brentana L, Dei CL. The 6 minute walking test in chronic heart failure: indications, interpretation and limitations from a review of the literature. *Eur J Heart Fail.* (2004) 6:687–91. doi: 10.1016/j.ejheart.2003.11.024
5. Bour J, Kellett J. Impedance cardiography: a rapid and cost-effective screening tool for cardiac disease. *Eur J Intern Med.* (2008) 19:399–405. doi: 10.1016/j.ejim.2007.07.007
6. Pianigiani S, Chevalier Y, Labey L, Pascale V, Innocenti B. Tibio-femoral kinematics in different total knee arthroplasty designs during a loaded squat: a numerical sensitivity study. *J Biomech.* (2012) 45:2315–23. doi: 10.1016/j.jbiomech.2012.06.014
7. Rankin EA, Alarcòn GS, Chang RW, Cooney LM, Costley LS, Delitto A, et al. NIH Consensus Statement on total knee replacement. *NIH Consens State Sci Statements.* (2003) 20:1–34. doi: 10.1016/j.arth.2003.12.065
8. Bruun-Olsen V, Heiberg KE, Wahl AK, Mengshoel AM. The immediate and long-term effects of a walking-skill program compared to usual physiotherapy care in patients who have undergone total knee arthroplasty (TKA): a randomized controlled trial. *Disabil Rehabil.* (2013) 35:2008–15. doi: 10.3109/09638288.2013.770084
9. Schulz, KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ* (2010) 340:c332. doi: 10.1136/bmj.c332
10. Kono K, Nishida Y, Moriyama Y, Yabe H, Taoka M, Sato T. Investigation of factors affecting the six-minute walk test results in hemodialysis patients. *Ther Apher Dial.* (2014) 18:623–7. doi: 10.1111/1744-9987.12177
11. Unver B, Kahraman T, Kalkan S, Yuksel E, Karatosun V. Reliability of the six-minute walk test after total hip arthroplasty. *HIP Int.* (2013) 23:541–5. doi: 10.5301/hipint.5000073
12. Ko V, Naylor JM, Harris IA, Crosbie J, Yeo AE. The six-minute walk test is an excellent predictor of functional ambulation after total knee arthroplasty. *BMC Musculoskelet Disord.* (2013) 14:145. doi: 10.1186/1471-2474-14-145
13. Svege I, Fernandes L, Nordsletten L, Holm I, Risberg MA. Long-term effect of exercise therapy and patient education on impairments and activity limitations in people with hip osteoarthritis: secondary outcome analysis of a randomized clinical trial. *Phys Ther.* (2016) 96:818–27. doi: 10.2522/ptj.20140520
14. Wang IK, Lu CY, Lin CL, Liang CC, Yen TH, Liu YL, et al. Comparison of the risk of de novo cardiovascular disease between hemodialysis and peritoneal dialysis in patients with end-stage renal disease. *Int J Cardiol.* (2016) 218:219–24. doi: 10.1016/j.ijcard.2016.05.036
15. Arnold JB, Walters JL, Ferrar KE. Does physical activity increase after total hip or knee arthroplasty for osteoarthritis? A systematic review. *J Orthop Sports Phys Ther.* (2016) 46:431–42. doi: 10.2519/jospt.2016.6449
16. McConnell S, Kolopack P, Davis AM. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): a review of its utility and measurement properties. *Arthritis Rheum.* (2001) 45:453–61. doi: 10.1002/1529-0131(200110)45:5<453::aid-art365>3.0.co;2-w
17. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol.* (1988) 15:1833–40.
18. Yennan P, Suputtitada A, Yuktanandana P. Effects of aquatic exercise and land-based exercise on postural sway in elderly with knee osteoarthritis. *Asian Biomed.* (2010) 4:739–45. doi: 10.2478/abm-2010-0096
19. Xie F, Li SC, Goeree R, Tarride JE, O'Reilly D, Lo NN, et al. Validation of Chinese Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) in patients scheduled for total knee replacement. *Qual Life Res.* (2008) 17:595–601. doi: 10.1007/s11136-008-9340-7

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 22 November 2021
doi: 10.3389/fcvm.2021.752955

Low Intrinsic Aerobic Capacity Limits Recovery Response to Hindlimb Ischemia

Elizabeth Granier[1,2], *Madaniah O. Zakari*[1,3], *Musaad B. Alsahly*[1,4], *Lauren G. Koch*[5], *Steven Britton*[6], *Laxmansa C. Katwa*[1] *and Robert M. Lust*[1,7]*

[1] Department of Physiology, Brody School of Medicine, East Carolina University, Greenville, NC, United States, [2] Department of Biological Science, St. Louis Community College-Meremac, St. Louis, MO, United States, [3] Department of Physiology, College of Medicine, Taibah University, Medina, Saudi Arabia, [4] Department of Physiology, College of Medicine, King Saud University, Riyadh, Saudi Arabia, [5] Department of Physiology and Pharmacology, University of Toledo, Toledo, OH, United States, [6] Departments of Anesthesiology and Molecular and Integrative Medicine, University of Michigan, Ann Arbor, MI, United States, [7] East Carolina Diabetes and Obesity Center, East Carolina University, Greenville, NC, United States

OPEN ACCESS

Edited by:
Jian Yang,
Fudan University, China

Reviewed by:
Ensieh Salehi,
Hormozgan University of Medical Sciences, Iran
Michel Desjarlais,
Centre de recherche Hopital Maisonneuve-Rosemont, Canada

***Correspondence:**
Robert M. Lust
lustr@ecu.edu

Specialty section:
This article was submitted to General Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

Received: *04 August 2021*
Accepted: *28 October 2021*
Published: *22 November 2021*

Citation:
Granier E, Zakari MO, Alsahly MB, Koch LG, Britton S, Katwa LC and Lust RM (2021) Low Intrinsic Aerobic Capacity Limits Recovery Response to Hindlimb Ischemia. Front. Cardiovasc. Med. 8:752955. doi: 10.3389/fcvm.2021.752955

Introduction: In this study, we determined the influence of intrinsic exercise capacity on the vascular adaptive responses to hind limb ischemia. High Capacity Running, HCR; Low Capacity Running, LCR, rats were used to assess intrinsic aerobic capacity effects on adaptive responses to ischemia.

Methods: Muscle samples from both ischemic and non-ischemic limb in both strains were compared, histologically for the muscle-capillary relationship, and functionally using microspheres to track blood flow and muscle stimulation to test fatigability. PCR was used to identify the differences in gene expression between the phenotypes following occlusive ischemia.

Results: Prior to ligation, there were not significant differences between the phenotypes in the exhaustion time with high frequency pacing. Following ligation, LCR decreased significantly in the exhaustion time compare with HCRs (437 ± 47 vs. 824 ± 56, $p < 0.001$). The immediate decrease in flow was significantly more severe in LCRs than HCRs (52.5 vs. 37.8%, $p < 0.001$). VEGF, eNOS, and ANG2 (but not ANG1) gene expression were decreased in LCRs vs. HCRs before occlusion, and increased significantly in LCRs 14D after occlusion, but not in HCRs. LCR capillary density (CD) was significantly lower at all time points after occlusion (LCR 7D = 564.76 ± 40.5, LCR 14D = 507.48 ± 54.2, both $p < 0.05$ vs. HCR for respective time point). NCAF increased significantly in HCR and LCR in response to ischemia.

Summary: These results suggest that LCR confers increased risk for ischemic injury and is subject to delayed and less effective adaptive response to ischemic stress.

Keywords: vascular occlusion, aerobic running capacity, exercise, peripheral artery occlusion, limb ischemia

INTRODUCTION

Peripheral artery occlusive disease (PAOD) is a major health problem with limited treatment options affecting 8-12 million Americans (1, 2). The pathophysiology of PAOD is characterized by an impaired perfusion to the lower extremities. Exercise training is one treatment option that improves quality of life and tissue perfusion characteristics, by inducing increased capillary density (3), increasing the surface area for exchange of oxygen and other substances between capillaries and muscle fibers, thereby limiting ischemic symptoms (4). Exercise training has been shown to increase capillary number within healthy skeletal muscle through the process of angiogenesis, mediated, at least in part, by vascular endothelial growth factor (VEGF) driven pathways (5–8). The mechanisms by which exercise training improves intermittent claudication in PAOD patients remains unclear (2, 9, 10). Clinical studies of PAOD indicate that patients limited by intermittent claudication who engage in any amount of weekly physical activity beyond light intensity, have a lower mortality rate than their sedentary counterparts who perform either no physical activity or only light-intensity activities (11), even after adjusting for other predictors of mortality, which include age, and body mass index (BMI). Thus, exercise training appears to induce adaptive remodeling within ischemic skeletal muscle, but the pathways and mechanisms responsible for this remodeling are still not well-characterized.

Exercise is a complex stimulus with multifactorial outcomes. These outcomes are determined by at least two genetic components (12–17). One component establishes the innate aerobic exercise capacity that each individual possesses irrespective of any subsequent training or activity (12–17), and the second genetic component establishes the pattern of responses to active exercise training (1, 2, 11, 18–20). It is estimated that up to 70% of the variation in exercise capacity are due to the genetic predisposition of an individual (12, 13). Many studies have focused on the active exercise training component (1, 2, 6, 7, 11, 18–21), but even within these studies, there is a heterogeneous response in subjects to training protocols (2, 6, 7, 11, 18–22). It is this finding that suggests the importance of investigating intrinsic exercise capacity and its impact on the response to ischemic stress.

Active exercise training in healthy individuals increases both perfusion and energy demand in the working muscle, although under strenuous exercise, the increase in demand is thought to exceed the increase in perfusion. This relative ischemic stress generates a remodeling stimulus for angiogenesis, but there must be limits because progressive loss of perfusion with advancing occlusive disease also induces a relative ischemia lower work intensity, but does not generate a comparable expansion of the vascular bed to offset it. The process of vascular remodeling is multifactorial, with vascular endothelial growth factor (VEGF) and its receptor family including VEGFR-1 [Fms-like tyrosine kinase 1 (FLT-1)], VEGFR-2 [Kinase insert domain-containing receptor (KDR) also known as fetal liver kinase (FLK-1)], and neuropilin-1 (NP-1) all participating (6, 7, 19). VEGFR-2 appears to respond following exercise training as well as with ischemic challenge independent of any active exercise (4, 19, 20). Other potential angiogenic factors that may influence intrinsic exercise capacity associated responses to ischemic challenge are angiopoietin 1 and 2 (Ang1 and Ang2) and nitric oxide (NO) (8, 18, 20, 23). Both factors are known to be involved in exercise training induced angiogenesis and ischemia induced angiogenesis, as well as the combination of both stressors. The angiopoietins are important cytokines that assist in vascular development and remodeling (24). Ang 1 promotes maturation and stabilization of vessels and is expressed widely throughout tissues, whereas Ang 2 competes with Ang 1 by displacing it from the activating Tie2 receptor. The Tie2 receptor is expressed at sites of vascular remodeling. Thus Ang1 dominance is associated with a stable vasculature while Ang2 dominance is associated with active angiogenesis (24). NO can be increased with VEGFR2 or KDR activation (24). The increase in NO production can be critical to VEGF signaling and the remodeling response of the skeletal muscle. The influence of intrinsic exercise capacity on the angiogenic response following an ischemic event has not been studied.

Low aerobic capacity or low cardiovascular fitness, is a strong predictor of early mortality within PAOD patients (2, 3, 9, 11). Koch and Britton (14–17), developed a rat model to investigate the role of intrinsic aerobic exercise capacity on responses and adaptations to chronic disease. Studies with this model show that the low endurance running capacity phenotype (LCR) rats are more prone to develop hepatic steatosis (25) and more sensitive to high fat diet-induced insulin resistance (26). These LCR rats displayed a higher incidence of both cardiovascular and metabolic syndrome risk factors than the high endurance running capacity (HCR) rats (27). Previous studies have found that the LCR phenotype has decreased capillary density when compared to the HCR counterparts (14–17, 27), which suggest that the LCR may have a decreased tolerance in hind limb ischemia models of PAOD. Studies of skeletal muscle responses to the stress of high fat feeding indicate that while the LCR's are less tolerant, the inducible responses are slower in onset but largely intact (26). However, while resting differences between the phenotypes are suggestive, it remains unknown whether the induced responses of peripheral ischemic challenge are altered by the intrinsic aerobic phenotype. Therefore, this study was designed to test the hypothesis that an increased intrinsic aerobic capacity will manifest more compensation in response to peripheral ischemia using a an established unilateral hind limb femoral artery occlusion (19, 20).

METHODS

Animal Strains

40 LCR and 40 HCR generation 22 rats were obtained from Drs. Lauren Koch and Steven Britton at the University of Michigan. Those authors have previously described the selection process of artificial selection used to generate the HCR and LCR strains (14–17). Briefly, two-way artificial selective breeding was used to create low capacity runner (LCR) and high capacity runner (HCR) strains that were divergent for treadmill running capacity (run time to exhaustion on a graded treadmill exercise test). The 13 lowest and 13 highest running capacity rats of each

sex were selected from the founder population (N: NIH stock) and randomly paired for mating. This pattern was repeated over subsequent generations to produce the divergent strains using a rotational breeding scheme for minimal inbreeding. In the present study animals from generation 22 were used. It is important to note that all the animals were housed under sedentary conditions, except for the 5 days at 11 weeks of age when the animals were phenotyped for treadmill running capacity. At all other times, animals had no exercise other than spontaneous cage activity. Once phenotyping was verified, animals were prepared for shipping at 14 weeks of age, or as soon after as weather conditions (airport tarmac temperatures $< 85^{\circ}$F) permitted. Once received by the Department of Comparative Medicine at ECU, the animals were maintained under mandatory quarantine for 10 weeks before they were released for study. Therefore, all animals were at least 24 weeks of age before they were available to be enrolled in a protocol. Rats were provided standard rat chow and water ad libitum, and were kept on a 12 h light/12 h dark time schedule until sacrifice. Animal procedures were conducted in accordance with American Physiological Society guidelines for the humane and safe use of animals, and all protocols involving animals used for these experiments were approved by the East Carolina University Animal Care and Use Committee.

Hind Limb Femoral Artery Occlusion

Femoral artery occlusion was produced as described previously by Lloyd et al. (19, 20). Briefly, rats were anesthetized with 90:10 ketamine/xylazine solution (dosage 0.08-0.1 ml mixture per 100 g body weight *i.p.*), and the incision site was prepared with Betadine and 70% alcohol. Utilizing a small incision, the right femoral artery was isolated and three separate ligatures were placed along the femoral vascular tree. One ligature was placed 5-6 mm distal to the inguinal ligament, a second was placed on a collateral artery arising from the inguinal fat pat, and the third was placed 5-6 mm distal to the first ligature. A perfusion deficit was verified by a color and temperature in the occluded limb, compared to the contralateral limb. When all three ligatures were in place, the incision was closed in layers, analgesia was administered (Buprenex, 0.1 ml per 100 g body weight, *i.p.*) and each rat was placed on a warming blanket under a heating lamp to recover. Once spontaneous movement and sternal recumbancy were observed, the animals were placed in their cages homes and returned to the animal facility. Animals were sacrificed at 7 (18 HCR and 18 LCR) or 14 days (10 HCR and 10 LCR) following placement of the ligatures.

Microsphere Injections

To determine relative bulk perfusion in ischemic and non-ischemic muscles, colored tracer microspheres were utilized, essentially as described in the literature in multiple studies (28, 29).

Briefly, on the day of study (7 or 14 days after occlusion) the animals were again anesthetized as described above, the right carotid artery was exposed and cannulated using a PE50 catheter, which was positioned in the left ventricle by retrograde advancement. Positioning of the catheter in the left ventricle was determined by observing the characteristic transition from arterial pressure to left ventricular pressure values and was verified postmortem by visual inspection of catheter tip placement in the left ventricle. Yellow, and persimmon (15 um) Dye-Trak microspheres (Dye-Trak; Triton Technology, San Diego, CA) were dispersed by sonication and vortex mixing. The number of microspheres for any given color (mean diameter, 15 um) injected into the left ventricle was about 900,000/0.3 ml. The microspheres were loaded into the catheter and given as a bolus injection followed by a flush of 0.5 ml of saline.

Microsphere injections were performed three times on the day of euthanasia, 7 days following surgery to occlude the right femoral artery. Yellow microspheres were injected first as a control, which allowed comparison of flow between the non-ischemic left gastrocnemius muscle, and the right, post-occlusion gastrocnemius. Following the first injection, the left femoral artery was ligated acutely, at similar locations to those used previously for the right femoral artery. Immediately after ligation, the persimmon microspheres were injected. Comparison of tracer densities was used to determine the difference between native collateral flow (left gastrocnemius) with the remodeled, post-ischemic perfusion (right gastrocnemius). Kidneys were also utilized for comparison of equal distribution and to assess approximate equal microsphere distribution between the phenotypes as the kidney weights were not different between the phenotypes.

Microsphere Tissue Digestion and Recovery

Unless otherwise indicated, all chemicals were obtained from Sigma-Aldrich (Sigma-Aldrich Inc., St. Louis, MO). All reagent solutions were generated in-house following manufacturer's directions for microsphere recovery and processing (Dye-Trak; Triton Technology, San Diego, CA). Following the last injection of microspheres, gastrocnemius, soleus and plantaris muscles were excised and fixed in formalin for 1 h. Tissue was weighed ($\sim$1.0-2.0 g) and then subjected to tissue digestion and processing as outlined by Dye-Trak. Once a pellet of blanched microspheres and any remaining debris was obtained, the supernatant solution was used for dye analysis. Photometric absorption of each dye solution was determined by UV/Visible Spectrophotometer (wavelength 300-700 nm with 1 nm optical band width). The composite spectrum of each dye solution was resolved into the spectra of the single constituents by a matrix inversion technique, using formulas provided by the manufacturer for that purpose. The absorption spectrum of each dye was measured separately from a control sample of each colored microsphere and was used as a reference for the matrix inversion, determining the contribution of each color to the measured composite spectra at 440, 495, 545, 672 nm. In the present study, the various vascular interventions precluded access to a reference withdrawal arterial blood sample to convert microsphere count to blood flow in ml/min/g tissue. Instead, the raw counts reflect relative flow. There were no significant differences in blood pressure between any of the animals at any of the injections, there were no significant differences in renal sphere counts with any of the

injections, and there were no significant differences between right and left kidneys Together, these controls suggest that there was consistent, uniform distribution of the tracers.

High Frequency Stimulation

As a gross functional test of differences between HCR and LCR phenotypes, demand ischemia was induced by direct electrical stimulation of the gastrocnemius muscle. The pacing protocol was similar to that described by Keeton et al. (30). Briefly, high frequency electrical stimulation was accomplished using a pair of wire electrodes, ∼5 mm apart, inserted directly into the body of the gastrocnemius muscle. Electrical impulses were delivered using a stimulator (Grass Instruments, Columbus OH) set to deliver repeated single pulses at a frequency of 5 Hz, 200-400 mV, and pulse duration of 1-ms duration. Preliminary experiments were used to establish the threshold voltage for stimulation response (100-200 mV), and a stimulation frequency that would produce spontaneous exhaustion of muscle contraction. The electrical stimulation protocol lasted until the muscle failed to contract with enough force sufficient to cause a visible displacement of the foot. Eight HCR and 8 LCR rats underwent high frequency pacing prior to hind limb femoral artery occlusion to establish baseline differences between the phenotypes, and 13 HCR and 14 LCR rats received pacing at the time of euthanasia to establish functional differences in the effective remodeling following femoral artery ligation.

Rosenblatt Staining and Analysis

Gastrocnemius muscles for each animal not used for microsphere studies of blood flow were cut in half and quickly frozen. One half was placed in optimal cutting temperature (O.C.T.) compound while the other half was stored for protein isolation. The muscle in the OCT was cut into transverse sections (thickness 10 μm) and underwent capillary staining as originally defined by Rosenblatt et al. (31). Briefly, Rosenblatt staining allows capillary visualization for subsequent photographs under 20 x magnification. From the images, measurements were obtained in five fields per section, 50 myocytes/field, and in at least five separate sections, with care taken to avoid repeated sampling of the same field in sequential sections. The following indices were measured: (1) number of capillaries around a fiber (NCAF), (2) the capillary to fiber ratio on an individual fiber basis (Cap/Fi), (3) the number of fibers sharing each capillary [share factor (SF)], and (4) capillary density (CD). This stain also provides the ability to distinguish between different muscle fiber types. Slow twitch fibers were counted and are presented as a percentage of the total fiber number.

RNA Isolation, Reverse Transcriptase-PCR, and Real-Time PCR

Total RNA was extracted from harvested gastrocnemius muscle using TriReagent (Sigma-Aldrich, USA) and cDNA was generated using the High Capacity cDNA kit from Applied Biosystems (Foster City, CA) following the manufacturer's protocol. Real-time PCR was performed using specific primers (**Table 1**) (Invitrogen, La Jolla, CA) and SYBR Green mix (Applied Biosystems, Foster City, CA) following the manufacturer's protocol and using GAPDH as the reference gene as CT values for this gene did not change with treatment. The Real-Time PCR detection system used was the ABI Prism 7900 sequence detection system (Applied Biosystems, Foster City, CA). LCR control samples were used for all data to be normalized with the $\Delta\Delta^{ct}$ method.

TABLE 1 | Real Time PCR Primers sequences.

Primer	Forward sequence	Reverse sequence
VEGF	TTCAAGCCGTCCTGTGTGC	TCCAGGGCTTCATCATTGC
Flt-1	CCTCGCCAGAAGTCGTATGG	CCTCGCCAGAAGTCGTATGG
KDR	TCAAGATCCTCATCCACATTGG	GGGCTTCGTGCAGGCA
Ang1	AGATACAACAGAATGCGGTTCAAA	TGAGACAAGAGGCTGGTTCCTAT
Ang2	TGGCTGGGCAACGAGTTT	TGGATCTTCAGCACGTAGCG
eNOS	GTGCTGGCATACAGAACCCA	CCATGTGGAACAGACCCCA
GAPDH	GCTGAGTATGTCGTGGAGTC	GTCAGATCCACAACGGATAC

Statistics

Statistical analysis was performed using SPSS software (SPSS, Chicago, IL). Data are expressed as means ± SEM, and a p-value < 0.05 was considered statistically significant. Student unpaired t-test were used to compare intrinsic differences between LCR and HCR run time to exhaustion and run distance. For microsphere and histology variables, simple effects (LCR control vs. LCR acute, LCR acute vs. LCR 7D, LCR 7D vs. LCR 14D, HCR control vs. HCR acute, HCR acute vs. HCR 7D, HCR 7D vs. HCR 14D, LCR control vs. HCR control, LCR acute vs. HCR acute, and LCR 7D vs. HCR 7D, LCR14D vs. HCR14D) were the comparisons of interest. A mixed model analysis of variance (2 x 3 ANOVA, two groups [LCR and HCR) x three time points (control, acute, 7D for microsphere data and control, 7D, 14D for all other data sets)] was performed using SPSS on all variables between LCR and HCR control, seven day, and 14 day endpoints. High frequency stimulation data was collected in two separate experiments, so the post ligation data was analyzed with a student t-test as was the pre ligation data. A generalized linear model of variances using SPSS was performed on these two data sets with the intent to assess if there was a main effect for ischemia. When there was a significant interaction, *post hoc* test were done with Bonferroni adjustment. Significant differences were accepted in all circumstances where $p < 0.05$.

RESULTS

To provide a functional measurement for comparison between the phenotypes, high frequency electrical stimulation of the gastrocnemius muscle was performed prior and following ligation in two separate experiments. Prior to ligation, there were not significant differences between the phenotypes in the time to exhaustion with high frequency pacing [LCR time (s) = 2,291 ± 186 vs. HCR time (s) = 2,571 ± 218]. Following ligation, both strains decreased the time to muscle exhaustion with pacing, consistent with having induced an injury, but there was a significant difference between the strains (LCR = 437 ±

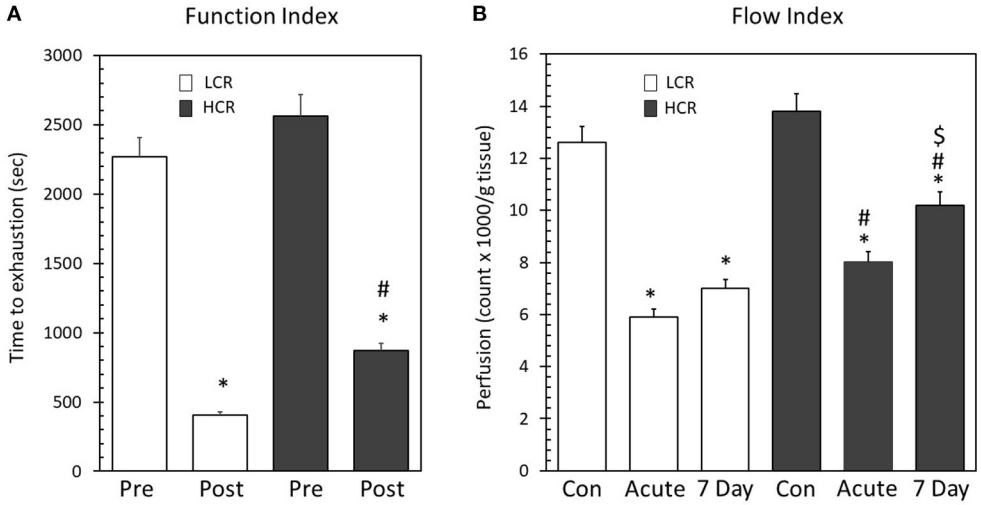


FIGURE 1 | (A) High frequency electrical stimulation before and following placement of unilateral hind limb ligation. There was no difference between the phenotypes prior to ligation. Following ligation, the time to exhaustion decreased significantly in both phenotypes (*$p < 0.05$ Pre vs. Post). The LCR in post ligation time to exhaustion was significantly less than the HCR ($^{\#}p < 0.05$ Post LCR vs. Post HCR). **(B)** Microsphere recovery from gastrocnemius, soleus, and plantaris muscles. Both phenotypes displayed significantly decreased blood flow following ligation (*$p < 0.05$ vs. phenotype control). LCR microspheres/g tissue was significantly less than the HCR at both the acute and 7D ischemic time points ($^{\#}p < 0.05$ vs. same time point between phenotypes). Following 7 days, the LCR did not significantly alter blood flow while the HCR significantly increased blood flow from acute ($^{\$}p < 0.05$ vs. 7 day time point within phenotype).

47 vs. HCR = 824 ± 56). The LCR gastrocnemius muscle time to exhaustion was significantly less than the HCR (**Figure 1A**), suggesting greater functional impairment in the LCR as a result of the occlusion.

Similar to the findings with pacing, there also were not differences in resting perfusion (LCR number of microspheres/g tissue = 13,424 ± 688 vs. HCR number of microspheres/g tissue = 12,563 ± 823). Not surprisingly, ligation of the femoral artery significantly decreased perfusion in both the LCR (6,383 ± 366) and HCR (7,821 ± 424) strains, but the decrease in perfusion was more severe in the LCR phenotype both immediately after ligation and 7 days after ligation (LCR = 6,880 ± 513 vs. HCR 9,522 ± 721) (**Figure 1B**). These data indicate that while both phenotypes decreased tissue perfusion in response to the hind limb ligature, the extent of perfusion deficit, and the resulting pattern of recovery over the next seven days was significantly different as a function of the phenotype.

mRNA expression for angiogenic growth factors was assessed with quantitative real time PCR (qRTPCR). VEGF expression was significantly lower in the LCR phenotype under baseline (pre-ischemic conditions (**Figure 2A**). Neither the LCR nor the HCR animals demonstrated significantly altered VEGF mRNA expression following 7D of ischemic challenge and baseline differences disappeared between the phenotypes at this time point. 14 days after ligation, the LCR significantly increased VEGF mRNA expression in the gastrocnemius muscle compared to both control (*__Figure 2A__) and 7D ischemic levels ($^{\$}$**Figure 2A**). Moreover, VEGF mRNA expression also was significantly greater in the LCRs than the HCRs 14 days after occlusion ($^{\#}$**Figure 2A**).

In contrast to VEGF, neither VEGF receptor (Flt-1) mRNA nor VEGF receptor (KDR) mRNA expression was significantly different between the phenotypes under baseline, pre-ischemic conditions. Neither the LCR nor the HCR animals demonstrated significantly altered Flt-1 or KDR mRNA expression following 7D of ischemic challenge. Similar to VEGF, Flt-1 mRNA expression increased significantly in the LCR ischemic muscle at 14 days, compared to either control (*__Figure 2B__) or 7D ischemic levels ($^{\$}$**Figure 2B**) and was also significantly greater than expression in the HCRs at 14 days post ischemia ($^{\#}$**Figure 2B**). However, these changes exhibited in Flt-1 were not in KDR mRNA expression (**Figure 2C**).

Angiopoietin 1 mRNA expression was significantly higher in the LCR phenotypes under baseline conditions ($^{\#}$**Figure 2D**) but neither phenotype significantly altered the expression of this growth factor and the differences present at baseline were no longer present at 7D or 14D.

Angiopoietin 2 mRNA expression was significantly higher in the HCR phenotype under baseline conditions ($^{\#}$**Figure 2E**), and did not change in this phenotype at either 7 or 14 days after occlusion. In contrast, the LCR phenotype showed significant increases in Ang 2 expression 14 days after occlusion ($^{*,\$}$**Figure 2E**), abolishing any differences that were present between the phenotypes before occlusion.

eNOS mRNA expression was significantly lower in the LCR phenotype under baseline conditions ($^{\#}$**Figure 2F**). Neither the LCR nor the HCR animals demonstrated significantly altered eNOS mRNA expression following 7D of ischemic challenge and baseline differences disappeared between the phenotypes at this time point. 14 days after ligation, the LCR significantly increased eNOS mRNA expression in the gastrocnemius muscle compared

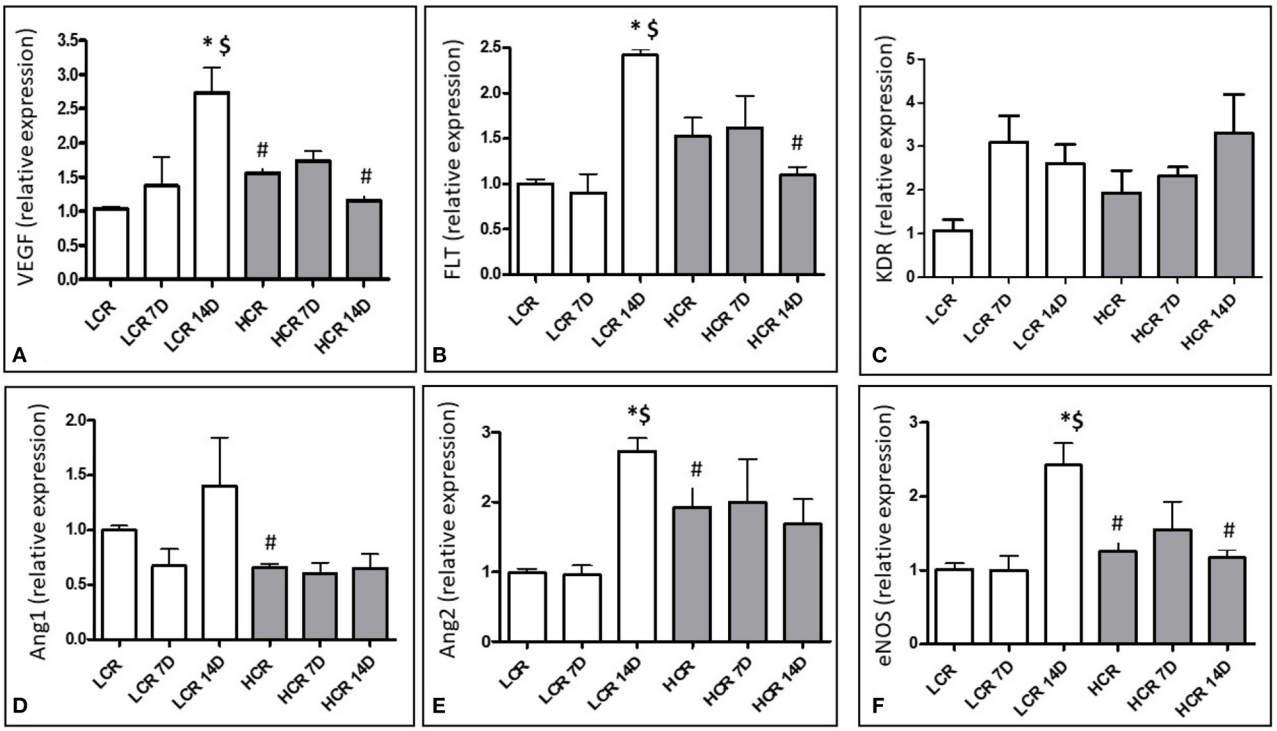


FIGURE 2 | Relative mRNA expression for VEGF **(A)**, Flt-1 **(B)**, KDR **(C)**, Angiopoietin 1 **(D)**, Angiopoietin 2 **(E)**, and eNOS **(F)**. $^{*}p < 0.05$ vs. control within phenotype; $^{\#}p < 0.05$ vs. same time point between phenotypes; $^{\$}p < 0.05$ vs. 7 day time point within phenotype.

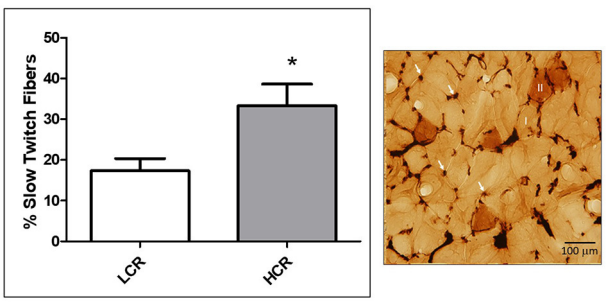


FIGURE 3 | Sample image of Rosenblatt attained muscle cross section (right). Arrows indicate capillaries and numerals indicate either type II (dark stained) or type I (light stained) muscle fibers. Left is a graphical summary showing the fraction of slow twitch muscle fibers within gastrocnemius muscle under baseline conditions. LCR had a significantly smaller percentage of slow twitch fibers compared to HCR ($^{*}p < 0.05$).

to both control (*Figure 2F) and 7D ischemic levels ($Figure 3). Moreover, eNOS mRNA expression also was significantly greater in the LCRs than the HCRs 14 days after occlusion (#Figure 2F).

Histology data indicate that the LCR has reduced capillary density (CD) (LCR = 417.81 ± 23.6) compared to the HCR in non-ischemic gastrocnemius muscle (HCR = 614.6 ± 57.5) ($^{\#}p < 0.05$, **Table 2**), consistent with previous reports (3, 28). The HCR phenotype increased capillary density at both 7 (918.54 ± 197.6) and 14 days (1,015.41 ± 174.9) after occlusion (*Table 2). In contrast, capillary density in LCRs was significantly lower at all time points (LCR 7 Day = 564.76 ± 40.5, LCR 14 Day = 507.48 ± 54.2) (#Table 2), and in contrast to HCRs, capillary density did not change in LCRs after occlusion. There were no differences in capillary contacts per fiber (NCAF) between phenotypes under control conditions (LCR = 4.547 ± 0.220 vs. HCR = 4.280 ± 0.217), but both phenotypes increased NCAF significantly in response to ischemia. However, the increase in the HCRs was earlier in onset, present at both 7 (5.170 ± 0.276) and 14 days after occlusion (5.210 ± 0.255) (*Table 2), while the LCR was significantly elevated only at the 14 day endpoint (6.220 ± 0.481) (*Table 2). At 14 days, the NCAF values had become significantly greater in the LCR compared to the HCR animals (#Table 2).

Similar to the NCAF results, the capillary to fiber ratio on the individual fiber basis (Cap/Fib) were not different under baseline conditions (LCR = 1.662 ± 0.089 vs. HCR = 1.555 ± 0.073), but increased in both phenotypes in response to occlusion. Again, the increase in the HCR phenotype was evident at both the 7 (1.896 ± 0.149) and 14 day (1.852 ± 0.097) time points compared to control (*Table 2), but a similar increase above control levels was not seen in the LCR animal until 14 days (2.248 ± 0.183) (*Table 2), at which point the NCAF values were significantly higher in the LCR than the HCR animals (#Table 2).

The percentage of slow twitch muscle fibers in the mixed gastrocnemius muscles from the LCR and HCR animals was

TABLE 2 | Skeletal muscle morphology and capillarization in the gastrocnemius muscle of control, 7 and 14 day ischemic tissue of LCR and HCR rats.

	LCR	HCR
Area μm^2		
Non-ischemic gastrocnemius	4349.8 ± 281.3	2783.6 ± 236.3$^{\#}$
7 day ischemic gastrocnemius	3031.4 ± 372.7*	2433.3 ± 369.8
14 day ischemic gastrocnemius	4938.5 ± 788.6$^{\$}$	2292.7 ± 622.2$^{\#}$
Perimeter μm		
Non-ischemic gastrocnemius	267.76 ± 8.57	211.85 ± 8.75
7 day ischemic gastrocnemius	224.57 ± 9.44	200.72 ± 14.4
14 day ischemic gastrocnemius	290.61 ± 26.95	190.29 ± 22.9
Capillary density, capillaries/mm^2 (CD)		
Non-ischemic gastrocnemius	417.81 ± 23.6	614.60 ± 57.5$^{\#}$
7 day ischemic gastrocnemius	564.76 ± 40.5	918.54 ± 197.6$^{*\#}$
14 day ischemic gastrocnemius	507.48 ± 54.2	1015.41 ± 174.9$^{*\#}$
Capillary contacts (NCAF)		
Non-ischemic gastrocnemius	4.547 ± 0.220	4.280 ± 0.217
7 day ischemic gastrocnemius	4.370 ± 0.584	5.170 ± 0.276*
14 day ischemic gastrocnemius	6.220 ± 0.481$^{*\$}$	5.210 ± 0.255$^{*\#}$
Individual capillary to fiber ratio (cap/fib)		
Non-ischemic gastrocnemius	1.662 ± 0.089	1.555 ± 0.073
7 day ischemic gastrocnemius	1.603 ± 0.233	1.896 ± 0.149*
14 day ischemic gastrocnemius	2.248 ± 0.183$^{*\$}$	1.852 ± 0.097$^{*\#}$
Share factor (SF)		
Non-ischemic gastrocnemius	2.896 ± 0.014	2.933 ± 0.062
7 day ischemic gastrocnemius	2.890 ± 0.038	2.938 ± 0.069
14 day ischemic gastrocnemius	2.935 ± 0.023	3.14 0.015

$^{\#}$*Significant differences between phenotypes at corresponding time point.*
**Significant differences from control condition within phenotype.*
$^{\$}$*Significant differences vs. 7 day ischemic value within phenotype.*

compared (**Figure 3**). The LCR rats had a significantly lower percentage of slow twitch fibers in the control gastrocnemius muscle compared to the HCRs ($^{*}p < 0.05$, **Figure 3**).

DISCUSSION

The development of intermittent claudication is a major decrement to the quality of life in patients (1, 2, 31–33). A mounting body of evidence suggests that exercise training can increase perfusion in ischemic tissue, improving quality of life and avoiding the necessity for surgical revascularization and other expensive therapies (1–3, 9, 33, 34). The majority of research on aerobic exercise training in PAOD patients has examined its effects upon vascular remodeling, including the mechanisms underlying changes in capillary density within the ischemic muscle (6, 7, 21, 22). However, many patients with intermittent claudication are unable to exercise or participate in exercise protocols due to pain in the ischemic limb or arthritic problems in joints, and exercise studies do not always provide definitive remodeling within tissue. Developing a better understanding of the genetic influences associated with intrinsic aerobic capacity and endurance capacity on the vascular remodeling process in response to ischemic challenge may help explain the variability in PAOD patients responses to aerobic exercise, and may provide new treatment options for individuals unable to participate in aerobic exercising protocols. The goal of this study was to investigate whether rats with low intrinsic running capacity have different vasculogenic responses following peripheral arterial occlusion than rats with high intrinsic running capacity.

The results of this study demonstrate that rats selectively bred, but not trained, for high endurance running capacity (HCR) differ in their response to ischemic stress in a model of PAOD compared to the low endurance running capacity (LCR) counterparts. These results provide strong evidence indicating that low endurance running capacity confers increased risk for ischemic injury and is subject to delayed and less effective adaptive response to ischemic stress.

LCR and HCR's were inherently different in capillary density before ischemia, with HCR rats having significantly higher capillary density than LCR rats. Under baseline conditions, the HCR strain also showed a higher relative expression of mRNA for VEGF, eNOS, Ang2 and significantly less relative expression of Ang1 compared to the LCR strain. These results are consistent with those found by Lloyd et al. (19), who showed similarly increased amounts of angiogenic markers in response to active aerobic exercise training protocols in rats, except that in the present studies, these were intrinsic differences predicated only on intrinsic aerobic phenotype, and not dependent on any active training component. Similar to the actively exercised rats, the HCRs appear to have an underlying increased angiogenic potential under basal conditions compared to the LCR phenotype.

LCR muscle cells showed a significantly larger area compared to the HCR, a finding consistent with Howlett et al. (35) who found that mean cross-sectional area of the HCR fiber was 35% lower compared to the LCR. The combination of smaller fiber area, more capillaries, and greater oxidative capacity in HCR rats may provide the basis for explaining the inherent higher VO_{2max} observed in these animals without aerobic exercise training, and would be consistent with increased resistance to ischemic injury.

Increased capillary density (CD) (capillaries/mm^2) has been shown to strongly correlate with increased skeletal muscle oxygen conductance in this model (25). We now extend those observations by demonstrating that the HCRs may have inherently better protection for maintenance of tissue perfusion under ischemic conditions. This was functionally evident with the prolonged time to exhaustion with high frequency electrical stimulation, and by higher post-ischemic perfusion levels. Although the initial drop in blood flow after occlusion is greater in the LCRs, consistent with provoking a more potent ischemic stress, the LCRs do not demonstrate a measurable recovery in perfusion at seven days. The HCRs initially lose less perfusion with acute arterial occlusion, presumably associated with better ischemic tolerance, and also recover perfusion in the post-ischemic tissue, consistent with anatomic remodeling, altered arteriolar/collateral tone favoring dilation, or both. This flow preservation, suggesting an improved tolerance for ischemic stress by the HCR, is further supported by the HCR's ability to maintain muscle fiber area (**Table 2**). Furthermore, despite less

ischemic pressure and negligible changes in fiber area, HCR rats showed a significant increase in capillary density at seven days despite negligible changes in the mRNA expression of angiogenic markers suggesting the possibility that the elevated baseline expression levels of the typical angiogenic growth factors in the HCRs were sufficient to drive any required angiogenesis. These might be more analogous to patients who develop claudication, but do not progress to critical limb ischemia.

Conversely, the LCR animals did not generate a measurable change in perfusion following seven days of ischemic pressure. These animals responded to seven days of femoral artery ligation with a significant loss of muscle fiber area consistent with atrophic loss of muscle mass. Perhaps because there was loss of muscle mass, there was a reduced ischemic signal source such that the LCR rats did not alter capillary density (CD), Cap/Fib ratio, or NCAF significantly from baseline levels, and perfusion did not recover. The LCR rats did not show significant changes in mRNA expression for any of the angiogenic factors from the baseline to the 7D ischemic time point, suggesting that the LCR rats initially respond to seven days of ischemia was a loss in fiber area and no angiogenic response, despite a substantial loss in perfusion. These might be more analogous to patients who develop critical limb ischemia.

Following 14 days of femoral artery occlusion, the HCRs continued to maintain fiber area but did not significantly alter any angiogenic markers from seven day levels, suggesting that after 14 days of ischemia, angiogenesis was no longer an active pathway within this phenotype and vascular remodeling processes had been completed. This finding is consistent with Lloyd et al. who reported that ischemia-induced angiogenesis typically alters mRNA within 7-10 days and returns toward baseline levels by about 14 days (19). Of particular interest in the present study was that HCRs appeared to increase the percentage of slow twitch fibers with 14 days of ischemia. A fast to slow fiber switch is normally seen in response to aerobic exercise training and aging (19), but ischemia and unloading is typically associated with a slow to fast phenotypic shift. The dynamic recovery response over a 2 week period in the HCRs appears to involve a shift in fiber type and an increase in fiber numbers, associated with higher pre-existing angiogenic signals and fueled by a better flow recovery. In contrast, after an initial fiber loss at 7 days, muscle fiber area in the LCRs significantly increased again 14 days after femoral artery occlusion, suggesting that there was a change in fiber size, but not fiber number, and an entirely different remodeling response. The increase in muscle fiber size may have been sufficient to recover a relative ischemia signal, as significant increases in mRNA expression for VEGF, Flt-1, eNOS, and Ang2 were observed at 14 days after occlusion. Together, these findings suggest that an angiogenic drive remains inducible in the LCR phenotype, but that the dynamic between muscle mass, muscle number, demand ischemia and vascular remodeling still is incompletely understood. Recent reports in mice (36), and subsequently in humans (37), have suggested a potential role for BAG-3 (Bcl-2-Associated Athanagene-3) coding variants in dictating the response to ischemia in skeletal muscle. This angiogenic stimulus may be in response to signals associated with hypertrophy of the LCR cells, but not with the occlusive stimulus, or may be occurring at 14 days as a synergistic action of the loading stimulus in combination with ischemic drive within the tissue.

The present study suggests that LCR rats have an altered response to hind limb femoral artery occlusion compared to the HCR rats. This altered response is partially due to the phenotypic differences under baseline conditions, including significantly less capillary density, less angiogenic factor potential, larger fiber area, and a smaller percentage of slow twitch muscle fibers within the gastrocnemius muscle in the LCR animals. With onset of occlusion, the LCRs also appear to have an altered inducible response compared to the HCR. These alterations include fiber area initially decreasing, followed by a rebound to a larger area, a potent angiogenic upregulation at 14D ischemia and no significant changes in the percentage of slow twitch muscle fibers. These data suggest that low intrinsic aerobic capacity may have increased injury associated with ischemic disease and will generate an altered response that may require a combination ischemic challenge, and signaling from some other stress, such as increased mechanical loading of the muscle, to adequately stimulate vasculogenic responses.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by Institutional Animal Care and Use Committee (IACUC) East Carolina University.

AUTHOR CONTRIBUTIONS

EG and RL participated in designing, conducting, data analysis, and writing. MA and MZ participated in data analysis and writing. SB and LGK provided the animals and participated in experimental design. LCK participated in data analysis and manuscript review. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by NIH grant number P40OD021331, National Institutes of Health, Office of Research Infrastructure Programs.

REFERENCES

1. Milani RV, Lavie CJ. The role of exercise training in peripheral arterial disease. *Vasc Med.* (2007) 12:351-8. doi: 10.1177/1358863X07083177

2. Zakari M, Alsahly M, Koch LG, Britton SL, Katwa LC, Lust RM. Are there limitations to exercise benefits in peripheral arterial disease? *Front Cardiovasc Med.* (2018) 5:173. doi: 10.3389/fcvm.2018.00173

3. Wang J, Zhou S, Bronks R, Graham J, Myers S. Effects of supervised treadmill walking training on calf muscle capillarization in patients with intermittent claudication. *Angiology.* (2018) 60:36-41. doi: 10.1177/0003319708317337
4. Terjung RL, Zarzeczny R, Yang HT. Muscle blood flow and mitochondrial function: influence of aging. *Int J Sport Nutr Exerc Metab.* (2002) 12:368-78. doi: 10.1123/ijsnem.12.3.368
5. Bylund AC, Hammarsten J, Holm J, Schersten T. Enzyme activities in skeletal muscles from patients with peripheral arterial insufficiency. *Eur J Clin Invest.* (1976) 6:425-9. doi: 10.1111/j.1365-2362.1976.tb00538.x
6. Prior BM, Lloyd PG, Ren J, Li H, Yang HT, Laughlin MH, et al. Time course of changes in collateral blood flow and isolated vessel size and gene expression after femoral artery occlusion in rats. *Am J Physiol Heart Circ Physiol.* (2004) 287:H2434-47. doi: 10.1152/ajpheart.00398.2004
7. Prior BM, Lloyd PG, Yang HT, Terjung RL. Exercise-induced vascular remodeling. *Exerc Sport Sci Rev.* (2003) 31:26-33. doi: 10.1097/00003677-200301000-00006
8. Yang HT, Prior BM, Lloyd PG, Taylor JC, Li Z, Laughlin MH, et al. Training-induceds vascular adaptations to ischemic muscle. *J Physiol Pharmacol.* (2008) 59(Suppl 7):57-70.
9. Stewart AH, Lamont PM. Exercise training for claudication. *Surgeon.* (2007) 5:291-9. doi: 10.1016/S1479-666X(07)80028-X
10. Stewart AH, Smith FC, Baird RN, Lamont PM. Local versus systemic mechanisms underlying supervised exercise training for intermittent claudication. *Vasc Endovasc Surg.* (2008) 42:314-20. doi: 10.1177/1538574408314442
11. Gardner AW, Montgomery PS, Parker DE. Physical activity is a predictor of all-cause mortality in patients with intermittent claudication. *J Vasc Surg.* (2008) 47:117-22. doi: 10.1016/j.jvs.2007.09.033
12. Bouchard C, Lesage R, Lortie G, Simoneau JA, Hamel P, Boulay MR, et al. Aerobic performance in brothers, dizygotic and monozygotic twins. *Med Sci Sports Exerc.* (1986) 18:639-46. doi: 10.1249/00005768-198612000-00006
13. Bouchard C, Rankinen T, Chagnon YC, Rice T, Pérusse L, Gagnon J, et al. Genomic scan for maximal oxygen uptake and its response to training in the HERITAGE Family Study. *J Appl Physiol.* (2000) 88:551–9. doi: 10.1152/jappl.2000.88.2.551
14. Britton SL, Koch LG. Animal models of complex diseases: an initial strategy. *IUBMB Life.* (2005) 57:631-8. doi: 10.1080/15216540500251684
15. Britton SL, Koch LG. Animal genetic models for complex traits of physical capacity. *Exerc Sport Sci Rev.* (2001) 29:7-14. doi: 10.1097/00003677-200101000-00003
16. Koch LG, Britton SL, Wisløff U. A rat model system to study complex disease risks, fitness, aging, and longevity. *Trends Cardiovasc Med.* (2012) 22:29-34. doi: 10.1016/j.tcm.2012.06.007
17. Koch LG, Britton SL. Theoretical and biological evaluation of the link between low exercise capacity and disease risk. *Cold Spring Harb Perspect Med.* (2018) 8:a029868. doi: 10.1101/cshperspect.a029868
18. Gavin TP, Wagner PD. Attenuation of the exercise-induced increase in skeletal muscle Flt-1 mRNA by nitric oxide synthase inhibition. *Acta Physiol Scand.* (2002) 175:201-9. doi: 10.1046/j.1365-201X.2002.00987.x
19. Lloyd PG, Prior BM, Li H, Yang HT, Terjung RL. VEGF receptor antagonism blocks arteriogenesis, but only partially inhibits angiogenesis, in skeletal muscle of exercise-trained rats. *Am J Physiol Heart Circ Physiol.* (2005) 88:H759-68. doi: 10.1152/ajpheart.00786.2004
20. Lloyd PG, Prior BM, Yang HT, Terjung RL. Angiogenic growth factor expression in rat skeletal muscle in response to exercise training. *Am J Physiol Heart Circ Physiol.* (2003) 284:H1668-78. doi: 10.1152/ajpheart.00743.2002
21. Prior BM, Yang HT, Terjung RL. What makes vessels grow with exercise training? *J Appl Physiol.* (2004) 97:1119-28. doi: 10.1152/japplphysiol.00035.2004
22. Hazarika S, Dokun AO, Li Y, Popel AS, Kontos CD, Annex BH. Impaired angiogenesis after hindlimb ischemia in type 2 diabetes mellitus: differential regulation of vascular endothelial growth factor receptor 1 and soluble vascular endothelial growth factor receptor 1. *Circ Res.* (2007) 101:948-56. doi: 10.1161/CIRCRESAHA.107.160630
23. Grundmann S, Piek JJ, Pasterkamp G, Hoefer IE. Arteriogenesis: basic mechanisms and therapeutic stimulation. *Eur J Clin Invest.* (2007) 37:755-66. doi: 10.1111/j.1365-2362.2007.01861.x
24. Gale NW, Yancopoulos GD. Growth factors acting *via* endothelial cell-specific receptor tyrosine kinases: VEGFs, angiopoietins, and ephrins in vascular development. *Genes Dev.* (1999) 13:1055-66. doi: 10.1101/gad.13.9.1055
25. Thyfault JP, Rector RS, Uptergrove GM, Borengasser SJ, Morris EM, Wei Y, et al. Rats selectively bred for low aerobic capacity have reduced hepatic mitochondrial oxidative capacity and susceptibility to hepatic steatosis and injury. *J Physiol.* (2009) 587(Pt 8):1805-16. doi: 10.1113/jphysiol.2009.169060
26. Noland RC, Thyfault JP, Henes ST, Whitfield BR, Woodlief TL, Evans JR, et al. Artificial selection for high-capacity endurance running is protective against high-fat diet-induced insulin resistance. *Am J Physiol Endocrinol Metab.* (2007) 293:E31-4. doi: 10.1152/ajpendo.00500.2006
27. Wisloff U, Najjar SM, Ellingsen O, Haram PM, Swoap S, Al-Share Q, et al. Cardiovascular risk factors emerge after artificial selection for low aerobic capacity. *Science.* (2005) 307:418-20. doi: 10.1126/science.1108177
28. Yaoita H, Sakabe A, Maehara K, Maruyama Y. Different effects of carvedilol, metoprolol, and propranolol on left ventricular remodeling after coronary stenosis or after permanent coronary occlusion in rats. *Circulation.* (2002) 105:975-80. doi: 10.1161/hc0802.104503
29. Yaoita H, Yoshinari K, Maehara K, Sando M, Watanabe K, Maruyama Y. Different effects of a high-cholesterol diet on ischemic cardiac dysfunction and remodeling induced by coronary stenosis and coronary occlusion. *J Am Coll Cardiol.* (2005) 45:2078-87. doi: 10.1016/j.jacc.2005.03.037
30. Keeton RB, Binder-Macleod SA. Low-frequency fatigue. *Phys Ther.* (2006) 86:1146-50. doi: 10.1093/ptj/86.8.1146
31. Rosenblatt JD, Kuzon WM, Jr., Plyley MJ, Pynn BR, McKee NH. A histochemical method for the simultaneous demonstration of capillaries and fiber type in skeletal muscle. *Stain Technol.* (1987) 62:85-92. doi: 10.3109/10520298709107973
32. Tefera G, Turnipseed W, Tanke T. Limb salvage angioplasty in poor surgical candidates. *Vasc Endovascular Surg.* (2003) 37:99-104. doi: 10.1177/153857440303700203
33. Waters RE, Terjung RL, Peters KG, Annex BH. Preclinical models of human peripheral arterial occlusive disease: implications for investigation of therapeutic agents. *J Appl Physiol.* (2004) 97:773-80. doi: 10.1152/japplphysiol.00107.2004
34. van RN, Piek JJ, Buschmann I, Hoefer I, Voskuil M, Schaper W. Stimulation of arteriogenesis; a new concept for the treatment of arterial occlusive disease. *Cardiovasc Res.* (2001) 49:543-53. doi: 10.1016/S0008-6363(00)00206-6
35. Howlett RA, Kirkton SD, Gonzalez NC, Wagner HE, Britton SL, Koch LG, et al. Peripheral oxygen transport and utilization in rats following continued selective breeding for endurance running capacity. *J Appl Physiol.* (2009) 106:1819-25. doi: 10.1152/japplphysiol.00914.2007
36. McClung JM, McCord TJ, Ryan TE, Schmidt CA, Green TD, Southerland KW, et al. BAG3 (Bcl-2-Associated Athanogene-3) coding variant in mice determines susceptibility to ischemic limb muscle myopathy by directing autophagy. *Circulation.* (2017) 136:281-96. doi: 10.1161/CIRCULATIONAHA.116.024873
37. Ryan TE, Yamaguchi DJ, Schmidt CA, Zeczycki TN, Shaikh SR, Brophy P, et al. Extensive skeletal muscle cell mitochondriopathy distinguishes critical limb ischemia patients from claudicants. *JCI Insight.* (2018) 3:e123235. doi: 10.1172/jci.insight.123235

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 26 November 2021
doi: 10.3389/fcvm.2021.751864

Influence of Intrinsic Aerobic Exercise Capacity and Sex on Cardiac Injury Following Acute Myocardial Ischemia and Reperfusion

*Musaad B. Alsahly [1,2], Madaniah O. Zakari [1,3], Lauren G. Koch [4], Steven Britton [5], Laxmansa C. Katwa [1] and Robert M. Lust [1,6]**

[1] Department of Physiology, Brody School of Medicine, East Carolina University, Greenville, NC, United States, [2] Department of Physiology, College of Medicine, King Saud University, Riyadh, Saudi Arabia, [3] Department of Physiology, College of Medicine, Taibah University, Medina, Saudi Arabia, [4] Department of Physiology and Pharmacology, University of Toledo, Toledo, OH, United States, [5] Departments of Anesthesiology and Molecular and Integrative Medicine, University of Michigan, Ann Arbor, MI, United States, [6] East Carolina Diabetes and Obesity Center, East Carolina University, Greenville, NC, United States

OPEN ACCESS

Edited by:
Jian Yang,
Fudan University, China

Reviewed by:
Ahsas Goyal,
GLA University, India
Krekwit Shinlapawittayatorn,
Chiang Mai University, Thailand

***Correspondence:**
Robert M. Lust
lustr@ecu.edu

Specialty section:
This article was submitted to General Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

Received: 02 August 2021
Accepted: 28 September 2021
Published: 26 November 2021

Citation:
Alsahly MB, Zakari MO, Koch LG, Britton S, Katwa LC and Lust RM (2021) Influence of Intrinsic Aerobic Exercise Capacity and Sex on Cardiac Injury Following Acute Myocardial Ischemia and Reperfusion. Front. Cardiovasc. Med. 8:751864. doi: 10.3389/fcvm.2021.751864

Purpose: Previous reports have suggested that active exercise aside, intrinsic aerobic running capacity (Low = LCR, high = HCR) in otherwise sedentary animals may influence several cardiovascular health-related indicators. Relative to the HCR phenotype, the LCR phenotype is characterized by decreased endothelial reactivity, increased susceptibility to reperfusion-induced arrhythmias following short, non-infarction ischemia, and increased diet-induced insulin resistance. More broadly, the LCR phenotype has come to be characterized as a "disease prone" model, with the HCRs as "disease resistant." Whether these effects extend to injury outcomes in an overt infarction or whether the effects are gender specific is not known. This study was designed to determine whether HCR/LCR phenotypic differences would be evident in injury responses to acute myocardial ischemia-reperfusion injury (AIR), measured as infarct size and to determine whether sex differences in infarction size were preserved with phenotypic selection.

Methods: Regional myocardial AIR was induced *in vivo* by either 15 or 30 min ligation of the left anterior descending coronary artery, followed by 2 h of reperfusion. Global ischemia was induced in isolated hearts *ex vivo* using a Langendorff perfusion system and cessation of perfusion for either 15 or 30 min followed by 2 h of reperfusion. Infarct size was determined using 2, 3, 5–triphenyltetrazolium chloride (TTC) staining, and normalized to area at risk in the regional model, or whole heart in the global model. Portions of the tissue were paraffin embedded for H&E staining and histology analysis.

Results: Phenotype dependent differences in infarct size were seen with 15 min occlusion/2 h reperfusion (LCR > HCR, $p < 0.05$) in both regional and global models. In both models, longer occlusion times (30 min/2 h) produced significantly larger infarctions in both phenotypes, but phenotypic differences were no longer present (LCR vs. HCR, p = n.s.). Sex differences in infarct size were present in each phenotype (LCR male > LCR

female, $p < 0.05$; HCR male > HCR female, $p < 0.05$ regardless of length of occlusion, or ischemia model.

Conclusions: There is cardioprotection afforded by high intrinsic aerobic capacity, but it is not infinite/continuous, and may be overcome with sufficient injury burden. Phenotypic selection based on endurance running capacity preserved sex differences in response to both short and longer term coronary occlusive challenges. Outcomes could not be associated with differences in system characteristics such as circulating inflammatory mediators or autonomic nervous system influences, as similar phenotypic injury patterns were seen *in vivo*, and in isolated crystalloid perfused heart *ex vivo*.

Keywords: aerobic capacity, HCR, LCR, intrinsic, gender, coronary occlusion

INTRODUCTION

Enhanced aerobic capacity has been associated with diminished morbidity, improved quality of life, and decrease risk for cardiovascular diseases (1–3). Coronary artery disease is currently the leading cause of mortality and morbidity in the western world. The most common fatal consequence of coronary artery disease is an acute myocardial infarction, and death due to coronary artery disease appears to decrease with treatments that include an aerobic exercise component (2, 3). It remains unclear whether the benefits of exercise derive primarily from altered risk profiles (lipid, obesity, etc.) or directly from intrinsic myocardial resistance to injury.

As understanding of the mechanisms involved with tissue injury following arterial occlusion (ischemia), and then subsequent appreciation of additional injury associated with relieving the occlusion (reperfusion) advanced (4–6), it became clear that periods of intermittent ischemia that either immediately preceded the ischemic event (ischemic preconditioning), or immediately preceded the reperfusion event (ischemic post-conditioning) could induce multiple pathways that could limit the extent of injury and improve recovery (4–7). Pre-and post-conditioning effects were associated with erythropoietin, the heme-oxygenase system, and atrial natriuretic peptide among many others (8–10), and those effects could I turn depend on underlying conditions such as diabetes, hyperlipidemia, and estrogen status (8–10). Practically though, both pre-conditioning and post-conditioning have had limited success, simply due to the inherent challenges of creating controlled, intentional ischemia. Over the last 15 years, the phenomenon of remote preconditioning has been introduced, where mild demand ischemic challenges in distal regions, such ands an arm or leg, would confer protection against subsequent ischemia in critical organs, such as heart (4). Active exercise increasingly has become the option of choice both for reducing the impact of underlying conditions/comorbidities, as well as upregulating processes that could be recruited by pharmacologically and mechanically induced protective strategies (4, 5).

Aerobic exercise capacity has genetic and environmental components. The genetic component define the intrinsic capacity for endurance exercise and appears to have two parts, the genes that regulate adaptive responses to active exercise training and the genes that determine intrinsic exercise capacity, regardless of actual activity (11–14). Although aerobic exercise training has beneficial effects on several of cardiovascular diseases, the variability in the physiological response to exercise training suggests potential impact of the genetic composition. It has been estimated that up to 60–70% of the variation in exercise capacity is due to the genetic component (11, 13, 14). It is not clear if the genetic component for enhanced exercise capacity alone can result in protection from cardiovascular diseases or whether the training stimulus is necessary to produce the positive results, or if a combination of both is required. The development of a novel rat model using treadmill based phenotypic selection as a basis for breeding rather than specific gene manipulation has advanced the ability to differentiate the genetic components from the environmental effects, such as exercise training, that also influence the aerobic capacity (15–17). This novel rat model contrasts intrinsic aerobic capacity as a phenotype, low-capacity runners (LCR) and high-capacity runners (HCR), provides a tool to experimentally address the intrinsic component of exercise and its contribution to cardiovascular disease (15). Untrained low endurance running capacity (LCR) rats were found to have a higher incidence of risk factors associated with cardiovascular disease than their untrained high endurance running capacity (HCR) counterparts (15, 18). The LCR rats were more insulin resistant, had higher mean blood pressures, decreased nitric oxide mediated vascular relaxation, and had lower expression of proteins critical to skeletal muscle fatty acid oxidation (15, 18). LCR animals were predisposed to weight gain and increased blood free fatty acid (FFA) levels compared to HCR counterparts when challenged with a high fat diet (18). Moreover, compared to the HCRs, the LCRs displayed higher arrhythmogenicity following short term myocardial ischemia and reperfusion (13).

Early studies in this model also demonstrated differences in several skeletal muscle metabolic and vascular endpoints. Early studies indicated that HCR rats demonstrated increased VO_{2max} that was attributed to an increased O_2 capacity and/or increased capillary density in skeletal muscle under both normoxic and hypoxic exercise conditions (19–21). Later studies also indicated that HCR rats had increased VO_{2max} while LCRs appeared to have decreased VO_{2max} values. In addition to increased

skeletal muscle capillary density and increased oxidative enzymes reported previously, HCRs now also were demonstrating higher maximum cardiac stroke volume (SV) values in comparison to their LCR counterparts (20).

Noland et al. demonstrated that the LCR phenotype gained more weight and lost insulin sensitivity on a high fat diet compared to HCR (18). Results also have suggested that artificial selection for endurance running capacity selects for intracellular pathways that provide protection against metabolic and cardiovascular stresses. At the cellular level, it has been demonstrated that HCRs show larger amplitude calcium transients and higher efficiency in energy production (19), along with faster skeletal sarcomeric shortening and relaxation (20, 22). Still, cardiac and peripheral muscle metabolism are quite different, as are collateral circulation patterns, insulin sensitivity and responses to ischemia. Despite suggestions that might suggest a cardioprotective effect of intrinsic aerobic capacity, it is not clear whether such an effect actually is present, or whether the known exercise benefit in cardiovascular disease management is limited to active exercise induced effects. While the breeding selection process was initiated and developed with equal cohorts of males and females, the great majority of experimental studies using the model have been in male offspring. There are well-know differences in cardiac ischemia outcomes between males and females (23, 24), and it is not clear whether an intrinsic exercise capacity effect on cardiac ischemia, if present, would be evident in both male and female HCR and LCR rats.

MATERIALS AND METHODS

Animal Strain

The development of LCR and HCR rats has been described previously in detail (16, 25–27). Rats were selected from a heterogeneous rat population in the N:NIH stock (National Institutes of Health, USA) based on inherent running capacity. Endurance running capacity was assessed at 11 weeks of age using run time and distance to exhaustion on a treadmill as parameters. The highest 20% in running capacity of each gender were randomly inbred/backbred to produce the HCR strain and the lowest 20% in running capacity were inbred/backbred to produce the LCR strain. Subsequent generations were assessed and bred in a similar fashion with precautions taken to minimize inbreeding (<1% per generation). Both female and male HRC and LCR rats, 16–18 months of age, from generation 17 were used in this investigation. There were a total of 8 groups: 4 groups (HCR male, HCR female, LCR male, LCR female, $n = 12$ each) underwent regional ischemia, and 4 groups (HCR male, HCR female, LCR male, LCR female, $n = 12$ each) underwent global ischemia. Half of each group ($n = 6$) went through either the 15 min or the 30 min ischemia challenge, followed by 2 h of reperfusion in all animals. Until study, all animals were maintained in constant temperature environments (22°C) with 12/12 light dark cycles, and *ad libitum* access to water and food (standard rat chow, Research Diets, New Brunswick NJ, USA). All animal procedures were approved by the East Carolina University Institutional Animal Care and Use Committee and conformed to the standards in the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals.

Regional Acute I/R Injury

Regional AIR was induced using procedures essentially as described previously (28, 29). Briefly, all animals were anesthetized (Ketamine/Xylazine) and mechanically ventilated with room air. The heart was exposed through a thoracotomy performed in the left fifth intercostal space. The pericardium was gently separated, and a ligation of the left anterior descending coronary artery was performed using 6.0 suture and a reversible snare. Occlusion was confirmed by cyanosis of the distal myocardial tissue. Following 15- or 30-min occlusion, the snare was released, and the tissue was reperfusion for 2 h. There is a high risk of lethal arrhythmia in this occlusion model, and the availability of animals was limited enough that expected mortality could have compromised the reliability of the infract size measurements, a primary endpoint. To limit the risk of arrhythmia and optimize successful completion of reperfusion, i.p. lidocaine was administered as prophylaxis 5 min before coronary occlusion, 5 min before reperfusion, and 15 min following reperfusion. Similarly, we avoided instrumenting the heart or manipulating the ventricle to the greatest extent possible so as to maintain the number of animals successfully completing the full IR protocol. The approach did work, but it also meant that hemodynamics and assessment of arrhythmia were not completed in the regional IR animals.

Global Acute Ischemia/Reperfusion Injury

Global AIR was induced using procedures essentially as described previously (30, 31). Briefly, after anesthesia was induced using (Ketamine/Xylazine), the thorax was opened and the beating heart was excised rapidly. The aorta was cannulated, the heart was mounted in a constant pressure, Langendorff system, and perfusion was immediately initiated using Krebs-Henseleit buffer (composition (mM): NaCl 118; KCl 4.7; $MgSO_4$ 1.2; KH_2PO_4 1.2; $NaHCO_3$ 25; $CaCl_2$ 1.4; glucose 11; pH 7.3–7.4) aerated with 95% O_2/5% CO_2. System and buffer temperatures were maintained at 37° continuously. Perfusion pressure was set to 80 mm Hg by reservoir height and verified by direct pressure sampling via stopcock at the level of the infusion cannula. Constant preload was established by placing an LV balloon and inflating to a diastolic pressure of 5 mm Hg. The hearts were not paced and were permitted to beat spontaneously. Electrocardiogram and LV pressures were obtained in these animals for subsequent hemodynamic and rhythm assessments. Rhythms were graded on an 9 point scale, ranging from 0, equating to fewer than 50 isolated premature ventricular contractions (PVCs) up to a score of 8, which equated to non-reverting (lethal) ventricular fibrillation within 1 min following reperfusion (30).

Determination and Quantification of Infarct Size

TTC staining is a well-established procedure for identifying infarct size (28–31). Following reperfusion in the regional

model, and while continuously anesthetized, the animals were euthanized by rapid excision of the heart. The aorta was cannulated and the heart was infused retrogradely with a 1.0% solution containing 2,3,5-triphenyltetrazolium chloride (TTC) to delineate the infarcted area. The coronary artery was re-occluded at the original ligature site and a 1.0% solution containing methylene blue was infused through the aortic cannula as counterstain to delineate the area at risk, followed by transverse sectioning of the entire heart. In the global ischemia model, the heart was removed from the apparatus and transverse sectioning was completed immediately. The sections were transferred to a shaker bath containing a 1% TTC solution and incubated for 5 min at 37°C. Once stained, all sections were photographed form both sides using a digital camera. From these photographs, the LV area, area at risk, and area of infarction in each image were determined using NIH image software (ImageJ, version 1.34s). In the regional model, the area at risk was expressed as a percentage of the LV area and the area of the infarcted zone was expressed as a percentage of the area at risk. In the global model, since the entire ventricle was "at risk," the infraction was expressed as % of whole heart.

Histology

Histology was performed on the same tissue sections used for infarct measurements. Following TTC staining and digital photography, one of the myocardial sections was fixed in 4% paraformaldehyde, embedded in paraffin wax, and cut at 5-um sections. Sections were stained with hematoxylin and eosin (H&E) and examined by light microscopy under high magnification (X 60). The number of infiltrated neutrophils in each high–power field was counted and normalized to the area of the field, based on the microscope specifications. Neutrophil counts were made on five sections per rat heart and on five fields per section.

Statistics

Differences between groups were determined by ANOVA and Tukey's *post hoc* test with significance determined when $p < 0.05$. Data in all figure are expressed as mean ± SD.

RESULTS

Acute I/R Injury

In the regional ischemia model, ligature placement was consistent and there were no significant differences in the area at risk among the groups (HCR males = 57.3% ± 4.0, LCR males = 53.0% ± 3.7, HCR females = 52.8% ± 3.2, LCR females = 56.7% ± 3.6) (**Figure 1**).

Myocardial Infarct Size

Thirty minutes of regional ischemia followed by 2 h of reperfusion generated no differences in infarct size between HCR and LCR. Infarct size was consistently smaller in female compared to male rats within each phenotype, but not between phenotypes (HCR males = 42.7% ± 4.3, LCR males = 44.7%, HCR females = 32.6% ± 3.2, LCR females = 31.9% ± 3.6) (**Figure 2**). Similar results also were seen in the global ischemia model (HCR males = 45.7% ± 4.4, LCR males = 49.9% ± 4.7, HCR females = 37.5% ± 3.6, LCR females = 36.6% ± 3.9) (**Figure 3**).

Thirty minute occlusion is the most common model in rat, but it is intended to produce substantial injury (near 50% of the risk area in regional ischemia; 40–50% of LC in global ischemia) in order to detect a meaningful effect when testing the efficacy of injury reducing interventions. To determine whether the insult was simply too severe and potentially overwhelmed any innate differences between phenotype, the studies were repeated but

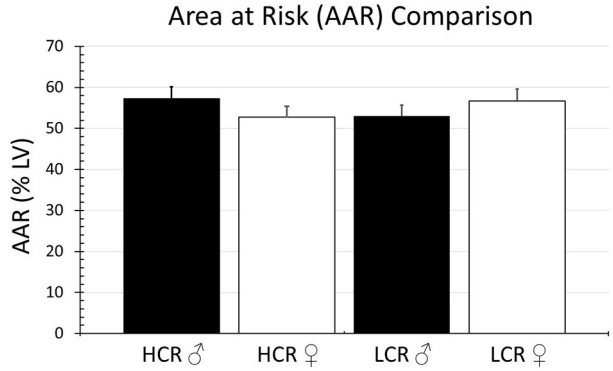


FIGURE 1 | Comparison of the percentage of the LV at risk for ischemia (AAR) in the regional ischemia model. The model was reproducible, and the amount myocardium rendered ischemic by coronary occlusion was comparable in all groups.

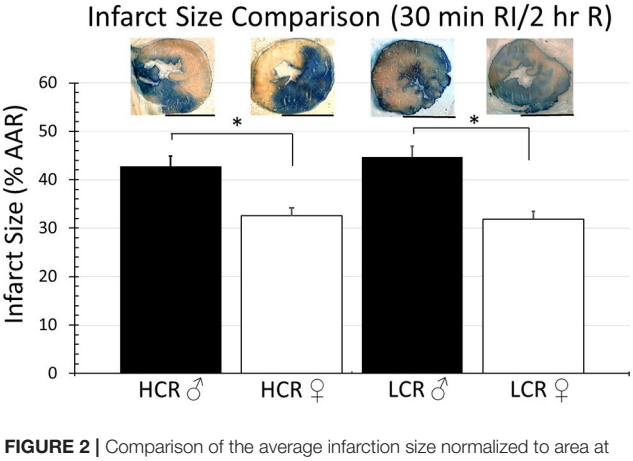


FIGURE 2 | Comparison of the average infarction size normalized to area at risk (%AAR) between HCR male/female and LCR male/female rats after 30 min ischemia and 2 h reperfusion using an *in situ* regional ischemia (RI) model. Scale bars in images indicate 5 mm. Significant differences were noted between sexes within each phenotype, but not between phenotypes for either sex (*$p < 0.05$ for the comparison indicated).

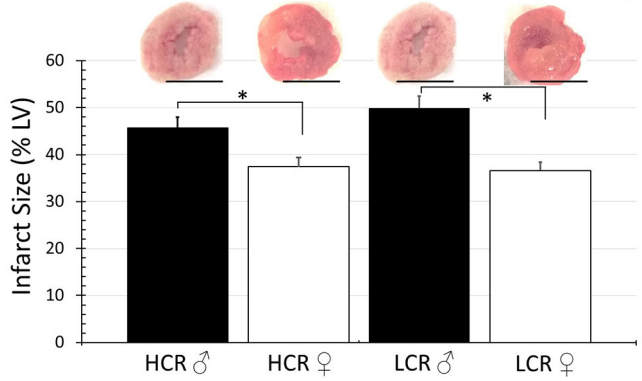


FIGURE 3 | Comparison of the average infarction size normalized to the whole heart between HCR male/female and LCR male/female rats after 30 min ischemia and 2 h reperfusion using an *ex vivo* buffer-perfused global ischemia (GI) model. Scale bars in images indicate 5 mm. Significant differences were noted between sexes within each phenotype, but not between phenotypes for either sex (*$p < 0.05$ for the comparison indicated).

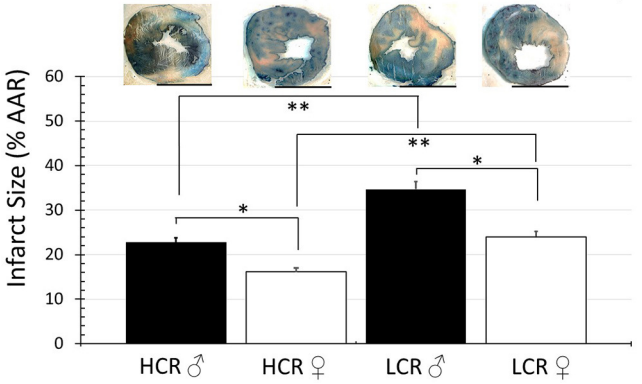


FIGURE 4 | Comparison of the average infarction size normalized to area at risk (%AAR) between HCR male/female and LCR male/female rats after 15 min ischemia and 2 h reperfusion using an *in situ* regional ischemia (RI) model. Infarct sizes were smaller for all groups compared to 30 min regional ischemia (**Figure 2**). Scale bars in images indicate 5 mm. Significant differences were noted between sexes within each phenotype, and also between phenotypes for each sex, with LCRS having larger average infarctions compared to HCRs (*$P < 0.05$ for the comparison indicated between sexes within phenotype; **$P < 0.05$ for the comparison indicated between phenotype within sex).

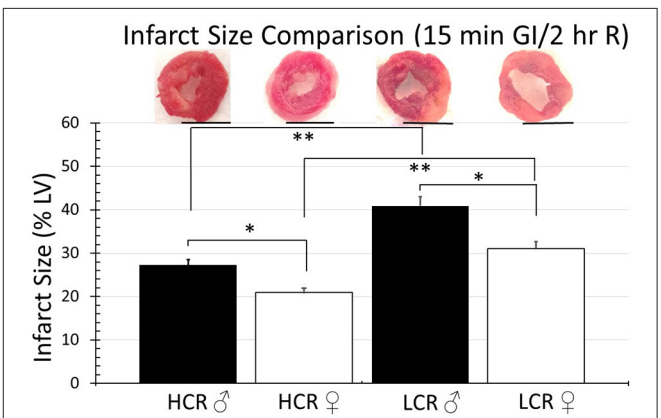


FIGURE 5 | Comparison of the average infarction size normalized to the whole heart between HCR male/female and LCR male/female rats after 15 min ischemia and 2 h reperfusion using an *ex vivo* buffer-perfused global ischemia (GI) model. Infarct sizes were smaller for all groups compared to 30 min global ischemia (**Figure 3**). Scale bars in images indicate 5 mm. Significant differences were noted between sexes within each phenotype, and also between phenotypes for each sex, with LCRS having larger average infarctions compared to HCRs (*$P < 0.05$ for the comparison indicated between sexes within phenotype; **$P < 0.05$ for the comparison indicated between phenotype within sex).

with occlusive time reduced to 15 min, again followed by 2 h of reperfusion. Under these circumstances, there was an expected overall reduction in infarction size in all groups, regardless of sex or phenotype, compared to the 30 min ischemia results. However, HCRs, both male and female, showed a larger decrease than the LCRs, and a reduction in infarct size by phenotype consistent with relative cardioprotection in HCRs that was phenotype, and sex specific (HCR males = 22.7% ± 2.9, LCR males = 34.7% ± 3.3, HCR females = 16.2% ± 2.0, LCR females = 24.0% ± 2.1) (**Figure 4**). Similar results also were seen in the global ischemia model (HCR males = 27.2% ± 2.4, LCR males = 40.9% ± 3.9, HCR females = 20.8% ± 2.0, LCR females = 31.1% ± 2.9) (**Figure 5**).

Histologic assessment of neutrophil infiltration in tissue sections from regional ischemia groups revealed a generalized increase in infiltration in the ischemic region of about 20% above remote regions from the same heart (**Figure 6A**). However, the level of infiltrate was not different between phenotypes, and contrary to infarct size, also was not different between male and female in either phenotype (HCR M, Ischemic 107.5 ± 9.2, Remote 81.6 ± 5.8; HCR F, Ischemic 111.1 ± 9.7, Remote 80.3 ± 5.5; LCR M, Ischemic 107.4 ± 7.9, Remote 80.8 ± 6.3; LCR F, Ischemic 109.3 ± 9.8, Remote 79.9 ± 5.4) (**Figure 6B**). There also was no difference between 30 min ischemia and 15 min ischemia (data not shown), suggesting that infiltrate is driven more by reperfusion than by ischemia.

The arrhythmia scores in the global ischemia cohorts are summarized in **Figure 7**. The incidence of reperfusion arrhythmia was higher with 30 min ischemia vs. 15 min in all groups. There were not differences within phenotypes between male and female animals, and there were not differences within sex when comparing across HCR and LCR strains.

A summary of changes in left ventricular developed pressure (LVDP, mm Hg), and the positive and negative rate of pressures change (+dP/dt and –dP/dt mm Hg/s, respectively), is provided in **Table 1**. Functional performance indices showed substantial and significant decreases with ischemia compared to baseline for both ischemic times, but 30 min of ischemia did not further decrease the function, or alternatively, shortening ischemia to 15 min was not enough to significantly recover the function, even though tissue injury was reduced (infarct size, **Figures 3**, **5**),

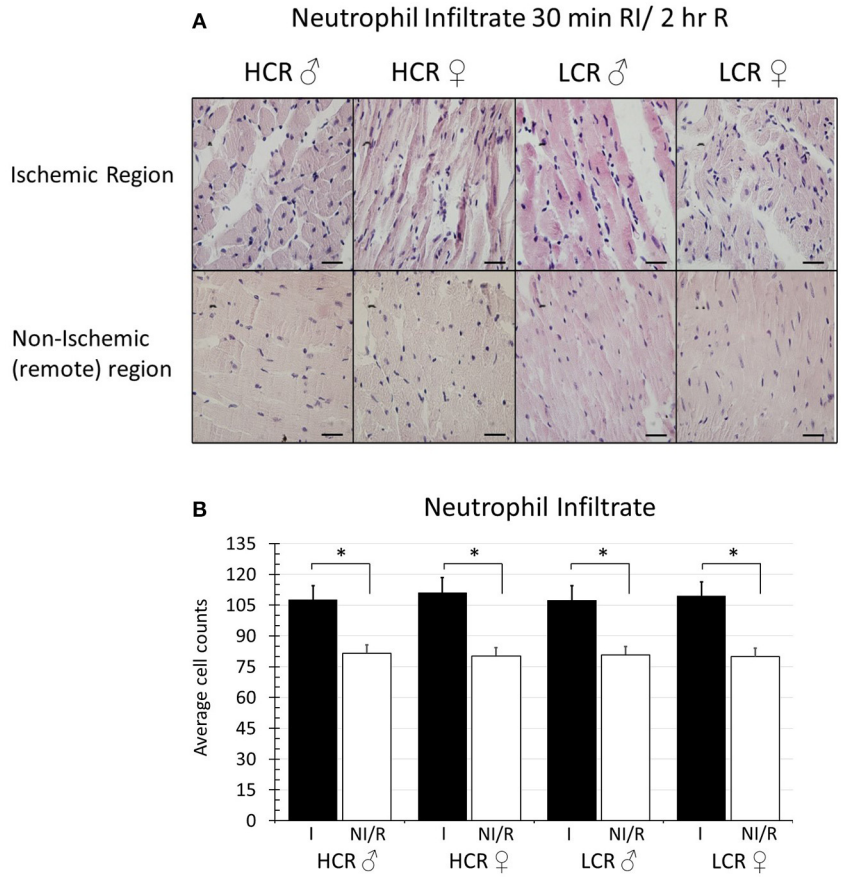


FIGURE 6 | (A) Sample histologic sections showing relative myocardial neutrophil infiltration after 30 min *in situ* regional ischemia (RI) and 2 h reperfusion by sex and by phenotype in samples from the ischemic region, and from non-ischemic, remote regions (right ventricle) from the same hearts (H&E staining, 60X). Scale bars in images represent 200 um. **(B)** Quantification of neutrophil infiltration (cell counts). Data represents average of 5 fields in each section, and 5 sections for each animal. Ischemic regions (I) showed higher levels of infiltration compared to non-ischemic remote (NI/R) regions, but the increased levels of infiltration were not different between sexes within either phenotype, and were not different between phenotypes for either sex (*$p < 0.05$ for the comparison indicated).

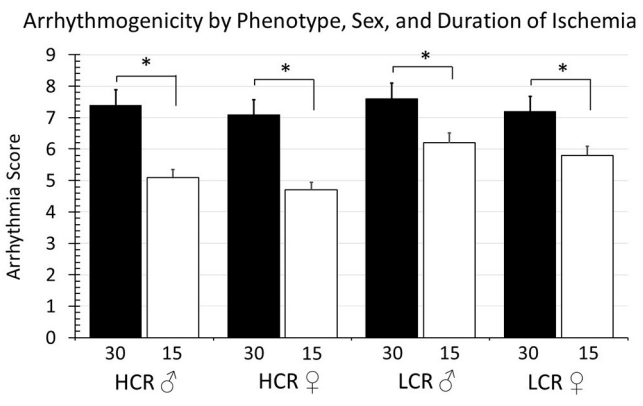


FIGURE 7 | Summary of arrhythmia scores according to duration of ischemia (30 vs. 15 min), strain (HCR vs. LCR), and sex (males vs. female). There were significant differences in the severity of arrhythmia (*$P < 0.05$ for the comparison indicated), with 30 min ischemic episode producing consistently higher arrhythmia scores than 15 min events, however there were not significant differences between strain or between sexes with strains.

suggesting that functional recovery is more complex than simple tissue salvage. There were no differences in these results between LCR and HCR strains comparing the same sex, or within either strain in male female comparisons.

DISCUSSION

In this study, using two different models of ischemia-reperfusion injury, it is clear that increased intrinsic aerobic capacity phenotype (HCR) did confer a level of cardioprotection relative to the reduced/low capacity phenotype (LCR) (**Figures 4**, **5**). The finding is consistent with a more general characterization of the HCR as "disease/injury resistant" phenotype, and the LCR as a "disease/injury prone" phenotype (25–27). Both phenotypes demonstrated comparable relative injury reduction in females relative to males, suggesting that the factors responsible for determining intrinsic aerobic capacity are not sex dependent, but that the responses determining response to cardiac ischemic injury are. The finding that similar results were seen in both

TABLE 1 | Summary of functional variables in global ischemia groups, by Phenotype, Sex, and duration of global ischemia.

	HCR ♂		HCR ♀		LCR ♂		LCR ♀	
Variable	**30I/120R**	**15I/120R**	**30I/120R**	**15I/120R**	**30I/120R**	**15I/120R**	**30I/120R**	**15I/120R**
LVDP-B	122 ± 12	118 ± 11	123 ± 11	119 ± 14	124 ± 10	119 ± 11	118 ± 13	119 ± 12
LVDP-R	22 ± 3	28 ± 4	26 ± 3	33 ± 3	24 ± 3	27 ± 7	27 ± 2	31 ± 3
+dP/dt B	4,332 ± 222	4,458 ± 355	3,997 ± 402	4,223 ± 405	3,987 ± 441	4,133 ± 367	3,994 ± 422	4,511 ± 333
+dP/dt R	721 ± 126	755 ± 155	758 ± 147	802 ± 112	776 ± 131	780 ± 142	818 ± 152	827 ± 147
–dP/dt B	2,791 ± 225	2,595 ± 302	2,666 ± 378	2,805 ± 314	2,746 ± 387	2,656 ± 379	2,681 ± 396	3,648 ± 336
–dP/dt R	450 ± 57	490 ± 58	518 ± 59	525 ± 62	455 ± 67	489 ± 64	505 ± 58	515 ± 63

30I/120R, 30 minutes global ischemia and 2 hours reperfusion; 15I/120R, 15 minutes global ischemia and 2 hours reperfusion; LVDB, LV developed pressure; B, baseline; R, reperfusion; +dP/dt, maximum rate of pressure development (mm Hg/sec); –dP/dt, maximum rate of pressure fall (mm Hg/sec).

intact regional ischemia models and in buffer perfused ischemia models *ex vivo* tends to suggest that the factors responsible for the differences in phenotype had more to do with inherent coronary and cardiac tissue characteristics than with any differences in circulating blood factors, or autonomic influences.

Noteworthy however, is that the cardioprotection associated with the HCR phenotype was lost with longer durations of ischemia. Extending the ischemic time from 15 to 30 min eliminated the difference in infarct size between the phenotypes (**Figures 2**, **3**). The sex difference within each phenotype remained. Relatively speaking, the difference in infarct size between 15 and 30 min was actually larger in the HCR than in the LCR, consistent with an accelerated rate of injury once the threshold for protection had been exceeded. The reperfusion periods were the same with both time periods. Neutrophil infiltration is a common hallmark associated with reperfusion injury and was not different between the phenotypes, suggesting the possibility that the loss of relative cardioprotection was more likely due to overwhelming intrinsic cardiac or coronary features during ischemia, rather than reperfusion.

The HCR phenotype has been associated with increased longevity generally (32), which means it might also be possible that there is less benefit from the phenotype in an acute injury model such as the one used in this study, than in a more chronic, progressive disease setting such as high fat feeding (18, 33). It is also possible that the effect seen here is tissue dependent, but others have reported no difference between phenotypes in survival from multisystem stress in a model of hemorrhagic shock (34). We also did not complete any longer-term outcomes following the ischemia reperfusion injury. It is possible that long term results in myocardial healing and progression to heart failure might have been different between phenotypes, despite similarities in initial injury (35, 36). Certainly, previous studies using this model have shown that the immune response is exaggerated in LCR (25–27), and particularly TNF-α (37) as well as interleukin-10 (38), all of which could alter the progression of post-ischemic remodeling. It also is important to note that lack of ischemic protection despite interventions such as exercise and diet control have been reported in humans as well when injury is sufficiently severe (39, 40).

Gender has been recognized as an important factor in determining the risk for cardiovascular diseases (23) and cardioprotective effects of sex hormones have been reported in both experimental and clinical studies (41). Moreover, gender differences have been well-established in models of ischemia reperfusion injury (23, 24). Bae and Zhang observed significantly less myocardial injury in female vs. male hearts following 25 min of ischemia and 2 h of reperfusion in Langendorff-perfused rat hearts (42). The current results suggest that gender effects on cardiac ischemic tolerance are preserved despite selection for intrinsic aerobic capacity. While there is much still to be determined, it is becoming increasingly clear that many of the sex related differences in outcomes from cardiovascular diseases could be related to sexual dimorphism at the mitochondrial level. Estrogen has a substantial influence on mitochondrial gene expression, which in turns influences biogenesis, apoptosis, energy production, calcium handling and ROS production (35).

In humans there is a strong association between active exercise and cardiovascular protection (43). Regular physical exercise has been shown effective in the secondary prevention of cardiovascular disease and is effective in attenuating the risk of premature death among men and women (44). In other rat models, it has been demonstrated that acute exercise training can induce cardioprotection that results in reduced infarctions following ischemia–reperfusion injuries (45, 46). However, there can be quite notable strain dependent differences in response to a wide range of physiological challenges (47). Humans are not entirely well-modeled by inbred animal strains. The HCR and LCR phenotypes were developed by phenotypic selection using an outbred background, as a model to better assess the genetic components of aerobic capacity (25–27). The HCR/LCR model has inherited differences in aerobic capacity without prior training. Wisloff et al. found that the LCR phenotype scored high on cardiovascular risk factors and the HCR score high for health factors (15) while Lujan et al. demonstrated that the LCR phenotype demonstrated increased ischemia-reperfusion–mediated ventricular tachyarrhythmias and the HCR phenotype decreased susceptibility to tachyarrhythmias following short duration, non-infarction ischemia (48).

One interesting hypothesis is that the higher level of intrinsic aerobic capacity creates relatively less opportunity to "pre-condition" the heart, if in fact the phenotype is inherently less vulnerable to demand induced ischemia (31, 42, 49). Similarly, the LCRS might exceed a "pre-conditioning" threshold more easily. If so, it could mean that active exercise protocols intended to improve cardiovascular health would be more effective if first "titrated" against intrinsic capacity.

It is also clear from subsequent studies that the adaptive/induced response to a training regimen is genetically determined independently from the intrinsic aerobic capacity (50). Animals characterized as HCR or LCR appear to have similar capacity to improve (or not) when exposed to an active exercise regimen. There has been the suggestion that active exercise might "rescue" the LCR phenotype (51), but the fact that the factors governing the response to exercise training and the intrinsic exercise capacity seem to sort differently genetically (33, 42, 52, 53) would suggest that might not be the case. What is clear is that the availability of the HCR and LCR phenotype for the first time provides the opportunity for much better insight into the dynamic interaction between the intrinsic capacity for exercise, and the dynamic response to an active exercise regimen.

Consistent with our findings suggesting an intrinsic tissue character to the HCR/LCR phenotype effect, and the possibility that there might be tissue specific variation, several studies have suggested that a major component of the differences in intrinsic capacity might be metabolically driven (50, 51, 53–57). Noland et al. found changes in metabolic FFA utilization was affected by phenotype and was more pronounced in skeletal muscle while cardiac tissue did not demonstrate these differences even with high fat feeding (18).

In summary, there appears to be a cardioprotective benefit associated with inborn aerobic capacity. The relative cardioprotection can be overwhelmed if the ischemic stress sufficiently severe. Higher intrinsic capacity was associated with more rapid infarct expansion, once the protective threshold was exceeded. The relative impact of intrinsic aerobic capacity was not dependent on sex, with females showing less tissue injury regardless of phenotype or duration of ischemia compared to the males. The mechanisms for the phenotypic differences in ischemic tolerance appear to be intrinsic to the tissue, and more related to ischemia than reperfusion associated events.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by Institutional Animal Care and Use Committee (IACUC) East Carolina University.

AUTHOR CONTRIBUTIONS

RML conceived experiments, analyzed data, wrote, and reviewed manuscript. MA, MZ, and LCK participated in data collection, analysis, and manuscript preparation. LGK and SB provided input on experimental design and model traits. LGK also reviewed data with RML. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Kokkinos P, Sheriff H, Kheirbek R. Physical inactivity and mortality risk. *Cardiol Res Pract.* (2011) 2011:924945. doi: 10.4061/2011/924945
2. Fleg JL, Piña IL, Balady GJ, Chaitman BR, Fletcher B, Lavie C, et al. Assessment of functional capacity in clinical and research applications: an advisory from the committee on exercise, rehabilitation, and prevention, council on clinical cardiology, American heart association. *Circulation.* (2000) 102:1591–7. doi: 10.1161/01.CIR.102.13.1591
3. Piña IL, Apstein CS, Balady GJ, Belardinelli R, Chaitman BR, Duscha BD, et al. Exercise and heart failure: a statement from the American heart association committee on exercise, rehabilitation, and prevention. *Circulation.* (2003) 107:1210–25. doi: 10.1161/01.CIR.0000055013.92097.40
4. Ferdinandy P, Hausenloy DJ, Heusch G, Baxter GF, Schulz R. Interaction of risk factors, comorbidities, and comedications with ischemia/reperfusion injury and cardioprotection by preconditioning, postconditioning, and remote conditioning. *Pharmacol Rev.* (2014) 66:1142–74. doi: 10.1124/pr.113.008300
5. Hausenloy DJ, Candilio L, Evans R, Ariti C, Jenkins DP, Kolvekar S, et al. Remote ischemic preconditioning and outcomes of cardiac surgery. *N Engl J Med.* (2015). 373:1408–17. doi: 10.1056/NEJMoa1413534
6. Zatta AJ, Kin H, Lee G, Wang N, Jiang R, Lust RM, et al. Infarct-sparing effect of myocardial postconditioning is dependent on protein kinase C signaling. *Cardiovasc Res.* (2006) 70:315–24. doi: 10.1016/j.cardiores.2005.11.030
7. Goyal A, Agrawal N. Ischemic preconditioning: interruption of various disorders. *J Saudi Heart Assoc.* (2017) 29:116–27. doi: 10.1016/j.jsha.2016.09.002
8. Varshney V, Goyal A, Gupta JK, Yadav HN. Role of erythropoietin in ischemic postconditioning induced cardioprotection in hyperlipidemic rat heart. *J Indian Col Cardiol.* (2017) 7:72–7. doi: 10.1016/j.jicc.2017.03.003
9. Gupta I, Goyal A, Singh NK, Yadav HN, Sharma PL. Hemin, a heme oxygenase-1 inducer, restores the attenuated cardioprotective effect of ischemic preconditioning in isolated diabetic rat heart. *Hum Exp Toxicol.* (2017) 36:867–75. doi: 10.1177/0960327116673169
10. Vishwakarma VK, Goyal A, Gupta JK, Upadhyay PK, Yadav HN. Involvement of atrial natriuretic peptide in abrogated cardioprotective effect of ischemic preconditioning in ovariectomized rat heart. *Hum Exp Toxicol.* (2018) 37:704–13. doi: 10.1177/0960327117730878
11. Bouchard C, Lesage R, Lortie G, Simoneau JA, Hamel P, Boulay MR, et al. Aerobic performance in brothers, dizygotic and monozygotic twins. *Med Sci Sports Exerc.* (1986) 18:639–46. doi: 10.1249/00005768-198612000-00006
12. An P, Pérusse L, Rankinen T, Borecki IB, Gagnon J, Leon AS, et al. Familial aggregation of exercise heart rate and blood pressure in response to 20 weeks of endurance training: the HERITAGE family study. *Int J Sports Med.* (2003) 24:57–62. doi: 10.1055/s-2003-37200
13. Bouchard C, Rankinen T, Chagnon YC, Rice T, Pérusse L, Gagnon J, et al. Genomic scan for maximal oxygen uptake and its response to training in the HERITAGE family study. *J Appl Physiol.* (2000) 88:551–9. doi: 10.1152/jappl.2000.88.2.551
14. Bouchard C, Daw EW, Rice T, Pérusse L, Gagnon J, Province MA, et al. Familial resemblance for VO2max in the sedentary state: the HERITAGE family study. *Med Sci Sports Exerc.* (1998) 30:252–8. doi: 10.1097/00005768-199802000-00013

15. Wisloff U, Najjar SM, Ellingsen O, Haram PM, Swoap S, Al-Share Q, et al. Cardiovascular risk factors emerge after artificial selection for low aerobic capacity. *Science.* (2005) 307:418–20. doi: 10.1126/science.1108177
16. Koch LG, Britton Sl. Artificial selection for intrinsic aerobic endurance running capacity in rats. *Physiol Genomics.* (2001) 5:45–52. doi: 10.1152/physiolgenomics.2001.5.1.45
17. Hussain SO, Barbato JC, Koch LG, Metting PJ, Britton SL. Cardiac function in rats selectively bred for low- and high-capacity running. *Am J Physiol Regul Integr Comp Physiol.* (2001) 281:R1787–91. doi: 10.1152/ajpregu.2001.281.6.R1787
18. Noland RC, Thyfault JP, Henes ST, Whitfield BR, Woodlief TL, Evans JR, et al. Artificial selection for high-capacity endurance running is protective against high-fat diet-induced insulin resistance. *Am J Physiol Metab.* (2007) 293:E31–41. doi: 10.1152/ajpendo.00500.2006
19. Howlett RA, Gonzalez NC, Wagner HE, Fu Z, Britton SL, Koch LG, et al. Selected contribution: skeletal muscle capillarity and enzyme activity in rats selectively bred for running endurance. *J Appl Physiol.* (2003) 94:1682–8. doi: 10.1152/japplphysiol.00556.2002
20. Gonzalez NC, Kirkton SD, Howlett RA, Britton SL, Koch LG, Wagner HE, et al. Continued divergence in VO_{2max} of rats artificially selected for running endurance is mediated by greater convective blood O_2 delivery. *J Appl Physiol.* (2006) 101:1288–96. doi: 10.1152/japplphysiol.01527.2005
21. Palpant NJ, Szatkowski ML, Wang W, Townsend D, Bedada FB, Koch LG, et al. Artificial selection for whole animal low intrinsic aerobic capacity co-segregates with hypoxia-induced cardiac pump failure. *PLoS ONE.* (2009) 4:e6117. doi: 10.1371/journal.pone.0006117
22. Bye A, Langaas M, Høydal MA, Kemi OJ, Heinrich G, Koch LG, et al. Aerobic capacity-dependent differences in cardiac gene expression. *Physiol Genomics.* (2008) 33:100–9. doi: 10.1152/physiolgenomics.00269.2007
23. Murphy E, Steenbergen C. Gender-based differences in mechanisms of protection in myocardial ischemia–reperfusion injury. *Cardiovasc Res.* (2007) 75:478–86. doi: 10.1016/j.cardiores.2007.03.025
24. O'Neil A, Scovelle AJ, Milner AJ, Kavanagh A. Gender/Sex as a social determinant of cardiovascular risk. *Circulation.* (2018) 137:854–64. doi: 10.1161/CIRCULATIONAHA.117.028595
25. Britton SL, Koch LG. Animal genetic models for complex traits of physical capacity. *Exerc Sport Sci Rev.* (2001) 29:7–14. doi: 10.1097/00003677-200101000-00003
26. Koch LG, Britton SL, Wisløff U. A rat model system to study complex disease risks, fitness, aging, and longevity. *Trends Cardiovasc Med.* (2012) 22:29–34. doi: 10.1016/j.tcm.2012.06.007
27. Koch LG, Britton SL. Theoretical and biological evaluation of the link between low exercise capacity and disease risk. *Cold Spring Harb Perspect Med.* (2018) 8:a029868. doi: 10.1101/cshperspect.a029868
28. Hazarika S, Van Scott MR, Lust RM. Myocardial ischemia-reperfusion injury is enhanced in a model of systemic allergy and asthma. *Am J Physiol Circ Physiol.* (2004) 286:H1720–5. doi: 10.1152/ajpheart.01064.2003
29. Hazarika S, Van Scott MR, Lust RM. Severity of myocardial injury following ischemia-reperfusion is increased in a mouse model of allergic asthma. *Am J Physiol Circ Physiol.* (2007) 292:H572–9. doi: 10.1152/ajpheart.01361.2005
30. Sloan RC, Moukdar F, Frasier CR, Patel HD, Bostian PA, Lust RM, et al. Mitochondrial permeability transition in the diabetic heart: contributions of thiol redox state and mitochondrial calcium to augmented reperfusion injury. *J Mol Cell Cardiol.* (2012) 52:1009–18. doi: 10.1016/j.yjmcc.2012.02.009
31. Brown DA, Jew KN, Sparagna GC, Musch TI, Moore RL. Exercise training preserves coronary flow and reduces infarct size after ischemia-reperfusion in rat heart. *J Appl Physiol.* (2003) 95:2510–8. doi: 10.1152/japplphysiol.00487.2003
32. Koch LG, Kemi OJ, Qi N, Leng SX, Bijma P, Gilligan LJ, et al. Intrinsic aerobic capacity sets a divide for aging and longevity. *Circ Res.* (2011) 109:1162–72. doi: 10.1161/CIRCRESAHA.111.253807
33. Thyfault JP. Intrinsic high aerobic capacity in male rats protects against diet-induced insulin resistance. *Endocrinology.* (2019) 160:1179–92. doi: 10.1210/en.2019-00118
34. Klemcke HG, Ryan KL, Britton SL, Koch LG, Dubick MA, Convertino VA. Rat strains bred for low and high aerobic running capacity do not differ in their survival time to hemorrhage. *Exp Biol Med.* (2009) 234:1503–10. doi: 10.3181/0812-RM-355
35. Vijay V, Han T, Moland CL, Kwekel JC, Fuscue JC, Desai VG. Sexual dimorphism in the expression of mitochondria-related genes in rat heart at different ages. *PLoS ONE.* (2015) 10:e0117047. doi: 10.1371/journal.pone.0117047
36. Garza MA, Wason EA, Zhang JQ. Cardiac remodeling and physical training post myocardial infarction. *World J Cardiol.* (2015) 7:52–64. doi: 10.4330/wjc.v7.i2.52
37. Deuchar GA, Opie LH, Lecour S. TNFα is required to confer protection in an in vivo model of classical ischaemic preconditioning. *Life Sci.* (2007) 80:1686–91. doi: 10.1016/j.lfs.2007.01.040
38. Cai ZP, Parajuli N, Zheng X, Becker L. Remote ischemic preconditioning confers late protection against myocardial ischemia–reperfusion injury in mice by upregulating interleukin-10. *Basic Res Cardiol.* (2012) 107:277 doi: 10.1007/s00395-012-0277-1
39. Yaoita H, Yoshinari K, Maehara K, Sando M, Watanabe K, Maruyama Y. Different effects of a high-cholesterol diet on ischemic cardiac dysfunction and remodeling induced by coronary stenosis and coronary occlusion. *J Am Coll Cardiol.* (2005) 45:2078–87. doi: 10.1016/j.jacc.2005.03.037
40. Yoshinari k, Yaoita h, Maehara K, Maruyama Y. Different therapeutic responses to treadmill exercise of heart failure due to ischemia and infarction in rats. *Cardiovasc Res.* (2005) 65:457–68. doi: 10.1016/j.cardiores.2004.10.039
41. Lagranha CJ, Silva TLA, Silva SCA, Braz GRF, da Silva AI, Fernandes MP, et al. Protective effects of estrogen against cardiovascular disease mediated via oxidative stress in the brain. *Life Sci.* (2018) 192:190–8. doi: 10.1016/j.lfs.2017.11.043
42. Bae S, Zhang L. Gender differences in cardioprotection against ischemia/reperfusion injury in adult rate hearts: focus on Akt and protein kinase C signaling. *J Parmacol Exp Ther.* (2005) 315:1125–35. doi: 10.1124/jpet.105.090803
43. Nystoriak MA, Bhatnager A. Cardiovascular effects and benefits of exercise. *Front Cardiovasc Med.* (2018) 5:135. doi: 10.3389/fcvm.2018.00135
44. Myers J. Exercise and cardiovascualr health. *Circ.* (2003) 107:e2–5. doi: 10.1161/01.CIR.0000048890.59383.8D
45. Demirel HA, Powers SK, Zergeroglu MA, Shanely RA, Hamilton K, Coombes J, et al. Short-term exercise improves myocardial tolerance to in vivo ischemia-reperfusion in the rat. *J Appl Physiol.* (2001) 91:2205–12. doi: 10.1152/jappl.2001.91.5.2205
46. Lennon SL, Quindry JC, French JP, Kim S, Mehta JL, Powers SK. Exercise and myocardial tolerance to ischaemia-reperfusion. *Acta Physiol Scand.* (2004) 182:161–9. doi: 10.1111/j.1365-201X.2004.01346.x
47. Barbato JC, Koch LG, Darvish A, Cicila GT, Metting PJ, Britton SL. Spectrum of aerobic endurance running performance in eleven inbred strains of rats. *J Appl Physiol.* (1998) 85:530–6. doi: 10.1152/jappl.1998.85.2.530
48. Lujan HL, Britton SL, Koch LG, DiCarlo SE. Reduced susceptibility to ventricular tachyarrhythmias in rats selectively bred for high aerobic capacity. *Am J Physiol Circ Physiol.* (2006) 291:H2933–41. doi: 10.1152/ajpheart.00514.2006
49. Zhang K-R, Liu H-T, Zhang H-F, Zhang Q-J, Li Q-X, Yu Q-J, et al. Long-term aerobic exercise protects the heart against ischemia/reperfusion injury via PI3 kinase-dependent and Akt-mediated mechanism. *Apoptosis.* (2007) 12:1579–88. doi: 10.1007/s10495-007-0090-8
50. Koch LG, Green CL, Lee AD, Hornyak JE, Cicila GT, Britton SL. Test of the principle of initial value in rat genetic models of exercise capacity. *Am J Physiol Regul Integ Comp Physiol.* (2005) 288:R466–72. doi: 10.1152/ajpregu.00621.2004
51. Lensu S, Pekkala SP, Mäkinen A, Karstunen N, Turpeinen AT, Hulmi JJ, et al. Beneficial effects of running and milk protein supplements on sirtuins and risk factors of metabolic disorders in rats with low aerobic capacity. *Metabol Open.* (2019) 4:100019. doi: 10.1016/j.metop.2019.100019
52. Vanderheyden WM, Kehoe M, Vanini G, Britton SL, Koch LG. Rat models for low and high adaptive response to exercise differ for stress-related memory and anxiety. *Physiol Rep.* (2021) 9:e14716. doi: 10.14814/phy2.14716
53. West DWD, Doering TM, Thompson JM, Budiono BP, Lessard SJ, Koch LG, et al. Low responders to endurance training exhibit impaired hypertrophy and divergent biological process responses in rat skeletal muscle. *Exp Physiol.* (2021) 106:714–25. doi: 10.1113/EP089301

54. Aon MA, Cortassa S, Juhaszova M, González-Reyes JA, Calvo-Rubio M, Villalba JM, et al. Mitochondrial health is enhanced in rats with higher vs. lower intrinsic exercise capacity and extended lifespan. *NPJ Aging Mech Dis.* (2021) 7:1. doi: 10.1038/s41514-020-00054-3
55. Farrash WF, Phillips BE, Britton SL, Qi N, Koch LG, Wilkinson DJ, et al. Myokine responses to exercise in a rat model of low/high adaptive potential. *Front Endocrinol.* (2021) 12:645881. doi: 10.3389/fendo.2021.645881
56. Feng X, Uchida Y, Koch L, Britton S, Hu J, Lutrin D, et al. Exercise prevents enhanced postoperative neuroinflammation and cognitive decline and rectifies the gut microbiome in a rat model of metabolic syndrome. *Front Immunol.* (2017) 8:1768. doi: 10.3389/fimmu.2017.01768
57. Tao L, Bei Y, Zhang H, Xiao J, Li X. Exercise for the heart: signaling pathways. *Oncotarget.* (2015) 6:20773–84. doi: 10.18632/oncotarget.4770

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 03 February 2022
doi: 10.3389/fcvm.2021.753672

Effect of Exercise Prescription Implementation Rate on Cardiovascular Events

Li-Yue Zhu[1†], Min-Yan Li[2,3†], Kun-Hui Li[2,3], Xiao Yang[1], Yi-Yong Yang[3], Xiao-Xia Zhao[1], Ting Yan[1], Meng-Meng Li[3], Si-Qi Luo[2,3], Mu-Lan Zhang[4] and Jin-Zi Su[3*]*

[1] Rehabilitation Center, Zhejiang Hospital, Hangzhou, China, [2] Department of Rehabilitation Medicine, The School of Health, Fujian Medical University, Fuzhou, China, [3] Department of Cardiology, The First Affiliated Hospital of Fujian Medical University, Fuzhou, China, [4] Fuyang District Traditional Chinese Medicine Hospital, Hangzhou, China

Background: Exercise prescription of cardiac rehabilitation (CR) is vital in patients with cardiovascular diseases (CVDs) and those carrying high risk for CVDs. However, the relation between the implementation rate of exercise prescription and cardiovascular events (CVEs) is unclear.

Design and Methods: In this retrospective study, using the administration data from the Rehabilitation Center in a hospital, patients aged ≥18 years with CVDs were consecutively enrolled from November 2018 to May 2021. Patients were divided into the high execution group (HEG) and low execution group (LEG) depending on whether they completed more than half the time of the exercise prescriptions. Baseline characteristics, ultrasonic cardiogram, cardiopulmonary exercise test, follow-up data, and CVEs were collected.

Results: The mean age of the 197 CR patients was 61.8 ± 13.7 years and the mean follow-up duration was 10.9 ± 4.2 months. Among them, 15 patients suffered CVEs: 4 in the HEG and 11 in the LEG. The incidence of CVEs showed significant differences between HEG and LEG (chi-square test). Free-event survival analysis using Kaplan–Meier survival plots showed that patients in LEG had poor survival. Cox proportional hazards regression analysis revealed that the prescription implementation rate was an independent predictor of CVEs.

Conclusions: Our study suggested a significant effect of exercise prescription execution rate on the occurrence of CVEs. Further, the HEG of exercise prescription was associated with lower CVDs.

Keywords: cardiac rehabilitation, cardiovascular diseases, exercise prescription, cardiovascular events, coronary heart disease

OPEN ACCESS

Edited by:
Richard Yang Cao, Shanghai Xuhui Central Hospital, China

Reviewed by:
Zhang Ying, Shanghai Xuhui Central Hospital, China
Jian Wu, Harbin Medical University, China

***Correspondence:**
Mu-Lan Zhang
meganzml@163.com
Jin-Zi Su
subo@fjmu.edu.cn

[†] These authors have contributed equally to this work

Specialty section:
This article was submitted to General Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

Received: *05 August 2021*
Accepted: *23 December 2021*
Published: *03 February 2022*

Citation:
Zhu L-Y, Li M-Y, Li K-H, Yang X, Yang Y-Y, Zhao X-X, Yan T, Li M-M, Luo S-Q, Zhang M-L and Su J-Z (2022) Effect of Exercise Prescription Implementation Rate on Cardiovascular Events. Front. Cardiovasc. Med. 8:753672. doi: 10.3389/fcvm.2021.753672

INTRODUCTION

Cardiovascular diseases (CVDs) are a serious global health concern. A systematic analysis for the Global Burden of Disease Study 2017 reported that CVDs affect approximately 485.6 million people worldwide (1). According to the National Center for Cardiovascular Diseases' most recent estimates, there are 330 million cases of CVDs in China, accounting for 40% of all deaths (2). With the development and progression of new treatment strategies, cardiac rehabilitation (CR)

has received a lot of attention. The American Heart Association (AHA), the American College of Cardiology (ACC), and the European Society of Cardiology (ESC) have all recognized and advocated CR as a vital aspect of modern cardiology (3, 4). At present, CR is still in its early stages of growth in China. Chinese cardiologists have proposed the Five Prescriptions rule, which integrate pharmacological prescription, exercise prescription, diet prescription, psychological prescription, and smoking-cessation prescription to provide comprehensive and holistic management and care for patients with CVDs.

Exercise training is regularly identified as the cornerstone of comprehensive CR in international guidelines (5). Exercise has been classified as Type 1A evidence in various CR guidelines and consensus in the fight against CVDs risk. The importance of exercise in CR is self-evident (5–7). Exercise training has been found in clinical research to improve blood pressure and cholesterol control in persons at risk of CVDs (8, 9). Patients with coronary artery disease (CAD) and heart failure may also see considerable improvements (10–12). Furthermore, exercise improves clinical prognosis by lowering illness incidence, overall mortality, cardiovascular disease-related mortality, rehospitalization rates, and the need for revascularization (13, 14).

A patient's prognosis is heavily influenced by the extent of exercise prescription that is carried out. However, in our clinical work, we frequently discover that even when physicians and therapists target individualized exercise prescriptions for patients, the exercise prescription implementation (i.e., type, frequency, volume, intensity of exercise, duration of sessions and programs, goals, and progressive training adaptations) varies significantly from patient to patient (15, 16). Given the link between exercise prescription rates and cardiovascular events (CVEs), a better knowledge of their relationship could help doctors improvise treatment strategies, improve patients' outcomes, and reduce medical costs. Thus, we investigated the prognostic effects of exercise prescription implementation on CVEs in CR patients to suggest directions for future work.

MATERIALS AND METHODS

Study Participants

A total of 197 patients with CR from November 8, 2018 to May 11, 2021 in the Rehabilitation Center of Zhejiang Hospital, Zhejiang Province, were included in this study, which was approved by the Ethics Committee of the hospital (No. 2014-KA-8). The inclusion criteria were (1) age≥18 years; (2) myocardial infarction, CAD, post percutaneous coronary intervention, hypertension, diabetes mellitus, heart failure, dilated cardiomyopathy, and/or other high-risk CVDs; and (3) the need for CR. The exclusion criteria were as follows: (1) symptomatic systolic blood pressure >200 mmHg or diastolic blood pressure >110 mmHg at rest or a drop in blood pressure >20 mmHg after sitting-up; (2) severe aortic stenosis; (3) acute systemic disease or fever; (4) uncontrolled severe atrial or ventricular arrhythmias, uncontrolled significant sinus tachycardia (>120 beats/min); (5) uncontrolled heart failure or third-degree atrioventricular block without a pacemaker; (6) active pericarditis or myocarditis, thrombophlebitis, recent thromboembolism, and ST-segment depression or elevation (>2 mm) at rest; (7) severe exercise system abnormalities that can limit exercise capacity and other metabolic abnormalities such as acute thyroiditis, hypokalemia, hyperkalemia, or hypovolemia; (8) pregnancy; and (9) severe mental illness or dementia in patients making them unable to cooperate. After enrollment, medical history including basic personal information (age, sex, current medical history, past history, and education) was collected, and an informed consent form was signed was by all participating patients.

Ultrasonic Cardiogram

Cardiac function was assessed using an ultrasonic cardiogram with Color Doppler Ultrasonography (Vivid E9, GE, USA) at a scanning frequency of 3.5 MHz and parasternal left ventricular long-axis views to measure left atrial internal diameter, left ventricular internal diameter, septal thickness, and posterior left ventricular wall thickness, as well as left atrioventricular valve flow spectrograms. Furthermore, early diastolic E-peak flow, E-peak deceleration time, late diastolic A-peak flow velocity, LV early/late diastolic peak flow velocity ratio (E/A), and LV isovolumic diastolic time were all evaluated at end-expiration velocity.

Cardiopulmonary Exercise Test

CPET (Cosmed, Rome, Italy) and OMNIA cardiorespiratory diagnostic software were used to assess aerobic capacity. CPET exercise program selected sub-maximum quantity exercise or symptom-limited exercise test by using a cardiopulmonary exercise tester (17). Lung function was measured before exercise, and oxygen consumption and other indicators, 12-lead electrocardiogram (ECG), and blood pressure were continuously monitored during exercise. After a 3-min resting period, the bicycle was pedaled at 55–65 r/min for 3 min without load, and then the power was increased in 10–20 W/min increments until symptom limitation was reached or the target exercise volume was reached. After achieving maximum workout power, a 5–10 min recuperation time was implemented. The heart rate, oxygen uptake, oxygen pulse, blood pressure, metabolic equivalent, and power of the patient were all continuously recorded. The cardiorespiratory analysis system analyzes sample data and generates reports that include information on the patient's resting and anaerobic threshold conditions.

Exercise Prescription Execution Ability and Grouping

Based on the CPET results, aerobic exercise training generates exercise prescriptions and intensities. During the inpatient phase, the CR physician formulated individual exercise prescriptions for the patients in the CR group, and the therapists instructed the implementation of rehabilitation exercises according to the exercise prescriptions: (1) Warm-up exercises: The muscles,

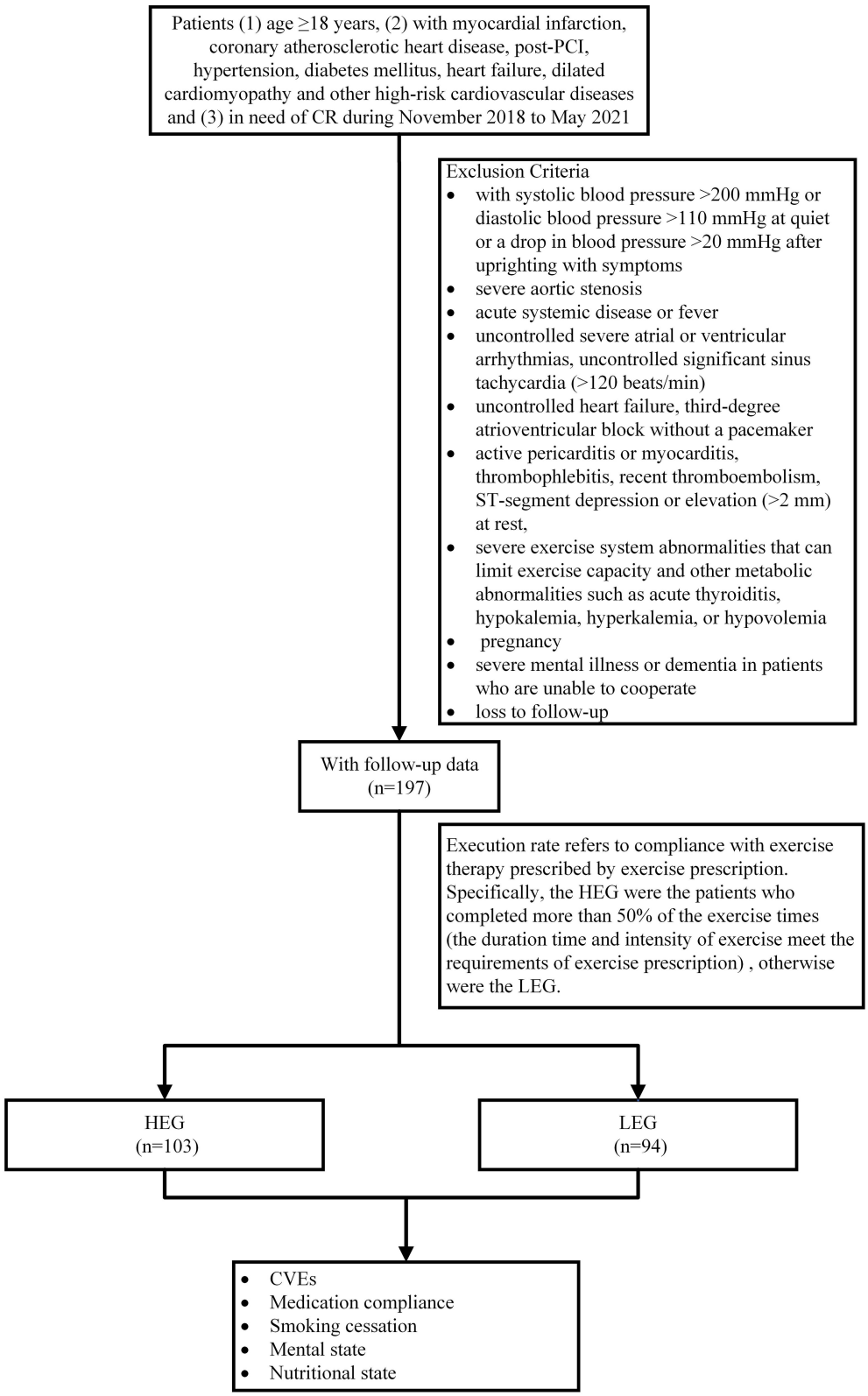


FIGURE 1 | Study design flowchart. PCI, percutaneous coronary interventions; CR, cardiac rehabilitation; HEG, high execution group; LEG, low execution group; CVEs, cardiovascular diseases.

joints, and cardiovascular system were warmed up for 10–15 min with low-intensity warm-up exercises. (2) Workouts were conducted in the hospital ward or exercise therapy room. Exercise methods included walking, power bicycles, dumbbells, joint stretching, 8 or 24 forms of Taijiquan, or exercise gymnastics. Real-time cardiac monitoring was performed with a BeneView T5 patient monitor or POLAR heart rate meter. Heart rate, rhythm, blood pressure, and fatigue level were closely observed and recorded. (3) Relaxation period: 5–10 min following the last recovery exercise. (4) Precautions: blood pressure was monitored before and after exercise, and ECG was monitored throughout. Patients were asked to exercise at an intensity corresponding to an RPE of 11–14 (18). The duration of each exercise was 30–45 min, once a day. The rehabilitation center was equipped with the above-mentioned Sports Art C52r power bicycle, Sports Art 6300HR running table, and other CR exercise equipment, with soothing background music, as well as oxygen, monitors, defibrillators, resuscitation drugs, and other resuscitation equipment. Concurrently, group health education was conducted twice a week, combined with individual education. The content format was mainly slide lectures combined with reading pamphlets to help correct risk factors for coronary heart disease, including guidance on smoking cessation, dietary guidance, psychological assessment, and emotional management to help establish a healthy lifestyle.

During the discharge phase, outpatient CR was conducted. Outpatient rehabilitation was performed three times a week, 36 times a cycle according to exercise prescriptions, with an assessment once every 4 weeks and adjustment of exercise prescriptions. Home CR was performed after 3 months. Some low-risk patients were discharged from the hospital for home CR, with telephonic follow-up every 2 weeks. Specifically, the high execution group (HEG) ($n = 104$) comprised patients who completed >50% of the exercise times (the duration time and intensity of exercise met the requirements of exercise prescription); all other patients were classified under the low execution group (LEG) ($n = 93$) (**Figure 1**).

Definition of CHD, PCI, CVEs, Medication Compliance, Smoking Cessation, Mental State, and Nutritional State

CHD: The Cardiovascular Disease Branch of the Chinese Medical Association's "Guide to the rational use of drugs in the primary level for stable coronary artery disease" was consulted for the definition of diagnostic criteria for coronary artery disease (19).

PCI: The "Chinese guidelines for percutaneous coronary interventions (2016)" were referred to for all percutaneous coronary procedures (20).

CVEs: These were defined as the composite endpoint of acute myocardial infarction recurrence, acute angina recurrence, acute heart failure, atrial fibrillation, stroke and death.

Medication compliance: The extent to which an individual consistently adhered to the medication recommended by the healthcare provider.

TABLE 1 | Baseline characteristics of patients.

Characteristic	HEG ($n = 103$)	LEG ($n = 94$)	*p*-value
Age, years	60.0 (52.0–69.0)	64.5 (54.0–73.3)	0.234
Male	78 (75.7)	72 (76.6)	0.887
BMI, kg/m^2	25.1 (23.2–27.2)	24.2 (22.4–26.7)	0.156
Smoke	23 (22.3)	26 (27.7)	0.387
Follow-up time, months	12.0 (7.0–14.0)	11.0 (7.0–14.0)	0.107
SBP, mmHg	130.0 (117.0–139.0)	126.0 (114.8–143.8)	0.644
DBP, mmHg	77.0 (69.0–87.0)	75.0 (66.0–84.5)	0.091
Laboratory data			
TC, mmol/L	4.2 (3.4–5.1)	3.9 (3.2–4.9)	0.307
TG, mmol/L	1.4 (1.0–1.9)	1.4 (1.0–1.8)	0.342
HDL, mmol/L	1.1 (0.9–1.2)	1.0 (0.8–1.2)	0.052
LDL, mmol/L	2.3 (1.6–2.8)	2.3 (1.7–2.9)	0.421
Comorbidities and interventions			
CHD	62 (60.2)	48 (51.1)	0.197
PCI	50 (80.6)	36 (75.0)	0.477
Anti-platelet agents	56 (90.3)	39 (81.3)	0.169
Statins	56 (90.3)	43 (89.6)	0.898
Hypertension	74 (71.8)	57 (60.6)	0.096
ACEI or ARB	51 (68.9)	37 (64.9)	0.628
β-blocker	41 (55.4)	28 (49.1)	0.475
CCB	27 (36.5)	19 (33.3)	0.708
Diuretic	15 (20.3)	14 (24.6)	0.558
Diabetes	34 (33.0)	22 (23.4)	0.135
Anti-diabetic	26 (76.5)	18 (81.8)	0.634
Ultrasonic cardiogram			
Aod, mm	31.3 (29.0–33.0)	30.1 (28.0–33.0)	0.124
LAD, mm	35.0 (33.0–38.0)	35.9 (33.0–39.1)	0.361
LVDd, mm	50.2 (47.3–52.2)	50.9 (47.4–52.9)	0.305
LVDs, mm	32.0 (29.0–33.9)	33.0 (28.8–34.0)	0.278
IVS, mm	10.1 (8.8–11.0)	10.0 (8.8–10.9)	0.763
LVPW, mm	9.6 (8.7–10.2)	10.1 (8.6–11.2)	0.070
FS, %	35.7 (33.0–38.7)	35.4 (32.8–39.3)	0.989
EF, %	63.9 (60.0–69.0)	64.9 (61.1–70.0)	0.454
E1, cm/s	68.2 (59.0–75.0)	70.0 (56.0–81.3)	0.215
A1, cm/s	83.3 (77.0–92.0)	82.0 (71.0–90.0)	0.565
E/A	0.8 (0.7–0.9)	0.8 (0.7–1.0)	0.379
Cardiopulmonary function exercise test			
Exercise duration, s	380.0 (306.0–455.0)	383.0 (303.8–456.3)	0.935
Peak work load, w	88.0 (60.0–110.0)	84.0 (65.3–114.8)	0.895
Peak VO_2, mL/min	1348.0 (1029.0–1643.0)	1319.5 (1068.0–1710.0)	0.880
Peak VO_2/kg, mL/ (min·kg)	19.2 (16.3–22.4)	19.6 (16.4–23.6)	0.436
Peak O_2/HR, mL/beat	10.8 (8.8–13.1)	11.1 (9.2–12.9)	0.670
Peak mets	5.5 (4.6–6.4)	5.6 (4.6–6.6)	0.547
AT, mL/min	1032.0 (824.0–1277.0)	947.0 (828.5–1150.8)	0.192

Continuous variables are expressed as median (IQR) and analyzed by the Mann–Whitney U rank sum test. Categorical variables are expressed as number and percentage and analyzed by the chi-square test. HEG, high execution group; LEG, low execution group; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; CHD, coronary atherosclerotic heart disease; PCI, percutaneous coronary intervention; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor antagonist; CCB, calcium channel blocker; Aod, aortic diameter; LAD, left atrial diameter; LVDd, left ventricular end diastolic diameter; LVDs, left ventricular systolic diameter; IVS, interventricular septal thickness; LVPW, left posterior wall; FS, fraction shortening; EF, left ventricular ejection fraction; E/A, ratio of peak E to peak A; Peak VO_2, peak oxygen uptake; Peak VO_2/kg, peak oxygen uptake per kilogram of body weight; Peak O_2/HR, oxygen pulse; Peak Mets, peak metabolic equivalent; AT, anaerobic threshold.

Smoking cessation: The smokers giving up their dependence on nicotine. Successful cessation was when the patient quit and did not resume smoking during the observation period.

TABLE 2 | Outcome of follow-up.

Characteristic	HEG ($n = 103$)	LEG ($n = 94$)	*p*-value
Outcome of follow-up			
Regular medication	102 (99.0)	82 (87.2)	0.001
Smoking cessation	13/23 (56.5)	16/26 (61.5)	0.721
Mental health	100 (97.1)	77 (81.9)	<0.001
Weight stability	86 (83.5)	69 (73.4)	0.084

Categorical data were expressed as number and percentage and analyzed by the chi-square test. HEG, high execution group; LEG, low execution group.

TABLE 3 | Incidence of cardiovascular events in study patients.

Characteristic	HEG ($n = 103$)	LEG ($n = 94$)	*p*-value
CVEs	4 (3.9)	11 (11.7)	0.039
Acute myocardial infarction	1	1	
Acute angina	2	4	
Acute heart failure		2	
Atrial fibrillation		1	
Stroke	1		
Death		3	

Categorical data were expressed as number and percentage and analyzed by the chi-square test. HEG, high execution group; LEG, low execution group; CVEs, cardiovascular events.

Mental state: The complete characteristics of psychological activities in a certain period of time, including anxiety, depression, tension, relaxation, sadness, and joy.

Nutritional state: It is closely related to food intake, digestion, absorption, and metabolism, and is used to reflect the level of material energy provided by all activities of the organism, and its status can be used as one of the criteria to identify health and disease, which is divided into good nutrition, malnutrition, and overnutrition.

Study Outcome and Follow-Up

All participants had access to standardized medicine as well as health promotion and risk-factor management. The primary outcome was recurrent CVEs status, and secondary outcomes included status of medication compliance, smoking cessation, mental state, and nutritional status. Information for the inpatient phase was derived from the case system, while information for the home rehabilitation phase was obtained by professional staff during telephonic follow-up visits or outpatient follow-up visits. Medication adherence was assessed using the Morisky 8-item Medication Adherence Questionnaire (MMAS-8). Psychological status was assessed using the Patient Health Questionnaire-9 (PHQ-9) and the Generalized Anxiety Disorder (GAD-7). Smoking status was assessed using the Fagerstrm Test for Nicotine Dependence (FTND). Nutritional status was assessed using the Inpatient Nutrition Risk Screening Scale 2002 (NRS2002). To avoid temporal bias, all individuals were followed-up until death or July 7, 2021.

Statistical Analyses

SPSS 26.0 statistical software (IBM Corporation, Armonk, NY, USA) was used for analysis. Continuous variables were expressed

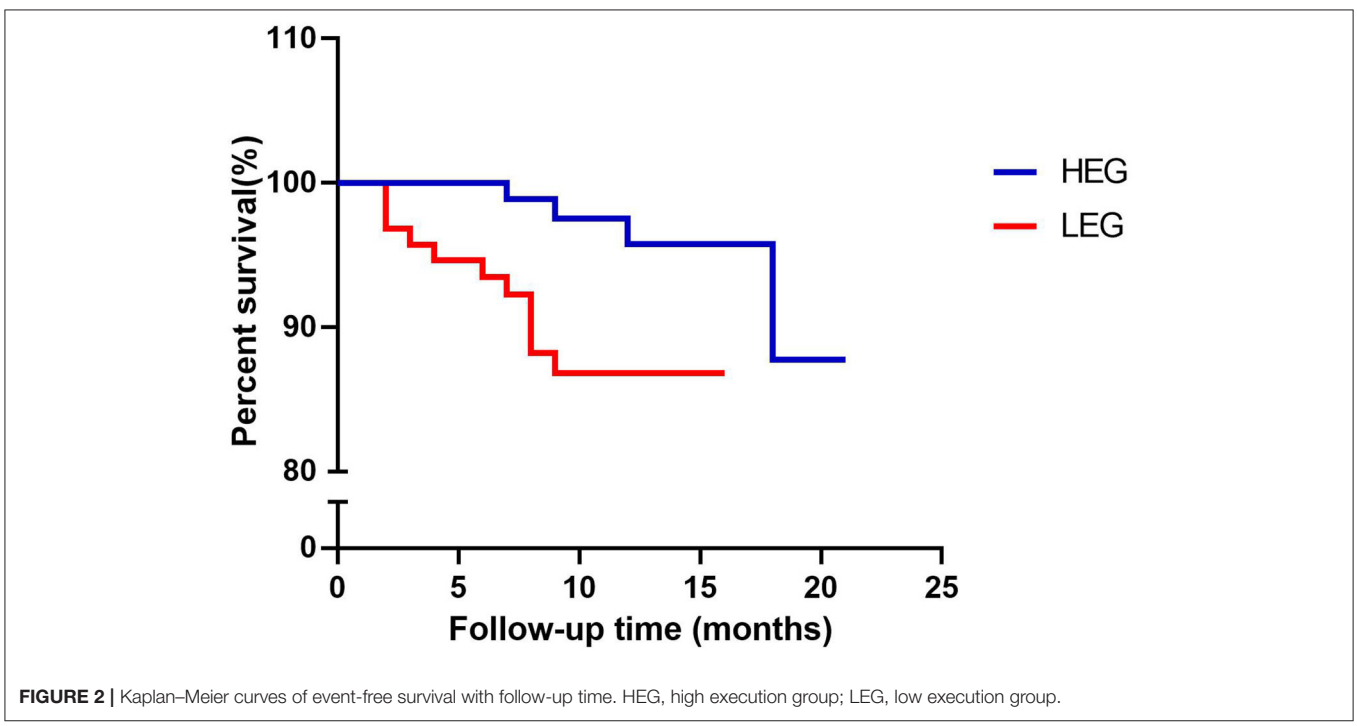


FIGURE 2 | Kaplan–Meier curves of event-free survival with follow-up time. HEG, high execution group; LEG, low execution group.

as M (Q1, Q3) using the Mann–Whitney U rank sum test, while categorical variables were expressed as percentages (%) using the chi-square test. Event-free survival was analyzed using Kaplan–Meier hypothesis testing between patients with HEG or LEG. Curves were compared with the log-rank test and the Breslow test. The association between exercise prescription implementation rate and CVEs was evaluated by Cox proportional hazards model. Univariate Cox analysis was first performed to screen all prognostic factors. Variables with clinical significance or $P < 0.05$ in the univariate analysis were selected for multivariate Cox analysis (backward method). Differences were considered statistically significant at $P < 0.05$.

RESULTS

Clinical Characteristics of Patients

The mean age of the 197 CR patients was 61.8 ± 13.7 years, and the mean follow-up duration was 10.9 ± 4.2 months. The

TABLE 4 | Univariate Cox analysis of proportional risks for CVEs.

Variable	*β*	Standard error	HR (95% CI)	Wald	*p*-value
Age	0.039	0.019	1.040 (1.002–1.080)	4.165	**0.041**
Male	−0.803	0.760	0.448 (0.101–1.987)	1.116	0.291
BMI	−0.111	0.084	0.895 (0.759–1.055)	1.752	0.186
Smoke	1.052	0.518	2.865 (1.037–7.914)	4.121	**0.042**
SBP	0.015	0.015	1.015 (0.986–1.044)	1.003	0.317
DBP	0.000	0.020	1.000 (0.962–1.040)	0.000	0.996
TC	−0.334	0.249	0.716 (0.440–1.166)	1.798	0.180
TG	−0.311	0.349	0.733 (0.370–1.451)	0.795	0.372
HDL	−0.420	1.082	0.657 (0.079–5.437)	0.151	0.698
LDL	0.093	0.298	1.097 (0.612–1.966)	0.098	0.755
CHD	0.449	0.550	1.567 (0.533–4.604)	0.666	0.414
Hypertension	−0.890	0.519	0.411 (0.149–1.135)	2.946	0.086
Diabetes	−0.830	0.761	0.436 (0.098–1.936)	1.191	0.275
Aod	0.081	0.056	1.085 (0.973–1.210)	2.136	0.144
LAD	0.040	0.035	1.041 (0.972–1.115)	1.336	0.248
LVDd	0.051	0.052	1.052 (0.950–1.165)	0.956	0.328
LVDs	0.009	0.044	1.009 (0.925–1.101)	0.044	0.833
IVS	−0.279	0.104	0.756 (0.617–0.927)	7.211	**0.007**
LVPW	−0.153	0.132	0.858 (0.662–1.112)	1.338	0.247
FS (%)	−0.003	0.043	0.997 (0.915–1.085)	0.006	0.937
EF (%)	0.001	0.030	1.001 (0.944–1.061)	0.001	0.975
E1	−0.002	0.014	0.998 (0.971–1.026)	0.019	0.890
A1	−0.016	0.014	0.984 (0.957–1.012)	1.223	0.269
E/A	0.321	0.648	1.378 (0.387–4.911)	0.245	0.621
Exercise duration	0.001	0.002	1.001 (0.996–1.005)	0.074	0.786
Peak work load	−0.006	0.007	0.994 (0.981–1.008)	0.720	0.396
Peak VO_2	0.000	0.001	1.000 (0.999–1.001)	0.003	0.953
Peak VO_2/kg	−0.022	0.047	0.979 (0.892–1.074)	0.209	0.648
Peak VO_2/HR	0.063	0.095	1.065 (0.885–1.281)	0.439	0.508
Peak MET	−0.047	0.183	0.954 (0.666–1.366)	0.067	0.796
VO_2 @AT	0.000	0.001	1.000 (0.998–1.001)	0.109	0.742
Unregular medication	0.105	1.038	1.111 (0.145–8.501)	0.010	0.919
Low execution of exercise	1.438	0.652	4.213 (1.175–15.107)	4.872	**0.027**
Non-smoking cessation	0.174	0.646	1.119 (0.336–4.218)	0.073	0.788
Mental unhealth	0.917	0.652	2.501 (0.697–8.971)	1.978	0.160
Weight instability	1.014	0.531	2.755 (0.974–7.796)	3.647	0.056

CVEs, cardiovascular events; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein; LDL-C, low density lipoprotein; CHD, coronary atherosclerotic heart disease; PCI, percutaneous coronary intervention; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor antagonist; CCB, calcium channel blocker; Aod, aortic diameter; LAD, left atrial diameter; LVDd, left ventricular end diastolic diameter; LVDs, left ventricular systolic diameter; IVS, interventricular septal thickness; LVPW, left posterior wall; FS, fraction shortening; EF, left ventricular ejection fraction; E/A, ratio of peak E to peak A; Peak VO_2, peak oxygen uptake; Peak VO_2/kg, peak oxygen uptake per kilogram of body weight; Peak O_2/HR, oxygen pulse; Peak Mets, peak metabolic equivalent; AT, anaerobic threshold. Bold values indicates $p < 0.05$.

proportion of HEG and LEG were 52.3 and 47.7% respectively. In demographic data, biochemical indicators, concomitant disorders, and ECG, there were no significant differences between the two groups. CPET was also not statistically significant between the two groups (**Table 1**).

Follow-Up of Patients

A total of 197 patients were followed-up. Regular medication and mental health were substantially better in the follow-up situation than in the LEG (regular medication: 99.0 vs. 87.2%, $P = 0.001$ mental health: 97.1 vs. 81.9%, $P < 0.001$) (**Table 2**).

Event-Free Survival

CVEs were shown to be considerably more common in LEG than in HEG ($P = 0.039$) (**Table 3**). During follow-up, four HEG patients (3.9%) suffered at least one cardiovascular event, including one acute myocardial infarction, two acute anginas, and one stroke. During follow-up, eleven LEG patients (11.7%) had at least one cardiovascular event, including one acute myocardial infarction, four acute anginas, two acute heart failures, one atrial fibrillation, and three deaths (**Table 3**). The Kaplan–Meier hypothesis testing method was used to analyze event-free survival. The Breslow test revealed a significant difference ($P = 0.008$) between the two groups, and the log-rank test also revealed a significant difference ($P = 0.016$) (**Figure 2**).

Cox Proportional Hazards Regression Analysis for CVEs

In univariate Cox analysis, age, smoking, interventricular septal thickness (IVS), and low execution of exercise were significant factors ($P < 0.05$) (**Table 4**). Considering their clinical importance, comorbidities and unregular medication were also selected for multivariate Cox analysis (backward method). Model 1 was adjusted for age, smoking, IVS, and low execution of exercise. Model 2 was adjusted for the variables in model 1 plus CHD, hypertension, and diabetes. Model 3 was adjusted for the variables in model 1 plus unregular medication. In all three Cox models, execution of exercise was found to be an independent predictor of CVEs (**Table 5**).

DISCUSSION

In this study, we followed-up 197 CR patients. We developed individualized exercise prescriptions for each patient based on their unique characteristics, and then classified them into HEG and LEG based on the exercise prescription's completion. We discovered through the study's analysis that varied exercise prescriptions had a substantially positive impact on the occurrence of CVEs. Moreover, prescription implementation rate was found to be an independent predictor of CVEs. The impact of better exercise prescription implementation on the incidence of CVEs has to be researched further, according to the study findings.

In our research, we discovered that patients who followed their exercise prescriptions at a higher rate had fewer CVE episodes. The results can be explained as two aspects. First, we looked at the baseline data and follow-up results and discovered that while there were no noticeable variations in the baseline, the follow-up outcomes differed substantially. When compared to the LEG, the HEG exhibited superior adherence in terms of regular medication-taking and mental health maintenance. Medication compliance largely reflects a patient's attitude toward medical advice. Moreover, good-users of drugs may also have better compliance with medical treatments and healthy lifestyle choices than users with poor compliance (21). Negative mood, whether overt or covert, is extremely likely to be one of the main non-cardiac reasons for lack of motivation and exercise

TABLE 5 | Multivariate Cox analysis of proportional risks for CVEs.

Model	Variable	β	HR (95%CI)	*p*-value
1	Low execution of exercise	1.387	4.003 (1.062–15.095)	**0.041**
	Age	0.052	1.054 (1.012–1.097)	**0.011**
	Smoke	1.365	3.914 (1.280–11.967)	**0.017**
	IVS	−0.324	0.723 (0.584–0.895)	**0.003**
2	Low execution of exercise	1.446	4.247 (1.067–16.911)	**0.040**
	Age	0.049	1.050 (1.006–1.097)	**0.026**
	Smoke	1.340	3.820 (1.252–11.657)	**0.019**
	IVS	−0.301	0.740 (0.594–0.921)	**0.007**
	CHD	0.560	1.751 (0.581–5.275)	0.320
	Hypertension	−0.659	0.517 (0.181–1.481)	0.219
	Diabetes	−0.450	0.637 (0.134–3.028)	0.571
3	Low execution of exercise	1.363	3.906 (1.024–14.906)	**0.046**
	Age	0.052	1.054 (1.012–1.097)	**0.011**
	Smoke	1.395	4.036 (1.292–12.606)	**0.016**
	IVS	−0.329	0.720 (0.581–0.893)	**0.003**
	Unregular medication	0.335	1.398 (0.169–11.575)	0.756

CVEs, cardiovascular events; IVS, interventricular septal thickness; CHD, coronary atherosclerotic heart disease. Bold values indicates $p < 0.05$.

discontinuance in CR (22, 23). CR is a self-contained and active process. Patients who adhere to their treatment plans are more likely to engage in physical activity. We paid more attention to the occurrence of CVEs. There were 4 CVEs in the HEG and 11 in the LEG among the endpoint events. The larger case numbers, more CVEs variants, and more severe occurrences that occurred in the LEG can be summarized. On the part of the event-free survival during the following-up time, the results of log-rank test reflected the long-term outcome, while the Breslow test showed the short-term outcome. When we combined the baseline data with the follow-up outcomes, we can see that the HEG with the same condition had considerably better adherence and a significantly lower risk and severity of CVEs than the LEG.

In a retrospective study from Belgium, which divided patients with CAD into supervised and unsupervised groups, the supervised group performed reasonably standardized multidisciplinary exercise rehabilitation for 3 months longer than the unsupervised group. The results showed that in patients with CHD, the supervised group had considerably fewer hospitalizations for adverse CVEs (24). Longer supervised exercise training, stricter adherence to pharmaceutical prescriptions, more healthy food counseling, and greater psychological distraction were all hypothesized to be connected with the clinical advantages found in this study. The findings of this study were similar to those of ours, which may have profited from their multidisciplinary collaboration. This study's findings were similar to ours in terms of trend; however, our statistical findings were not as significant as theirs, which could be attributed to their bigger sample size and multidisciplinary joint intervention (25).

High-risk, older cardiac patients were placed into two groups in a single-blind randomized clinical trial on CR in the Netherlands: normal treatment and CR intervention. There were no significant differences in readmission and mortality rates between the two groups after 6 months, and the event rate was slightly lower in the usual care group than in the CR intervention group, despite the CR intervention group receiving more standardized and systematic comprehensive rehabilitation (26). This study did not come up with the same results as ours. This could be because the high-risk elderly have a higher chance of mortality and CVEs; hence, there was no meaningful difference between the two groups. As a result, the impact of exercise prescription execution must be investigated further.

Our study has some limitations. First, because this was a retrospective case study rather than a randomized controlled trial, the possibility of selection bias impacting the results of the study cannot be ruled out. Second, the study had a single-center design with a small sample size, which could limit the generalizability of the results. Third, the follow-up information was insufficient. In the future, we will more rigorously standardize patient enrollment criteria, develop randomized controlled clinical trials for specific disease populations, and conduct longitudinal and prospective analyses to further clarify the effect of different exercise prescription execution rates on CVEs.

To summarize, although we found a substantial effect of exercise prescription execution rate on unfavorable CVEs, this study has limitations and the potential advantages of high CR exercise prescription execution rates must be verified in more refined, bigger, and longer-term trials. Furthermore, to adopt better management techniques and enhance clinical prognosis, efforts should be made to discover significant elements that can promote patient compliance.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

L-YZ, J-ZS, and M-LZ conceived the idea, designed the study, and established the methodology. XY, X-XZ, and TY were responsible for follow-up, data collection, and collation. M-YL and K-HL wrote and revised the manuscript. M-ML and S-QL were in charge of software, literature retrieval, and visualization. M-YL, K-HL, and Y-YY carried out the analyses. All authors reviewed and approved the manuscript prior to submission.

FUNDING

This work was supported by the Science and Technology Project of Fujian Province, China (No. 2020Y0023), Medical Science and Technology Project of ZheJiang Province (No. 2014KA8), and Zhejiang Province Public Welfare Technology Application Research Project (No. 2015C33121).

ACKNOWLEDGMENTS

We gratefully acknowledge all the participants in this study and staff members of the follow-up team.

REFERENCES

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. (2018) 392:1789–858. doi: 10.1016/S0140-6736(18)32279-7
2. National Center for Cardiovascular Diseases. *Annual Report on Cardiovascular Health and Diseases in China 2019*. 1st ed. Beijing: Science Press (2020).

3. Piepoli MF, Corrà U, Benzer W, Bjarnason-Wehrens B, Dendale P, Gaita D, et al. Secondary prevention through cardiac rehabilitation: from knowledge to implementation. A position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation. *Eur J Cardiovasc Prev Rehabil.* (2010) 17:1–17. doi: 10.1097/HJR.0b013e3283313592
4. Leon AS, Franklin BA, Costa F, Balady GJ, Berra KA, Stewart KJ, et al. Cardiac rehabilitation and secondary prevention of coronary heart disease: an American Heart Association (AHA) scientific statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity), in collaboration with the American association of Cardiovascular and Pulmonary Rehabilitation. *Circulation.* (2005) 111:369–76. doi: 10.1161/01.CIR.0000151788.08740.5C
5. Piepoli MF, Hoes AW, Agewall S, Albus C, Verschuren WMM. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *Int J Behav Med.* (2016) 69:2315–81. doi: 10.1016/j.rec.2016.09.009
6. Arnett D, Blumenthal R, Albert M, Buroker A, Goldberger Z, Hahn E, et al. 2019 ACC/AHA Guideline on the primary prevention of cardiovascular disease: a report of the American college of cardiology/American Heart Association task force on clinical practice guidelines. *Circulation.* (2019) 140:e596–646. doi: 10.1161/cir.0000000000000678
7. Thomas R, Beatty A, Beckie T, Brewer L, Brown T, Forman D, et al. Home-based cardiac rehabilitation: a scientific statement from the American Association of Cardiovascular and Pulmonary Rehabilitation, the American Heart Association, and the American College of Cardiology. *J Am Coll Cardiol.* (2019) 74:133–53. doi: 10.1016/j.jacc.2019.03.008
8. Jansen S, Hoorweg B, Hoeks S, van den Houten M, Scheltinga M, Teijink J, et al. A systematic review and meta-analysis of the effects of supervised exercise therapy on modifiable cardiovascular risk factors in intermittent claudication. *J Vasc Surg.* (2019) 69:1293–308.e2. doi: 10.1016/j.jvs.2018.10.069
9. Reed J, Pipe A. Practical approaches to prescribing physical activity and monitoring exercise intensity. *Can J Cardiol.* (2016) 32:514–22. doi: 10.1016/j.cjca.2015.12.024
10. Cai H, Zheng Y, Liu Z, Zhang X, Li R, Shao W, et al. Effect of pre-discharge cardiopulmonary fitness on outcomes in patients with ST-elevation myocardial infarction after percutaneous coronary intervention. *BMC Cardiovasc Disord.* (2019) 19:210. doi: 10.1186/s12872-019-1189-x
11. Moreno-Suarez I, Scheer A, Lam K, Dembo L, Spence A, Hayward C, et al. High-intensity interval training in patients with left ventricular assist devices: A pilot randomized controlled trial. *J Heart Lung Transplant.* (2020) 39:1380–8. doi: 10.1016/j.healun.2020.08.005
12. Deng B, Shou X, Ren A, Liu X, Wang Q, Wang B, et al. Effect of aerobic training on exercise capacity and quality of life in patients older than 75 years with acute coronary syndrome undergoing percutaneous coronary intervention. *Physiother Theory Pract.* (2020) 1–10. doi: 10.1080/09593985.2020.1825580
13. Journath G, Hammar N, Vikström M, Linnersjö A, Walldius G, Krakau I, et al. A Swedish primary healthcare prevention programme focusing on promotion of physical activity and a healthy lifestyle reduced cardiovascular events and mortality: 22-year follow-up of 5761 study participants and a reference group. *Br J Sports Med.* (2020) 54:1294–9. doi: 10.1136/bjsports-2019-101749
14. Tryfonos A, Green D, Dawson E. Effects of catheterization on artery function and health: when should patients start exercising following their coronary intervention? *Sports Med.* (2019) 49:397–416. doi: 10.1007/s40279-019-01055-3
15. Hansen D, Niebauer J, Cornelissen V, Barna O, Neunhäuserer D, Stettler C, et al. Exercise prescription in patients with different combinations of cardiovascular disease risk factors: a consensus statement from the EXPERT working group. *Sports Med.* (2018) 48:1781–97. doi: 10.1007/s40279-018-0930-4
16. Beatty A, Truong M, Schopfer D, Shen H, Bachmann J, Whooley M. Geographic variation in cardiac rehabilitation participation in medicare and veterans affairs populations: opportunity for improvement. *Circulation.* (2018) 137:1899–908. doi: 10.1161/circulationaha.117.029471
17. Rieger, Brian W. Principles of exercise testing and interpretation: including pathophysiology and clinical applications. 3rd edition. *Med Sci Sports Exerc.* (2000) 32:1364. doi: 10.1097/00005768-200007000-00030
18. Borg GAV. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc.* (1982) 14:377–81.
19. Chinese Medical Association, Chinese Society of Clinical Pharmacy, Chinese Medical Journals Publishing House, Chinese Society of General Practice, Editorial Board of Chinese Journal of General Practitioners of Chinese Medical Association, Expert Group of Guidelines for Rational Medication in Primary Care Institution, Guideline for rational medication of stable coronary artery disease in primary care. *Chin J Gen Pract.* (2021) 20:423–34. doi: 10.3760/cma.j.cn114798-20210209-00150
20. Section of Interventional Cardiology of Chinese Society of Cardiology of Chinese Medical Association, Specialty Committee on Prevention and Treatment of Thrombosis of Chinese College of Cardiovascular Physicians, Editorial Board of Chinese Journal of Cardiology, Chinese guidelines for percutaneous coronary interventions. *Chin J Cardiol.* (2016) 44:382–400. doi: 10.3760/cma.j.issn.0253-2758.2016.05.006
21. Kirkegård J, Mortensen FV, Cronin-Fenton D. Antihypertensive drugs and pancreatic cancer risk in patients with chronic pancreatitis: a Danish nationwide population-based cohort study. *Br J Cancer.* (2019) 121:622–4. doi: 10.1038/s41416-019-0562-y
22. Wittmer M, Volpatti M, Piazzalonga S, Hoffmann A. Expectation, satisfaction, and predictors of dropout in cardiac rehabilitation. *Eur J Prev Cardiol.* (2012) 19:1082–8. doi: 10.1177/1741826711418163
23. Gordon BR, McDowell CP, Hallgren M, Meyer JD, Lyons M, Herring MP. Association of efficacy of resistance exercise training with depressive symptoms: meta-analysis and meta-regression analysis of randomized clinical trials. *JAMA Psych.* (2018) 75:566–76. doi: 10.1001/jamapsychiatry.2018.0572
24. Kuznetsova T, Thijs L, Knez J, Herbots L, Zhang Z, Staessen JA. Prognostic value of left ventricular diastolic dysfunction in a general population. *J Am Heart Assoc.* (2014) 3:e000789. doi: 10.1161/JAHA.114.000789
25. Hansen D, Mathijs W, Michiels Y, Bonné K, Alders T, Hermans A, et al. Phase III multidisciplinary exercise-based rehabilitation is associated with fewer hospitalizations due to adverse cardiovascular events in coronary artery disease patients. *Eur J Prev Cardiol.* (2020) zwaa038. doi: 10.1093/eurjpc/zwaa038
26. Jepma P, Verweij L, Buurman B, Terbraak M, Daliri S, Latour C, et al. The nurse-coordinated cardiac care bridge transitional care programme: a randomised clinical trial. *Age Ageing.* (2021) 50:2105–15. doi: 10.1093/ageing/afab146

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 08 February 2022
doi: 10.3389/fcvm.2021.752531

High Intensity Interval Training Leads to Similar Inflammatory Activation as Seen With Traditional Training in Chronic Heart Failure

Arlana G. Taylor[1,2], *Andrew I. Ignaszewski*[2], *Shannon S. D. Bredin*[3,4], *John S. Hill*[5], *Erin M. Shellington*[3,4] *and Darren E. R. Warburton*[1,3,6]*

[1] Cardiovascular Physiology and Rehabilitation Laboratory, University of British Columbia, Vancouver, BC, Canada, [2] Healthy Heart Program, St. Paul's Hospital, Vancouver, BC, Canada, [3] Indigenous Health and Physical Activity Program, University of British Columbia, Vancouver, BC, Canada, [4] Laboratory for Knowledge Mobilization, University of British Columbia, Vancouver, BC, Canada, [5] University of British Columbia James Hogg Research Centre, Institute of Heart and Lung Health, Vancouver, BC, Canada, [6] Experimental Medicine Program, University of British Columbia, Vancouver, BC, Canada

OPEN ACCESS

Edited by:
Jian Yang,
Fudan University, China

Reviewed by:
Chia-Liang Tsai,
National Cheng Kung University, Taiwan
Gilson Dorneles,
Federal University of Health Sciences of Porto Alegre, Brazil

***Correspondence:**
Darren E. R. Warburton
darren.warburton@ubc.ca

Specialty section:
This article was submitted to General Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

Received: *03 August 2021*
Accepted: *21 December 2021*
Published: *08 February 2022*

Citation:
Taylor AG, Ignaszewski AI, Bredin SSD, Hill JS, Shellington EM and Warburton DER (2022) High Intensity Interval Training Leads to Similar Inflammatory Activation as Seen With Traditional Training in Chronic Heart Failure. Front. Cardiovasc. Med. 8:752531. doi: 10.3389/fcvm.2021.752531

Background: Inflammatory activation has been associated with the severity and progression of chronic heart failure (CHF). Although cardiac rehabilitation is an important therapy, acute bouts of exercise may lead to increases in pro-inflammatory cytokines with exercise intensity mediating these changes.

Objective: To evaluate the acute inflammatory response in patients living with CHF during a randomized trial following Steady State (SS) or High Intensity Interval (HIIT) training.

Methods: Patients living with CHF ($n = 14$) were stratified (for body mass and aerobic power) and randomized into SS and HIIT cycle exercise. The HIIT exercise training involved 2 min work:recovery phases at 90:40% heart rate reserve. The SS exercise training involved continuous exercise at 65% of heart rate reserve (matched total work). Acute inflammatory markers were evaluated (via ELISA) at baseline, immediately following the bout, and at 6, 24, and 48 h post-exercise.

Results: There was limited differences in the changes in inflammatory biomarkers across time between the HIIT and SS groups. Both groups experienced a significant ($p < 0.05$) change in Interleukin-6 immediately post-exercise.

Conclusions: A single bout of HIIT or SS does not result in excessive inflammatory activation in CHF patients. Acute HIIT and SS result in similar changes in inflammatory markers. These findings have important implications for exercise training and rehabilitation programs in persons living with CHF.

Keywords: heart failure, exercise, training, inflammatory markers, cytokines, heart failure, interval training, cardiac rehabilitation

INTRODUCTION

Inflammatory activation with increased plasma/serum cytokine levels has been described as an important factor for the progression of chronic heart failure (CHF) (1, 2). Cytokines appear to act as catabolic factors in the pathogenesis of skeletal muscle wasting and cardiac cachexia (3–5). This has important implications as muscle mass is an important determinant of exercise and functional capacity (6). Moreover, the progressive loss of muscle mass, cachexia (i.e., weight loss due to an underlying illness), and low levels of muscular strength are strong predictors of the risk for premature mortality (5, 7, 8). Emerging research has demonstrated the important relationship between cytokines, health, and cardiovascular fitness. Lower levels of physical activity, functional status, and/or cardiovascular fitness have been associated with higher levels of inflammation in apparently healthy individuals (9) and persons living with chronic medical conditions (10).

Exercise training remains an important therapeutic intervention in the management of CHF improving exercise capacity, Quality of Life, and various neurohormonal abnormalities (11–14). Acute bouts of exercise can lead to increases in pro-inflammatory cytokines (15–17). In contrast, there is evidence that longer duration (6 weeks to 4 months) exercise training trials may lead to small reductions in pro-inflammatory markers (18–20). However, the evidence in this field remains unclear likely owing to a variety of factors, such as high heterogeneity of participant populations and/or exercise programs studied, low exercise training adherence, and different clinical characteristics or outcomes (14). For instance, some studies have demonstrated that strenuous high intensity physical activity can cause sub-clinical skeletal muscle injury with the potential for an excessive inflammatory reaction and immune suppression (in healthy individuals) (15). A recent 12-week exercise training study revealed that pro-inflammatory markers may be increased in healthy adults following exercise (21). Whereas, another investigation (18) revealed that 12 weeks of group-based cardiac rehabilitation (involving both high intensity interval (HIIT) and moderate intensity steady state (SS) training groups) resulted in a reduced inflammatory state in persons living with CHF.

In the presence of an increased baseline of inflammatory factors, it is possible that even small amounts of physical activity can acutely increase plasma/serum cytokines in extremely deconditioned individuals (such as those living with CHF). Further to this, persons living with CHF who have relatively low inflammatory markers may improve their cardiorespiratory fitness significantly more than those with high inflammatory markers following an exercise program that includes interval training (22). Overall, there is a complicated and unclear relationship between exercise duration (acute and chronic) and intensity as it relates to inflammatory markers in healthy adults, persons living with CHF, and persons living with other chronic medical conditions (23).

The majority of evidence in the field of exercise science and medicine relates to apparently healthy individuals (24). To date, the most appropriate form of exercise training for persons living with CHF is not known. Traditional rehabilitation for CHF involves low to moderate intensity SS exercise training designed to remain below a symptom threshold. However, several researchers have challenged the traditional rehabilitation model and advocated for the incorporation of HIIT (25–30). These recommendations have been increasingly incorporated into national and international cardiac rehabilitation guidelines (31–34). Although HIIT has been shown to lead to significant benefits in cardiovascular fitness and function and other markers of health status (including Quality of Life), there is still debate regarding the observed benefits in comparison to those seen after traditional SS. Several randomized trials have demonstrated superior cardiovascular and/or health outcomes after HIIT (29, 30, 35, 36), with a potentially greater stimulus to the working muscles (37, 38) in patients living with CHF in comparison to traditional SS training. However, others have demonstrated similar changes in health outcomes after HIIT and SS training in persons living with CHF (39).

To date, limited research has examined the acute effects of HIIT on pro-inflammatory markers. In particular, to our knowledge no study has examined the temporal changes in pro-inflammatory markers in persons living with CHF after HIIT in comparison to traditional SS training. This has important implications for rehabilitation practices for persons living with CHF, as it is critical to ensure an optimal training stimulus while minimizing the risk for over-activation of the inflammatory system. Accordingly, the primary purpose of this study was to examine the effects of HIIT in comparison to traditional SS training on inflammatory biomarkers. We also sought to examine the time course of changes in inflammatory markers following acute bouts of HIIT and SS exercise training. We hypothesized [based on work from apparently healthy individuals (40) and persons living with coronary arterty disease (26)] that HIIT and SS would have similar acute effects on inflammatory markers in CHF and those inflammatory markers would return to baseline levels within 48 h.

METHODOLOGY

Study Design

A convenience sample of males living with CHF were recruited from St. Paul's Hospital (Vancouver, Canada) to participate in a randomized controlled study. Sixteen patients were identified as eligible participants and approached regarding the study. Two participants were excluded due to a lack of time to complete the study. Fourteen male participants completed the study assessments (**Figure 1**). All participants were physically inactive, were over the age of 45 yr, had a peak aerobic power (VO_2peak) <25 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ (7.1 METs), and a left ventricular ejection fraction <35%. Exclusion criteria included: musculoskeletal limitation affecting the ability to use a cycle ergometer, pulmonary disorders that markedly limit exercise, existing contraindications to exercise training, and/or patients who were recently (within last 6 months) involved in an exercise program.

After completing a baseline assessment, participants were stratified (for body mass and VO_2peak) and randomized to complete a single bout of either a SS or HIIT on a cycle

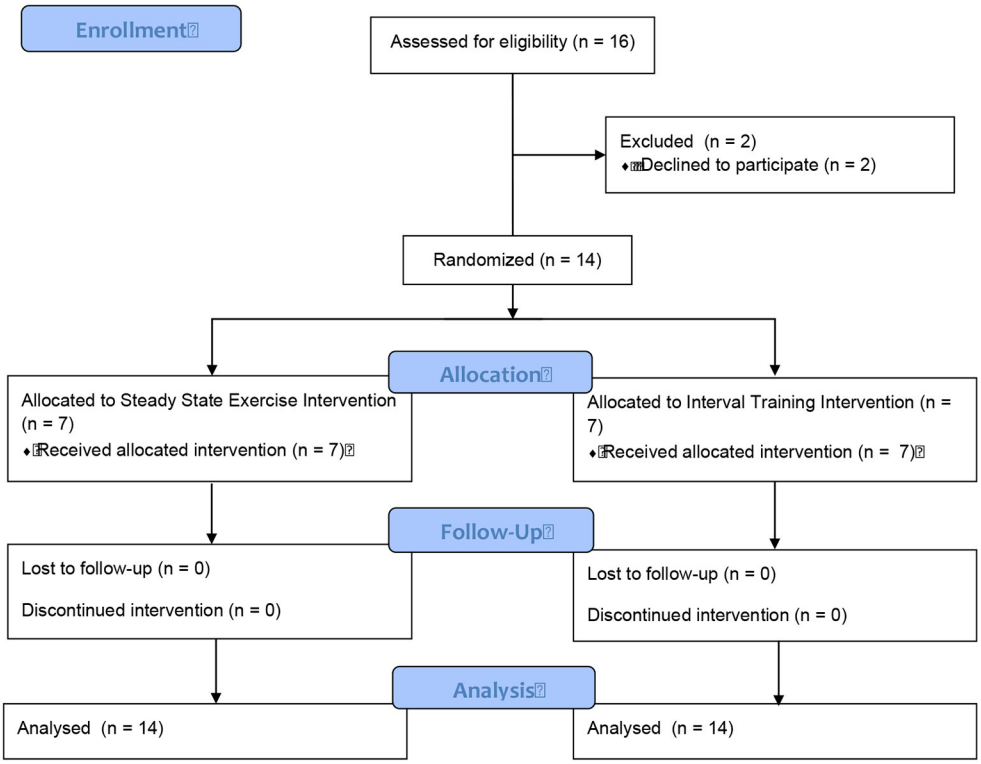


FIGURE 1 | Study flow diagram.

ergometer (Model 818, Stockholm, Sweden) while monitored on a 3-lead telemetry system. The randomization sequence was created with a 1:1 allocation using random block sizes of two by an independent research physician. The treatment allocation was kept blind (via opaque and sealed envelopes) to the research physician and research team until after the randomization procedures.

Participant characteristics are shown in **Table 1** and demonstrate that the treatment groups were similar at baseline. All participants gave their written informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the University of British Columbia (UBC) Providence Health Care Research Ethics Board and the UBC Clinical Research Ethics Board (H05-50260).

Participants underwent blood sampling at baseline, and four separate occasions following the training session (immediately post, 6 h post, 24 h post, and 48 h post). Participants were instructed to take all their medications as prescribed and to complete a food record for 3 days prior to testing as well as to complete a food record for the 3 days prior to the training session.

Sample Size

Our sample size was based on previous investigations from our team examining the effects of HIIT vs. traditional SS aerobic exercise training in persons living with coronary artery disease ($n = 14$) (26). Based on this study, we anticipated that there would be moderate to large effects sizes for transient changes in markers of muscle injury post-training with similar responses between training conditions.

Exercise Stress Testing

All participants completed an incremental exercise test using an electronically braked cycle ergometer with direct gas monitoring via a calibrated metabolic cart (Vmax, SensorMedics) to assess VO_2peak (27) (**Table 2**). The patients completed a symptom-limited incremental exercise protocol (5–10 W/min) with continuous 12-lead electrocardiography, and the assessment of blood pressure and oxygen saturation every 2 min. Criteria for terminating the exercise test included electrocardiogram changes associated with myocardial ischemia, volitional fatigue, a respiratory exchange ratio of >1.1, a leveling off in oxygen consumption, systolic blood pressure > 200 mm Hg, diastolic blood pressure >100 mmHg, dyspnea, or calf/thigh pain (27). The baseline and exercise cardiorespiratory measures are presented in **Table 2**.

Exercise Protocol

Both exercise training groups engaged in a single supervised exercise training bout on a cycle ergometer (Model 818, Stockholm, Sweden) (**Table 3**). Participants were monitored with 3-lead telemetry, as well as portable heart rate monitors (PolarTM). Rating of Perceived Exertion (RPE) was collected

TABLE 1 | Participant characteristics (values are means ± SD).

Variable	Steady-state training group ($n = 7$)	Interval training group ($n = 7$)
Age (y)	60.1 ± 6.7	57.9 ± 9.8
Height (cm)	177.7 ± 5.3	177.7 ± 5.4
Weight (kg)	96.3 ± 23.4	96.0 ± 13.5
BMI ($kg \cdot m^2$)	30.2 ± 5.34	30.5 ± 4.6
Ejection Fraction	0.24 ± 0.07	0.30 ± 0.11
VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$)	14.9 ± 5.3	12.5 ± 3.9
Diabetes mellitus		
Type 1 DM	1	2
Type 2 DM	1	1
New York heart association class		
Class 1	2	0
Class 2	4	5
Class 3a	1	2
Diagnosis		
Ischemic	3	4
Valvular	1	0
Dilated	1	0
Idiopathic	0	3
Rhythm		
NSR	3	6
Atrial fibrillation/flutter	1	0
Paced	3	1
Ventricular pacemaker	2	2
AICD	3	4
CHF onset (yr)		
<1 yr	0	1
1–5 yr	5	3
6–10 yr	1	2
11–20 yr	1	1
NT ProBNP ($pg \cdot mL^{-1}$)		
500–1,000	4	2
1,001–2,000	1	1
2,001–3,000	1	1
3,001–4,000	1	1
4,001–5,000	0	1
5,001–10,000	0	1
>10,000	1	0
Hemoglobin		
Low	1	2
Normal	6	5
Medications		
ASA	4	4
Beta blocker (CoReg, atenolol, monocor, bisoprolol)	7	6
ARB (atacand)	5	4
Digoxin	4	4
Diuretic (lasix)	6	7
Amiodarone (antiarrhythmic)	1	2
Cholesterol-lowering (lipitor, crestor, simvastatin)	2	3
Anti-coagulant (coumadin)	5	4
Plavix	0	1
ACE inhibitor (altace, captopril, accupril)	3	2
Calcium channel blocker (norvasc)	2	1
Vasodilators (nitroglycerine: patch, spray, tablets; hydralazine)	2	1
Hyperglycemic agents (Metformin, Glyburide, Insulin)	2	3
Other (testosterone, eltroxin, synthroid, pantolec, allopurinol, effexor, welbutrin, celexa, cholchicine, valium, halcion)	5	3

No significant differences between participants at baseline ($p < 0.05$).
ARB, angiotensin II receptor blocker; ACE, angiotensin-converting-enzyme inhibitor.

TABLE 2 | Cardiorespiratory responses at rest and during incremental to maximal exercise testing (values are means ± SD).

Variable	Steady-state training group ($n = 7$)	Interval training group ($n = 7$)
Rest		
Heart rate (bpm)	88.6 ± 21.8	72.7 ± 23.5
Oxyhemoglobin saturation (%)	97.6 ± 1.4	98.3 ± 1.0
Systolic blood pressure (mmHg)	101.3 ± 16.4	105.0 ± 10.8
Diastolic blood pressure (mmHg)	65.7 ± 9.6	68.3 ± 10.5
Oxygen pulse ($mL \cdot beat^{-1}$)	2.7 ± 0.7	3.6 ± 0.9
VO_2 ($mL \cdot kg^{-1} \cdot min^{-1}$)	3.1 ± 0.5	3.6 ± 0.9
VO_2 ($L \cdot min^{-1}$)	0.3 ± 0.1	0.3 ± 0.1
Peak exercise		
Heart rate (bpm)	117.9 ± 17.4	104.4 ± 31.5
Oxyhemoglobin saturation (%)	96.7 ± 2.6	96.0 ± 2.9
Systolic blood pressure (mmHg)	124.9 ± 29.1	136.6 ± 26.6
Diastolic blood pressure (mmHg)	65.7 ± 9.6	68.3 ± 10.5
Oxygen pulse ($mL \cdot beat^{-1}$)	11.6 ± 4.0	11.2 ± 3.8
VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$)	14.9 ± 5.3	12.5 ± 3.9
VO_{2peak} ($L \cdot min^{-1}$)	1.4 ± 0.5	1.1 ± 0.3

No significant differences between groups.

throughout each exercise bout. Blood pressure was taken before, during, and after the exercise session using an aneroid sphygmomanometer and stethoscope. An equivalent workload was determined for both SS and HIIT in order that total volume of exercise (i.e., isovolumetric) was similar for each group (26, 27) (**Table 2**). All individuals underwent a standardized 5 min warm-up and a 5 min cool-down prior to, and following, the conditioning exercise. The duration of the conditioning exercise (i.e., 20 min) for both SS and HIIT programs was based on the standard "first" exercise training session in the cardiac rehabilitation program at St. Paul's Hospital.

TABLE 3 | Exercise responses during steady state and interval training sessions (values are means ± SD).

Variable	Steady-state training group ($n = 7$)	Interval training group ($n = 7$)
Heart rate (bpm)	105 ± 8	40%: 91 ± 16
		90%: 109 ± 26*
		Average: 100 ± 21
Rating of perceived exertion (0–10)	4.2 ± 0.6	40%: 3.0 ± 1.2
		90%: 5.6 ± 1.4*
		Average: 4.3 ± 1.2
Work Rate (W)	54.6 ± 25.3	40%: 31.3 ± 11.8
		90%: 70.3 ± 26.5*
		Average: 50.8 ± 19.1
METs	2.8 ± 1.0	40%: 1.4 ± 0.4
		90%: 3.2 ± 1.0*
		Average: 2.3 ± 0.7
Rate pressure product (mmHg·bpm)	13,802 ± 2,664	40%: 10,869 ± 2,317
		90%: 14,539 ± 4,713*
		Average: 12,704 ± 3,490
Total work (J)	65,486 ± 30,388	60,943 ± 22,978

*Average refers to the mean response across the 20 min interval session involving 10 min of high and low intensity exercise (90 and 40%, respectively). Total work was calculated across the 20 min exercise session for both training groups. *Significant ($p < 0.05$) difference between interval training intensities (i.e., 90 > 40%). No significant difference between training groups.*

Steady-State Group

The SS group was trained as per the traditional training model (i.e., 65% heart rate reserve/VO_2 reserve) based on the results of a recent cardiopulmonary exercise test (see **Table 3**). This is consistent with previous work from our group in individuals with coronary artery disease (20) and CHF (22). The average training METs was 2.8 ± 1.0.

Interval Training Group

We used the HIIT training protocol (i.e., 2 min work phases at 90% of Heart Rate/VO_2 reserve and 2 min active recovery bouts at 40% Heart Rate/VO_2 reserve) that we have previously used safely and effectively in persons living with coronary artery disease (26) and persons living with CHF (27). The average training intensity for each participant in the HIIT group was equivalent to that which would have occurred if the individual had been randomized to the SS group (**Table 3**). Total work output was calculated as a combination of both the high intensity (i.e., 90% VO_2peak) and low intensity (i.e., 40% VO_2peak) phases of the workout (20) (**Table 3**). The average training METs were 1.4 ± 0.4 and 3.2 ± 1.0, respectively, during the low and high intensity work phases.

Measurement of Inflammatory Activation

As outlined above, all participants underwent analysis of plasma markers of Tumor Necrosis Factor alpha (TNF-α), Interleukin-6 (IL-6), high sensitivity C-Reactive Protein (CRP), IL-8, and IL-10 at five separate time periods. N-terminal prohormone of brain natriuretic peptide (NT ProBNP) was also assessed. All blood samples were drawn into blood collection tubes from the antecubital vein (with the participant in a seated position) and then immediately immersed in a refrigerated centrifuge and centrifuged within 15 min of collection. Plasma levels of each cytokine (TNF-α, IL-6, IL-8, IL-10, and CRP) and NT ProBNP were measured using a commercially available high-sensitivity ELISA (enzyme-linked immunosorbent assay) kits [Biosource (IL-8, IL-10, TNF-α), Biocheck (hsCRP), R & D Systems (IL-6)] according to the manufacturer's instructions.

Statistical Analyses

The baseline characteristics and physiological responses to exercise were evaluated using paired *t*-tests. Changes in plasma cytokine markers at baseline and at four time periods (i.e., immediately, 6, 12, and 24 h) following a single bout of either ST or HIIT exercise were examined using a mixed model Analysis of Variance with Tukey *post-hoc* comparisons. The relationship between various physiological parameters of interest and baseline levels of inflammatory and skeletal muscle injury markers were determined by Pearson Correlation Coefficient. The level of significance was set *a priori* at $p < 0.05$. All data are presented as means ± SD.

RESULTS

There were no significant differences in baseline physiological characteristics between the randomized SS and HIIT groups (**Table 1**). Similarly, there were no significant differences between groups with respect to the cardiorespiratory responses at rest and during incremental to maximal exercise testing (**Table 2**).

By design, there was a significant difference between the 40 and 90% interval stages for heart rate, work rate, METs, Rate Pressure Product, and Total Work. When comparing the average values across the entire SS and HIIT sessions there was no significant differences in heart rate, work rate, METs, Rate Pressure Product, and Total Work (**Table 3**).

There was a main effect for changes in IL-6 with time [$F_{(4, 48)} = 3.484$, $p = 0.014$, Partial Eta = 0.225; Observed Power = 0.825] (**Figure 2**). The IL-6 increased from baseline to immediately post and then returned to near baseline levels at all other time points. There was no statistical significance in IL-6 levels between groups [$F_{(1, 12)} = 1.803$, $p = 0.204$, Partial Eta = 0.131; Observed Power = 0.235] and there was no significant time by group interaction effect [$F_{(4, 48)} = 0.874$, $p = 0.486$, Partial Eta = 0.068; Observed Power = 0.257].

There were no significant changes in IL-8 following the exercise bout in either the SS or HIIT groups [$F_{(4, 48)} = 1.339$, $p = 0.269$, Partial Eta = 0.100; Observed Power = 0.386] (**Figure 3**). There was also no significant differences between groups [$F_{(1, 12)} = 0.931$, $p = 0.354$, Partial Eta = 0.072; Observed Power = 0.144] and there was no significant time by group interaction effect [$F_{(4, 48)} = 1.759$, $p = 0.153$, Partial Eta = 0.128; Observed Power = 0.497].

For IL-10, the Mauchly's Test of Sphericity was statistically significant indicating that the variances of the differences were not equal for the main effect of time. Accordingly,

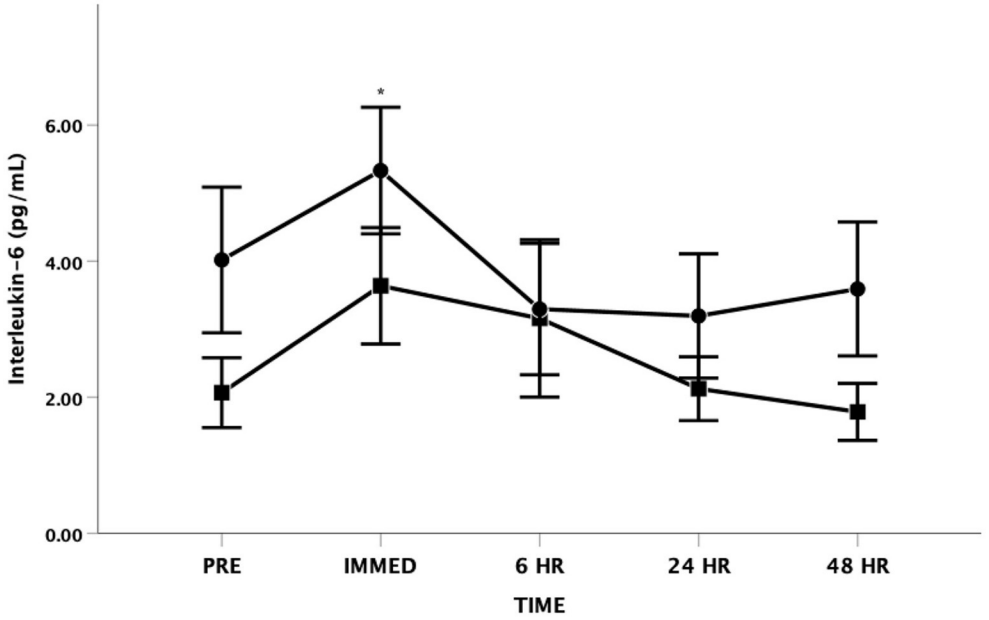


FIGURE 2 | Interleukin-6 (IL-6) as a function of time. Means ± SD. *Main effect for time observed immediately post-exercise ($p < 0.05$). Circle = Steady State; Square = Interval. Error Bars = ± SEM.

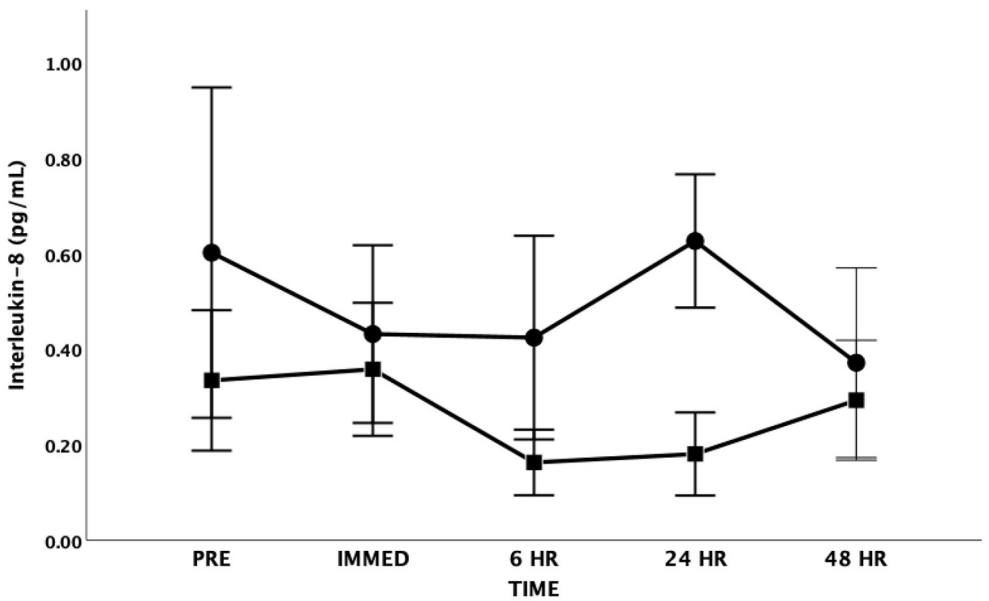


FIGURE 3 | Interleukin-8 (IL-8) as a function of time. Means ± SD. Circle = Steady State; Square = Interval. Error Bars = ± SEM.

the Greenhouse-Geisser correction was applied revealing no significant main effect for time [$F_{(1.7,\ 19.8)} = 2.861$, $p = 0.089$, Partial Eta = 0.193; Observed Power = 0.455] (**Figure 4**). There was also no significant difference between groups [$F_{(1,\ 12)} = 0.080$, $p = 0.782$, Partial Eta = 0.007; Observed Power = 0.058] and no significant time by group interaction effect [$F_{(1.7,\ 19.8)} = 1.863$, $p = 0.185$, Partial Eta = 0.134; Observed Power = 0.314].

There were no significant differences in TNF-α at any time point [$F_{(4,\ 48)} = 0.305$, $p = 0.873$, Partial Eta = 0.025; Observed Power = 0.112] or between groups [$F_{(1,\ 12)} = 0.902$, p = 0.361, Partial Eta = 0.070; Observed Power = 0.141] (**Figure 5**). There

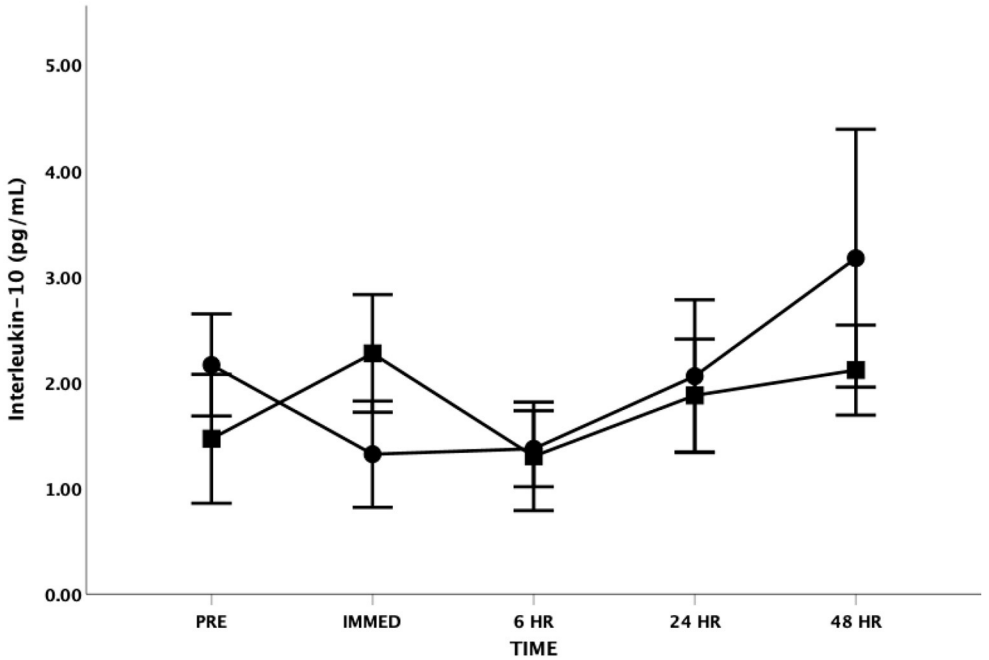


FIGURE 4 | Interleukin-10 (IL-10) as a function of time. Means ± SD. Circle = Steady State; Square = Interval. Error Bars = ± SEM.

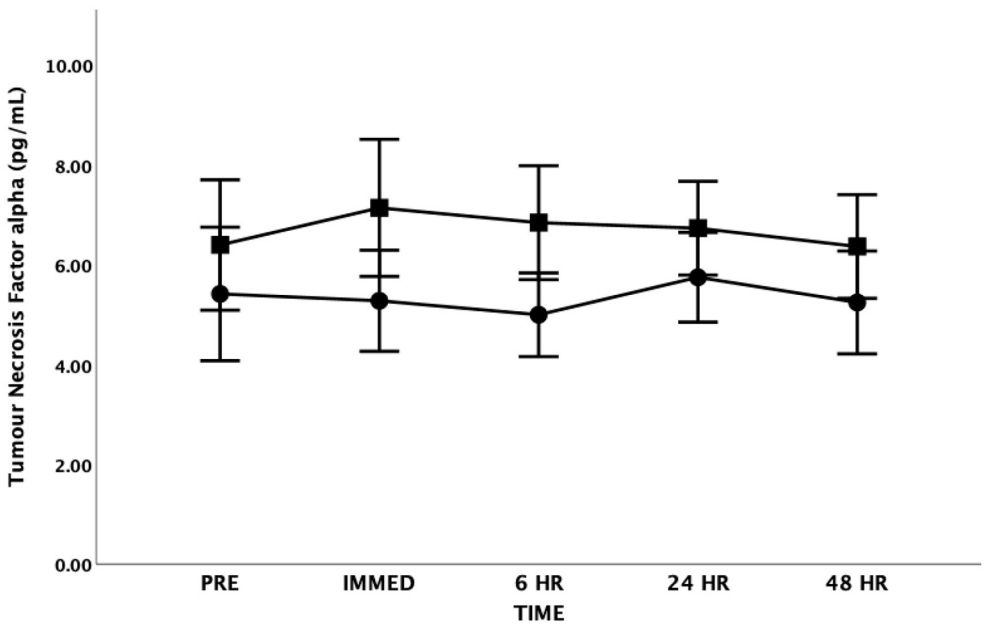


FIGURE 5 | Tumor Necrosis Factor-alpha (TNF-α) as a function of time. Means ± SD. Circle = Steady State; Square = Interval. Error Bars = ± SEM.

was also no interaction effect between time and group [$F_{(4, 48)} = 0.412$, $p = 0.799$, Partial Eta = 0.033; Observed Power = 0.137].

For CRP, the Mauchly's Test of Sphericity was statistically significant indicating that the variances of the differences were not equal for the main effect of time. Accordingly, the Greenhouse-Geisser correction was applied revealing no significant main effect for time [$F_{(1.5, 18.4)} = 0.855$, $p = 0.414$, Partial Eta = 0.066; Observed Power = 0.160] (**Figure 6**). There was also no significant difference between groups [$F_{(1, 12)} = 1.980$, $p = 0.185$, Partial Eta = 0.142; Observed Power = 0.254] and no significant time by group interaction effect [$F_{(1.5, 18.4)} = 0.442$, $p = 0.598$, Partial Eta = 0.036; Observed Power = 0.105].

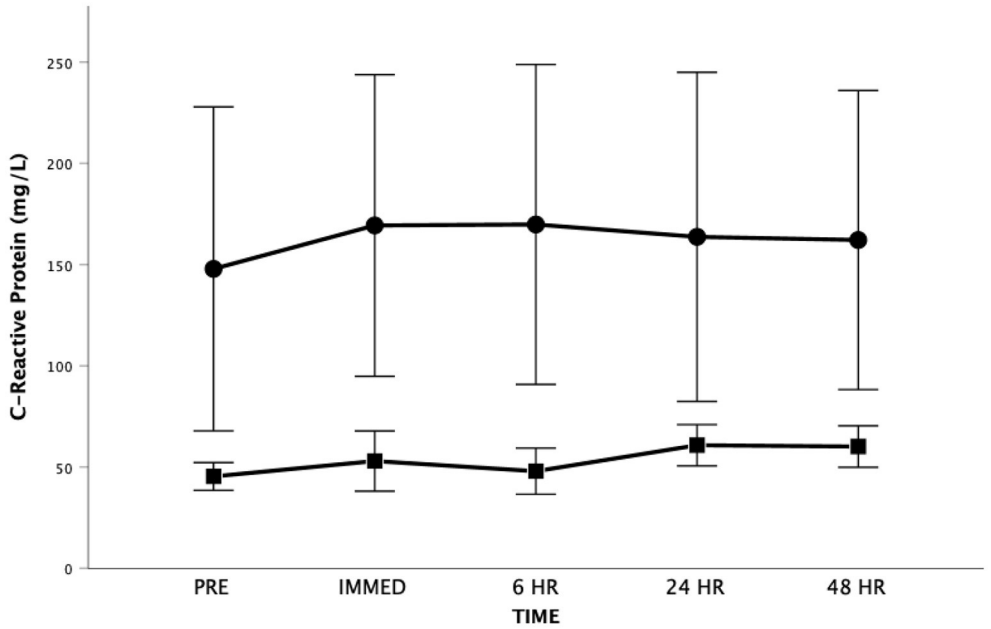


FIGURE 6 | High sensitivity C-Reactive Protein as a function of time. Means ± SD. Circle = Steady State; Square = Interval. Error Bars = ± SEM.

TABLE 4A | Baseline relationship between clinical indicators.

	Ejection Fraction	Oxygen Consumption	Height	Weight	NT Pro BNP	Age
Ejection Fraction	1.00	0.01	−0.05	−0.11	0.18	−0.08
Oxygen Consumption	0.01	1.00	0.23	0.23	0.04	0.37
Height	−0.05	0.23	1.00	0.57*	0.45	0.27
Weight	−0.11	0.23	0.57	1.00	−0.29	−0.30
NT ProBNP	0.18	0.04	0.45	−0.29	1.00	0.44
Age	−0.08	0.37	0.27	−0.30	0.44	1.00

**Marked correlations are significant at $p < 0.05$. The heat map correlation is designed such that a correlation of −1 is represented with red, a correlation of 0 (mid-point) is represented with yellow, and a correlation of +1 is represented with a color of dark green.*

TABLE 4B | The baseline relationship between various inflammatory biomarkers.

	CRP	IL-6	IL-8	IL-10	TNF-α
CRP	1.00	0.65*	0.81*	0.43	0.44
IL-6	0.65*	1.00	0.63*	0.27	0.41
IL-8	0.81*	0.63*	1.00	0.49	0.41
IL-10	0.43	0.27	0.49	1.00	0.36
TNF-α	0.44	0.41	0.41	0.36	1.00

NT ProBNP, N-terminal pro b-type natriuretic; CRP, high sensitivity C-Reactive protein; IL-6, Interleukin 6; IL-8, Interleukin 8; IL-10 Interleukin 10; TNF-α, Tumor Necrosis Factor alpha.

**Marked correlations are significant at $p < 0.05$. The heat map correlation is designed such that a correlation of −1 is represented with red, a correlation of 0 (mid-point) is represented with yellow, and a correlation of +1 is represented with a color of dark green.*

Both groups had baseline CRP levels that would be considered above normal values. It should be highlighted that one participant had high sensitivity CRP levels that approximated 600 mg/L at all time periods (explaining the variance seen in this measure).

Pearson Correlation Coefficients were determined for physiological variables of interest and markers of inflammation at baseline (see **Tables 4A**, **4B**). There were significant correlations ($p < 0.05$) for IL-6 and CRP (0.65), IL-8 and CRP (0.81), and IL-6 and IL-8 (0.63). There was also a significant correlation between participant height and weight (0.57).

DISCUSSION

To our knowledge this study is the first randomized trial to evaluate the acute and temporal effects of HIIT in comparison to traditional SS exercise training on markers of inflammatory function in persons living with CHF. The present study confirmed our hypothesis and demonstrated that there were no differences between the HIIT group and the SS training group for markers of inflammatory activation following either acute SS or HIIT training in inactive and low fitness persons living with CHF. Our secondary hypothesis was also supported with the inflammatory markers returning to baseline within 48 h.

Chronic systemic inflammation is commonly observed with physical inactivity, obesity, and in persons living with chronic medical conditions (such as cancer and diseases of the cardiovascular system) (41). Chronic inflammation has been linked to the development of insulin resistance, tumor growth, and atherosclerosis (41). Accordingly, a growing body of research has examined the role of regular physical activity and exercise training on markers of systemic inflammation in apparently healthy individuals and those living with chronic medical conditions (41, 42).

Examining the acute effects of exercise provides unique insight into the potential health benefits of exercise in persons living with CHF. It is important to highlight that compelling research has revealed that skeletal muscle can produce and secrete cytokines [termed "myokines" (43)] that apply autocrine, paracrine, and/or endocrine effects (41, 43). Contractile activity appears to be the key regulatory factor for the expression and secretion of myokines (41).

Interleukin-6 is produced by several cells such as stimulated monocytes/macrophages, fibroblasts, endothelial cells, and skeletal muscle fibers (41). Interleukin-6 was traditionally classified as a pro-inflammatory cytokine with its elevation being commonly associated with systemic inflammation and insulin resistance; however, more recently its anti-inflammatory properties (particularly during exercise conditions) have also been highlighted (41).

Our baseline IL-6 values were elevated in both HIIT and SS groups in comparison to what is often observed in apparently healthy adults supporting data from other studies in persons living with CHF (44–49). In persons living with CHF, elevated IL-6 has been related to impaired cardiac function (e.g., lowered ejection fraction), decreased cardiac functional class, muscle wasting, poor exercise tolerance, the degree of neurohumoral activation, and/or the progression and deterioration of CHF (44, 50–52).

It is important to acknowledge the potential anti-inflammatory effects of IL-6 release during exercise conditions. Interleukin-6 can be classified as a myokine as it is produced by contracting skeletal muscles and is released into the circulation in large quantities (41, 53). Plasma IL-6 is generally thought to increase in an exponential fashion with exercise (54). It is not uncommon for IL-6 levels to increase more than 100-fold with strenuous exercise then rapidly return to baseline conditions (55). As reviewed by Febbraio and Pedersen (55) the appearance of IL-6 in blood precedes other cytokines and exhibits the greatest changes. The IL-6 temporal response is related to exercise intensity, duration, the muscle mass recruited, and endurance capacity (53, 54, 56). The temporal response (kinetics) appears to differ between the type of muscle concentration (i.e., concentric vs. eccentric) (55). Originally the exercise-related increase in IL-6 was thought to be the result of muscle damage. However, research has demonstrated marked post-exercise increases in IL-6 independent of markers of muscle damage (41, 57, 58).

Our findings are consistent with previous research that demonstrates IL-6 increases in response to concentric muscle actions (such as employed during cycle ergometry), However, we did not observe as great of increases in exercise IL-6 as seen by other researchers examining the IL-6 response to maximal exercise in persons living with CHF (48, 49). These differences may be related to the relatively short duration of exercise in our study and the average training intensity employed. Our findings are supported by a recent study (59) that compared light intensity vs. moderate intensity SS exercise in persons living with CHF; overall, the light intensity had lower IL-6 following the session. However, 1 h post-exercise there was an increase in IL-6 similar to the current study. In our study, the average training intensity was controlled between the HIIT and SS groups, further highlighting the importance of understanding exercise intensity as it relates to inflammatory markers in persons living with CHF.

Pedersen et al. highlight that IL-6 plays several important biological roles including the induction of lipolysis, the suppression of TNF-α production, and the stimulation of cortisol production (53). Schnyder and Handschin (41) argued that the exercise-related release of IL-6 has pleiotropic effects by increasing glucose uptake and fatty acid oxidation and enhanced insulin secretion that supports increased glucose uptake into the working muscles.

Several authors have emphasized the important anti-inflammatory roles IL-6 may play during exercise conditions (41, 53, 55). Investigators have suggested that elevations in IL-6 in response to exercise may play an important anti-inflammatory role by inhibiting the production of TNF-α (54). Importantly, TNF-α has direct inhibitory effects on insulin signaling and the ability of IL-6 to inhibit TNF-α production may represent an important mechanism whereby exercise enhances insulin sensitivity (56). In the current study, although IL-6 increased immediately post-exercise, TNF-α did not significantly change following either SS or HIIT. It is possible that IL-6 had an inhibitory effect on TNF-α in the current study as suggested by other researchers (56, 60). This is consistent with other researchers who report that maximal IL-6 levels are found immediately after the exercise followed by a rapid decline (54, 55). Our findings are supported by a review paper on cytokine kinetics that reported more than half of the studies examining TNF-α could not confirm significant increases after exercise (61). However, other researchers have found an increase in both IL-6 and TNF-α levels immediately following maximal exercise in both patients with mild to moderate CHF and in normal controls (49). These researchers concluded that increases in basal IL-6 and TNF-α levels are associated with high sympathetic nervous system activity and exercise intolerance in patients with mild to moderate CHF.

It should be acknowledged that other factors may play a role in the lack of change in TNF-α levels in either the SS or the HIIT group at any time point following the exercise bout. Suzuki et al. highlight that TNF-α is rapidly cleared from the circulation into the urine as a result of a short half-life (14–18 min) (61). If TNF-α is rapidly expelled into the urine it is possible that the immediate post-blood sample taken in our study within 1 h of cessation of exercise would have missed this window especially if the increase in TNF-α levels were relatively small given the duration and intensity of each exercise bout. Furthermore, as noted by Lee et al. (62) the lack of changes in TNF-α seen following

exercise may be due to the measurement method; skeletal muscle biopsy may show a different story, which would be important to understanding the effects of inflammatory markers on exercise capacity for adults living with CHF.

In the current study, the baseline TNF-α levels were elevated when compared to data from apparently healthy controls (63) research (5.9 $\pm$ 3.3 vs. 2.5 $\pm$ 1.8 pg·mL^{-1}). These findings are consistent with other research that has reported increased TNF-α levels in persons living with CHF (45, 46, 49, 63). Our findings support the work of others highlighting the systemic inflammation that presents in persons living with CHF.

Interleukin-8 is a chemokine secreted by several cell types (such as monocytes, neutrophils, epithelial cells, fibroblasts, endothelial cells, mesothelial cells, and tumor cells) (64). It is a chemoattractant and activator of neutrophils (and other immune cells) that is released in response to several stimuli (such as sheer stress, ischemia, hypoxia, and stimuli that activate the nuclear factor (NF)-κB pathway) (64, 65). Interleukin-8 is also associated with the promotion of angiogenesis (41).

Elevated IL-8 levels are commonly observed in chronic medical conditions associated with systemic inflammation. Also, elevated IL-8 has been associated with poor medical outcomes in persons living with CHF (65). Previous studies have reported elevated IL-8 levels in persons living with CHF in comparison to apparently healthy controls (66, 67). For instance, Larsen et al. reported that IL-8 levels were markedly elevated in males with New York Heart Association class II to III stable, ischemic CHF (mean age 67 $\pm$ 8 y) when compared to age and sex-matched healthy controls (67). The CHF group had IL-8 levels of 12.7 $\pm$ 9.2 pg·mL^{-1}, whereas there was no detectable level of IL-8 in the healthy controls. In our current study, the IL-8 levels were detectable; however, they were not elevated to the same extent especially in the presence of elevated baseline levels of other cytokines (i.e., TNF-α, IL-6, and CRP). It is possible that etiology of CHF may have an influence on the expression of this cytokine.

Elevated IL-8 levels have been observed after exercise, particularly exercise that involves both eccentric and concentric phases (such as running) (68). Marked increases in IL-8 (e.g., 7–11-fold) immediately following prolonged strenuous events (such as marathons and half-marathons) have also been observed in apparently healthy adults (69, 70). Interestingly, other researchers have found no (or limited) change in IL-8 following largely concentric exercise (e.g., rowing or cycle ergometry) (71, 72). In fact, eccentric exercise appears to have a greater effect on IL-8 than concentric exercise (41).

In our current study, there were no significant changes in IL-8 after both SS and INT in persons living with CHF. This is consistent with other researchers that have examined IL-8 after concentric exercise in apparently healthy individuals (71, 72). This is likely the result of the relatively short duration (i.e., 20 min) of exercise, the overall lower intensity of exercise, and the nature of the muscle contractions (i.e., concentric) during bicycle ergometry (41).

Interleukin-10 is believed to be one of the most important and potent anti-inflammatory cytokines in CHF (44). It is known to down-regulate the production of TNF-α and IL-6 and other cell-mediated immune responses (44). Circulating IL-10 concentrations have been reported to be either increased or decreased in CHF patients compared to apparently healthy age-matched controls (63, 73, 74). For instance, Stumpf et al. looked at serum levels of IL-10 in patients with advanced CHF compared to age-matched controls and found significantly reduced plasma levels of IL-10 (2.3 $\pm$ 1.9 pg·mL^{-1} compared to healthy controls 5.2 $\pm$ 2.3) (63). Similarly, in our current study we observed reduced IL-10 levels (1.8 $\pm$ 1.4 pg·mL^{-1}) when compared to the healthy controls from the research by Stumpf et al. These authors also looked at the ratio of TNF-α to IL-10 and found it to be significantly higher in the CHF group vs. the control group (3.2 $\pm$ 1.2 vs. 0.4 $\pm$ 0.2). In our current research, the ratio of TNF-α to IL-10 was very similar to that of Stumpf et al. (3.2 $\pm$ 2.4) indicating an immunological imbalance in favor of inflammation in our participants living with CHF (63).

Activity-induced IL-10 is produced by stretching and compressing the epithelial cells (75), as well as in response to high levels of other pro-inflammatory markers (such as IL-6 and TNF-α). Other researchers report the relative change in IL-10 following strenuous exercise follows a similar time-course as IL-6, albeit, to a lesser degree (76) and with a slight delay in the response (24). However, there is no clear consensus on the effect of strenuous exercise on IL-10 (24). Some authors report significant increases in IL-10 following strenuous exercise (77–80) while others report limited change (15, 81). A recent systematic review revealed that the changes in IL-10 after intense exercise in healthy adults ranged from 1.57 to 32.99 times (24). Researchers have argued that exercise intensity is a key determinant of the IL-10 response to acute exercise (79) with the greatest changes being seen after strenuous high intensity exercise (24); however, a recent systematic review in healthy individuals revealed that exercise duration and not intensity was the most important predictor of exercise-related changes in IL-10 following acute exercise (40). In our current study, IL-10 did not change significantly following either SS or HIIT exercise. The average relative intensity of both the SS and HIIT exercise bouts would be considered moderate intensity. This in combination with the short duration of the training sessions (both SS and HIIT) in our study supports previous research in healthy individuals (15, 24).

C-Reactive Protein is produced by hepatocytes in response to a variety of inflammatory cytokines (e.g., IL-6) and has been shown to be a non-specific marker of systemic inflammation (82). The serum concentration of high sensitivity CRP is known to be an independent predictor of adverse cardiovascular events, including death, the need for transplantation and worsening CHF requiring hospitalization (83–86). A recent study (87) involving persons living with CHF revealed that CRP was associated with reduced exercise tolerance ($r = -0.65$), lower VO_2 at the anaerobic threshold ($r = -0.66$), and lower VO_2peak ($R = -0.70$), reflecting worsened cardiovascular performance. In the current study, the baseline high sensitivity CRP values were elevated (**Figure 6**) possibly reflecting the severity of the heart dysfunction and/or other comorbid conditions that accompany CHF in our participants.

Research on the effects of strenuous exercise on CRP levels is limited particularly in persons living with CHF. As reviewed by Cerqueira et al. (24) strenuous exercise is generally associated with an increase in CRP in healthy individuals that peaks 24 h or more after exercise with a greater increase after high intensity exercise. However, the results in healthy and in particular CHF participants are somewhat equivocal. In our study, CRP did not show any statistically significant change over all time periods or between the SS or HIIT groups. Similar equivocal findings are seen when comparing the changes in CRP that are seen with exercise training. For instance, a recent meta-analysis failed to find evidence of effects of exercise interventions on CRP in persons living with CHF (19). This is contrary to another meta-analysis (88) that revealed a small and significant decrease in CRP after exercise training in healthy adults.

Significant correlations between CRP and IL-6 and IL-8 and IL-6 and IL-8, respectively, were found in the current study. These relationships are not surprising given that CRP and IL-6 have both been associated with increased severity of left ventricular dysfunction and increased NYHA functional class and that high levels of IL-8 have been shown to predict CHF in patients following anterior myocardial infarction (51, 59, 89, 90). All participants in the current study had ejection fractions <35% and were primarily classified in the NYHA functional classes II to III, indicating moderate to severe CHF. Additional support for this finding is data from studies suggesting that CRP may function to markedly exaggerate the actions of IL-6 from endothelial cells and therefore, the increased vascular production of IL-6 may represent a positive feedback loop for the continued production of CRP from the liver (76, 91, 92).

Limitations

It is important to acknowledge the limitations of this randomized clinical trial. For instance, the small sample size limits the generalizability to like-patients (i.e., persons living with CHF with New York Heart Association Classification of Class I-III that have low aerobic fitness levels). Furthermore, because of the convenience sample, it is likely that there is some impact of selection bias and participant selection, consistent with human experimentation in clinical settings. It could be argued that since the participants self-selected to participate in an exercise intervention that they may represent a healthier or more health-conscious group of persons living with CHF. As such, the levels of inflammatory markers may not be representative of all persons living with CHF. However, it should be highlighted that the aerobic fitness levels (VO_2peak $= 13.6 \pm 4.6$ mL·kg^{-1}·min^{-1}; METs $= 3.9 \pm 1.3$) and clinical characteristics of the participants are consistent of persons living with CHF (27) that have a higher risk for premature mortality.

Consistent with the field of research, we opted to conduct unadjusted statistical analyses in this investigation and therefore, we did not control for confounding factors, such as variation in age, medications and their interactions, variation in CHF class, and other disease status. Due to the small sample size, it is unlikely that any confounders would have demonstrated important adjustments to the data. Moreover, stratified sampling procedures were used to help reduce the variability between groups. This study examined the effects of an acute bout of exercise, which does not generalize to long-term effects of exercise on inflammatory markers in adults living with CHF; however, it is important to understand inflammatory profiles at various intensities and duration to understand the profiles of inflammatory markers in this high-risk group that stands to benefit greatly from exercise.

CONCLUSIONS

Exercise training plays an essential role in the optimal treatment of patients living with CHF with clear evidence of an overall reduction in premature mortality. There is evidence suggesting that inflammatory status plays a key role in determining the responsiveness to exercise training in persons living with CHF (14, 22). Currently, it is not clear the effects HIIT on inflammation and the time course of inflammatory marker changes following HIIT and SS exercise. The results of this investigation suggest that when either SS or HIIT exercise is prescribed at a similar volume of exercise on a cycle ergometer, there is no indication of excessive or differential activation of the inflammatory system. This research has important implications for persons living with CHF, practitioners, and cardiac rehabilitation practices. The finding of no significant difference in inflammatory activation between SS and HIIT supports the inclusion of HIIT in the menu of activities provided to persons living with CHF.

Further research is warranted to examine the long-term effects of SS or HIIT exercise training in persons living with CHF. Future research should examine the effects of various modalities, dosages, and intensities of exercise on inflammatory markers to further improve clinical exercise prescriptions for person living with CHF.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of British Columbia Providence Health Care Research Ethics Board and the University of British Columbia Clinical Research Ethics Board (H05-50260). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AT, AI, JH, and DW: conceptualization, methodology, and investigation. AT, ES, SB, and DW: formal analysis and data curation. AI, JH, SB, and DW: resources. AT and DW: writing—original draft preparation, visualization, and project administration. AT, AI, ES, JH, SB, and DW: writing—review

and editing. AI and DW: supervision. DW: funding acquisition. All authors contributed to the article and approved the submitted version.

FUNDING

This research was supported by the Canada Foundation for Innovation (Project #7611), the BC Knowledge Development Fund (Project #7611), the Michael Smith Foundation for Health Research (Scholar Award to DW), the Canadian Institutes of Health Research (No. IA5-156528), and the Natural Sciences and Engineering Research Council of Canada (No. NSERC RGPIN-2018-04613). AT received graduate support from the University of British Columbia.

ACKNOWLEDGMENTS

We would like to acknowledge the participants in this study and the various undergraduate and graduate students from the Cardiovascular Physiology and Rehabilitation Laboratory at the University of British Columbia that assisted with the study.

REFERENCES

1. Gielen S, Adams V, Mobius-Winkler S, Linke A, Erbs S, Yu J, et al. Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. *J Am Coll Cardiol*. (2003) 42:861–8. doi: 10.1016/S0735-1097(03)00848-9
2. Askevold ET, Gullestad L, Dahl CP, Yndestad A, Ueland T, Aukrust P. Interleukin-6 signaling, soluble glycoprotein 130, and inflammation in heart failure. *Curr Heart Fail Rep*. (2014) 11:146–55. doi: 10.1007/s11897-014-0185-9
3. Libera LD, Vescovo G. Muscle wastage in chronic heart failure, between apoptosis, catabolism and altered anabolism: a chimaeric view of inflammation? *Curr Opin Clin Nutr Metab Care*. (2004) 7:435–41. doi: 10.1097/01.mco.0000134374.24181.5b
4. Josiak K, Jankowska EA, Piepoli MF, Banasiak W, Ponikowski P. Skeletal myopathy in patients with chronic heart failure: significance of anabolic-androgenic hormones. *J Cachexia Sarcopenia Muscle*. (2014) 5:287–96. doi: 10.1007/s13539-014-0152-z
5. Koshikawa M, Harada M, Noyama S, Kiyono K, Motoike Y, Nomura Y, et al. Association between inflammation and skeletal muscle proteolysis, skeletal mass and strength in elderly heart failure patients and their prognostic implications. *BMC Cardiovasc Disord*. (2020) 20:228. doi: 10.1186/s12872-020-01514-0
6. Saitoh M, Dos Santos MR, Emami A, Ishida J, Ebner N, Valentova M, et al. Anorexia, functional capacity, and clinical outcome in patients with chronic heart failure: results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF). *ESC Heart Fail*. (2017) 4:448–57. doi: 10.1002/ehf2.12209
7. Krysztofiak H, Wleklik M, Migaj J, Dudek M, Uchmanowicz I, Lisiak M, et al. Cardiac cachexia: a well-known but challenging complication of heart failure. *Clin Interv Aging*. (2020) 15:2041–51. doi: 10.2147/CIA.S273967
8. Youn JC, Choi SW, Lee HS, Han S, Shin EC, Baek SH, et al. Prognostic value of leg muscle strength in acute heart failure syndrome. *Med Sci Sports Exerc*. (2021) 53:19–25. doi: 10.1249/MSS.0000000000002432
9. Lira FS, Rosa JC, Pimentel GD, Souza HA, Caperuto EC, Carnevali LC Jr, et al. Endotoxin levels correlate positively with a sedentary lifestyle and negatively with highly trained subjects. *Lipids Health Dis*. (2010) 9:82. doi: 10.1186/1476-511X-9-82
10. March DS, Lai KB, Neal T, Graham-Brown MPM, Highton PJ, Churchward DR, et al. Circulating endotoxin and inflammation: associations with fitness, physical activity and the effect of a six-month programme of cycling exercise during haemodialysis. *Nephrol Dial Transplant*. (2021) 178:1–9. doi: 10.1093/ndt/gfab178
11. Taylor RS, Walker S, Ciani O, Warren F, Smart NA, Piepoli M, et al. Exercise-based cardiac rehabilitation for chronic heart failure: the EXTRAMATCH II individual participant data meta-analysis. *Health Technol Assess*. (2019) 23:1–98. doi: 10.3310/hta23660
12. Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, et al. 2017 Comprehensive update of the canadian cardiovascular society guidelines for the management of heart failure. *Can J Cardiol*. (2017) 33:1342–433. doi: 10.1016/j.cjca.2017.08.022
13. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA*. (2009) 301:1439–50. doi: 10.1001/jama.2009.454
14. Adamopoulos S, Davos CH. Determining exercise training responders through inflammatory status in heart failure. *Eur J Prev Cardiol*. (2017) 24:1015–6. doi: 10.1177/2047487317703823
15. Brenner IK, Natale VM, Vasiliou P, Moldoveanu AI, Shek PN, Shephard RJ. Impact of three different types of exercise on components of the inflammatory response. *Eur J Appl Physiol Occup Physiol*. (1999) 80:452–60. doi: 10.1007/s004210050617
16. Mann DL, Reid MB. Exercise training and skeletal muscle inflammation in chronic heart failure: feeling better about fatigue. *J Am Coll Cardiol*. (2003) 42:869–72. doi: 10.1016/S0735-1097(03)00847-7
17. Niebauer J, Clark AL, Webb-Peploe KM, Coats AJ. Exercise training in chronic heart failure: effects on pro-inflammatory markers. *Eur J Heart Fail*. (2005) 7:189–93. doi: 10.1016/j.ejheart.2004.07.012
18. Papathanasiou JV, Petrov I, Tsekoura D, Dionyssiotis Y, Ferreira AS, Lopes AJ, et al. Does group-based high-intensity aerobic interval training improve the inflammatory status in patients with chronic heart failure? A randomized controlled trial. *Eur J Phys Rehabil Med*. (2021). doi: 10.23736/S1973-9087.21.06894-5. [Epub ahead of print].
19. Pearson MJ, Mungovan SF, Smart NA. Effect of aerobic and resistance training on inflammatory markers in heart failure patients: systematic review and meta-analysis. *Heart Fail Rev*. (2018) 23:209–23. doi: 10.1007/s10741-018-9677-0
20. Adamopoulos S, Parissis J, Karatzas D, Kroupis C, Georgiadis M, Karavolias G, et al. Physical training modulates proinflammatory cytokines and the soluble Fas/soluble Fas ligand system in patients with chronic heart failure. *J Am Coll Cardiol*. (2002) 39:653–63. doi: 10.1016/S0735-1097(01)01795-8
21. Sloan RP, Shapiro PA, McKinley PS, Bartels M, Shimbo D, Lauriola V, et al. Aerobic exercise training and inducible inflammation: results of a randomized controlled trial in healthy, young adults. *J Am Heart Assoc*. (2018) 7:e010201. doi: 10.1161/JAHA.118.010201
22. Fernandes-Silva MM, Guimaraes GV, Rigaud VO, Lofrano-Alves MS, Castro RE, de Barros Cruz LG, et al. Inflammatory biomarkers and effect of exercise on functional capacity in patients with heart failure: insights from a randomized clinical trial. *Eur J Prev Cardiol*. (2017) 24:808–17. doi: 10.1177/2047487317690458
23. Murphy EA, Enos RT, Velazquez KT. Influence of exercise on inflammation in cancer: direct effect or innocent bystander? *Exerc Sport Sci Rev*. (2015) 43:134–42. doi: 10.1249/JES.0000000000000054
24. Cerqueira E, Marinho DA, Neiva HP, Lourenco O. Inflammatory effects of high and moderate intensity exercise-a systematic review. *Front Physiol*. (2019) 10:1550. doi: 10.3389/fphys.2019.01550
25. Wisloff U, Stoylen A, Loennechen JP, Bruvold M, Rognmo O, Haram PM, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. *Circulation*. (2007) 115:3086–94. doi: 10.1161/CIRCULATIONAHA.106.675041
26. Warburton DE, McKenzie DC, Haykowsky MJ, Taylor A, Shoemaker P, Ignaszewski AP, et al. Effectiveness of high-intensity interval training for the

rehabilitation of patients with coronary artery disease. *Am J Cardiol*. (2005) 95:1080–4. doi: 10.1016/j.amjcard.2004.12.063
27. Safiyari-Hafizi H, Taunton J, Ignaszewski A, Warburton DE. The Health Benefits of a 12-Week Home-Based Interval Training Cardiac Rehabilitation Program in Patients With Heart Failure. Can J Cardiol (2016) 32:561–7. doi: 10.1016/j.cjca.2016.01.031
28. Freyssin C, Verkindt C, Prieur F, Benaich P, Maunier S, Blanc P. Cardiac rehabilitation in chronic heart failure: effect of an 8-week, high-intensity interval training versus continuous training. *Arch Phys Med Rehabil*. (2012) 93:1359–64. doi: 10.1016/j.apmr.2012.03.007
29. Angadi SS, Mookadam F, Lee CD, Tucker WJ, Haykowsky MJ, Gaesser GA. High-intensity interval training vs. moderate-intensity continuous exercise training in heart failure with preserved ejection fraction: a pilot study. *J Appl Physiol.* (2014) 119:753–8. doi: 10.1152/japplphysiol.00518.2014
30. Haykowsky MJ, Timmons MP, Kruger C, McNeely M, Taylor DA, Clark AM. Meta-analysis of aerobic interval training on exercise capacity and systolic function in patients with heart failure and reduced ejection fractions. *Am J Cardiol*. (2013) 111:1466–9. doi: 10.1016/j.amjcard.2013.01.303
31. Stone JA. *Canadian Guidelines for Cardiac Rehabilitation and Cardiovascular Disease Prevention: Translating Knowledge Into Action*. Canadian Association of Cardiac Rehabilitation, Winnipeg, Manitoba, Canada (2009).
32. Stone JA, Arthur HM, Canadian Association of Cardiac Rehabilitation Guidelines Writing Group. Canadian guidelines for cardiac rehabilitation and cardiovascular disease prevention, second edition, 2004: executive summary. *Can J Cardiol*. (2005) 21(Suppl. D):3D−19.
33. Schwaab B, Bjarnason-Wehrens B, Meng K, Albus C, Salzwedel A, Schmid JP, et al. Cardiac rehabilitation in german speaking countries of europe-evidence-based guidelines from Germany, Austria and Switzerland LLKardReha-DACH-Part 2. *J Clin Med*. (2021) 10:3071. doi: 10.3390/jcm10143071
34. Price KJ, Gordon BA, Bird SR, Benson AC. A review of guidelines for cardiac rehabilitation exercise programmes: is there an international consensus? *Eur J Prev Cardiol*. (2016) 23:1715–33. doi: 10.1177/2047487316657669
35. Li D, Chen P, Zhu J. the effects of interval training and continuous training on cardiopulmonary fitness and exercise tolerance of patients with heart failure-a systematic review and meta-analysis. *Int J Environ Res Public Health*. (2021) 18:6761. doi: 10.3390/ijerph18136761
36. Meyer K, Schwaibold M, Westbrook S, Beneke R, Hajric R, Gornandt L, et al. Effects of short-term exercise training and activity restriction on functional capacity in patients with severe chronic congestive heart failure. *Am J Cardiol*. (1996) 78:1017–22. doi: 10.1016/S0002-9149(96)00527-9
37. Meyer K, Foster C, Georgakopoulos N, Hajric R, Westbrook S, Ellestad A, et al. Comparison of left ventricular function during interval versus steady-state exercise training in patients with chronic congestive heart failure. *Am J Cardiol*. (1998) 82:1382–7. doi: 10.1016/S0002-9149(98)00646-8
38. Meyer K, Samek L, Schwaibold M, Westbrook S, Hajric R, Beneke R, et al. Interval training in patients with severe chronic heart failure: analysis and recommendations for exercise procedures. *Med Sci Sports Exerc*. (1997) 29:306–12. doi: 10.1097/00005768-199703000-00004
39. Benda NM, Seeger JP, Stevens GG, Hijmans-Kersten BT, van Dijk AP, Bellersen L, et al. Effects of high-intensity interval training versus continuous training on physical fitness, cardiovascular function and quality of life in heart failure patients. *PLoS ONE.* (2015) 10:e0141256. doi: 10.1371/journal.pone.0141256
40. Cabral-Santos C, de Lima Junior EA, Fernandes I, Pinto RZ, Rosa-Neto JC, Bishop NC, et al. Interleukin-10 responses from acute exercise in healthy subjects: a systematic review. *J Cell Physiol*. (2019) 234:9956–65. doi: 10.1002/jcp.27920
41. Schnyder S, Handschin C. Skeletal muscle as an endocrine organ: PGC-1alpha, myokines and exercise. *Bone.* (2015) 80:115–25. doi: 10.1016/j.bone.2015.02.008
42. Handschin C, Spiegelman BM. The role of exercise and PGC1alpha in inflammation and chronic disease. *Nature.* (2008) 454:463–9. doi: 10.1038/nature07206
43. Pedersen BK, Febbraio MA. Muscle as an endocrine organ: focus on muscle-derived interleukin-6. *Physiol Rev*. (2008) 88:1379–406. doi: 10.1152/physrev.90100.2007
44. Anker SD, von Haehling S. Inflammatory mediators in chronic heart failure: an overview. *Heart.* (2004) 90:464–70. doi: 10.1136/hrt.2002.007005
45. Anker SD, Ponikowski PP, Clark AL, Leyva F, Rauchhaus M, Kemp M, et al. Cytokines and neurohormones relating to body composition alterations in the wasting syndrome of chronic heart failure. *Eur Heart J*. (1999) 20:683–93. doi: 10.1053/euhj.1998.1446
46. Anker SD, Clark AL, Kemp M, Salsbury C, Teixeira MM, Hellewell PG, et al. Tumor necrosis factor and steroid metabolism in chronic heart failure: possible relation to muscle wasting. *J Am Coll Cardiol*. (1997) 30:997–1001. doi: 10.1016/S0735-1097(97)00262-3
47. Kinugawa T, Kato M, Yamamoto K, Hisatome I, Nohara R. Proinflammatory cytokine activation is linked to apoptotic mediator, soluble Fas level in patients with chronic heart failure. *Int Heart J*. (2012) 53:182–6. doi: 10.1536/ihj.53.182
48. Kinugawa T, Kato M, Ogino K, Igawa O, Hisatome I, Shigemasa C, et al. Neurohormonal determinants of peak oxygen uptake in patients with chronic heart failure. *Jpn Heart J*. (2003) 44:725–34. doi: 10.1536/jhj.44.725
49. Kinugawa T, Kato M, Ogino K, Osaki S, Tomikura Y, Igawa O, et al. Interleukin-6 and tumor necrosis factor-alpha levels increase in response to maximal exercise in patients with chronic heart failure. *Int J Cardiol*. (2003) 87:83–90. doi: 10.1016/S0167-5273(02)00200-0
50. Toth MJ, Ades PA, Tischler MD, Tracy RP, LeWinter MM. Immune activation is associated with reduced skeletal muscle mass and physical function in chronic heart failure. *Int J Cardiol*. (2006) 109:179–87. doi: 10.1016/j.ijcard.2005.06.006
51. Kanda T, Takahashi T. Interleukin-6 and cardiovascular diseases. *Jpn Heart J*. (2004) 45:183–93. doi: 10.1536/jhj.45.183
52. Cicoira M, Zanolla L, Franceschini L, Rossi A, Golia G, Zamboni M, et al. Skeletal muscle mass independently predicts peak oxygen consumption and ventilatory response during exercise in noncachectic patients with chronic heart failure. *J Am Coll Cardiol*. (2001) 37:2080–5. doi: 10.1016/S0735-1097(01)01306-7
53. Pedersen BK, Steensberg A, Fischer C, Keller C, Keller P, Plomgaard P, et al. The metabolic role of IL-6 produced during exercise: is IL-6 an exercise factor? *Proc Nutr Soc*. (2004) 63:263–7. doi: 10.1079/PNS2004338
54. Pedersen BK, Febbraio M. Muscle-derived interleukin-6–a possible link between skeletal muscle, adipose tissue, liver, and brain. *Brain Behav Immun*. (2005) 19:371–6. doi: 10.1016/j.bbi.2005.04.008
55. Febbraio MA, Pedersen BK. Muscle-derived interleukin-6: mechanisms for activation and possible biological roles. *FASEB J*. (2002) 16:1335–47. doi: 10.1096/fj.01-0876rev
56. Pedersen BK, Steensberg A, Fischer C, Keller C, Keller P, Plomgaard P, et al. Searching for the exercise factor: is IL-6 a candidate? *J Muscle Res Cell Motil*. (2003) 24:113–9. doi: 10.1023/A:1026070911202
57. Ostrowski K, Schjerling P, Pedersen BK. Physical activity and plasma interleukin-6 in humans–effect of intensity of exercise. *Eur J Appl Physiol*. (2000) 83:512–5. doi: 10.1007/s004210000312
58. Pedersen BK, Steensberg A, Fischer C, Keller C, Ostrowski K, Schjerling P. Exercise and cytokines with particular focus on muscle-derived IL-6. *Exerc Immunol Rev*. (2001) 7:18–31.
59. Ribeiro-Samora GA, Rabelo LA, Ferreira ACC, Favero M, Guedes GS, Pereira LSM, et al. Inflammation and oxidative stress in heart failure: effects of exercise intensity and duration. *Braz J Med Biol Res*. (2017) 50:e6393. doi: 10.1590/1414-431x20176393
60. Bruunsgaard H, Pedersen BK. Age-related inflammatory cytokines and disease. *Immunol Allergy Clin North Am*. (2003) 23:15–39. doi: 10.1016/S0889-8561(02)00056-5
61. Suzuki K, Nakaji S, Yamada M, Totsuka M, Sato K, Sugawara K. Systemic inflammatory response to exhaustive exercise. Cytokine kinetics. *Exerc Immunol Rev*. (2002) 8:6–48.
62. Lee CT, Chen LW, Chien MY. Effects of exercise training on anabolic and catabolic markers in patients with chronic heart failure: a systematic review. *Heart Fail Rev*. (2017) 22:723–730. doi: 10.1007/s10741-017-9639-y
63. Stumpf C, Lehner C, Yilmaz A, Daniel WG, Garlichs CD. Decrease of serum levels of the anti-inflammatory cytokine interleukin-10 in patients with advanced chronic heart failure. *Clin Sci*. (2003) 105:45–50. doi: 10.1042/CS20020359
64. Qazi BS, Tang K, Qazi A. Recent advances in underlying pathologies provide insight into interleukin-8 expression-mediated inflammation and angiogenesis. *Int J Inflam*. (2011) 2011:908468. doi: 10.4061/2011/908468

65. Nymo SH, Hulthe J, Ueland T, McMurray J, Wikstrand J, Askevold ET, et al. Inflammatory cytokines in chronic heart failure: interleukin-8 is associated with adverse outcome. Results from CORONA. *Eur J Heart Fail*. (2014) 16:68–75. doi: 10.1093/eurjhf/hft125
66. Cappuzzello C, Di Vito L, Melchionna R, Melillo G, Silvestri L, Cesareo E, et al. Increase of plasma IL-9 and decrease of plasma IL-5, IL-7, and IFN-gamma in patients with chronic heart failure. *J Transl Med*. (2011) 9:28. doi: 10.1186/1479-5876-9-28
67. Larsen AI, Aukrust P, Aarsland T, Dickstein K. Effect of aerobic exercise training on plasma levels of tumor necrosis factor alpha in patients with heart failure. *Am J Cardiol*. (2001) 88:805–8. doi: 10.1016/S0002-9149(01)01859-8
68. Suzuki K, Nakaji S, Yamada M, Liu Q, Kurakake S, Okamura N, et al. Impact of a competitive marathon race on systemic cytokine and neutrophil responses. *Med Sci Sports Exerc*. (2003) 35:348–55. doi: 10.1249/01.MSS.0000048861.57899.04
69. Nielsen HG, Oktedalen O, Opstad PK, Lyberg T. Plasma cytokine profiles in long-term strenuous exercise. *J Sports Med*. (2016) 2016:7186137. doi: 10.1155/2016/7186137
70. Ostrowski K, Rohde T, Asp S, Schjerling P, Pedersen BK. Chemokines are elevated in plasma after strenuous exercise in humans. *Eur J Appl Physiol*. (2001) 84:244–5. doi: 10.1007/s004210170012
71. Henson DA, Nieman DC, Nehlsen-Cannarella SL, Fagoaga OR, Shannon M, Bolton MR, et al. Influence of carbohydrate on cytokine and phagocytic responses to 2 h of rowing. *Med Sci Sports Exerc*. (2000) 32:1384–9. doi: 10.1097/00005768-200008000-00005
72. Chan MH, Carey AL, Watt MJ, Febbraio MA. Cytokine gene expression in human skeletal muscle during concentric contraction: evidence that IL-8, like IL-6, is influenced by glycogen availability. *Am J Physiol Regul Integr Comp Physiol*. (2004) 287:R322–7. doi: 10.1152/ajpregu.00030.2004
73. Wykretowicz A, Furmaniuk J, Smielecki J, Deskur-Smielecka E, Szczepanik A, Banaszak A, et al. The oxygen stress index and levels of circulating interleukin-10 and interleukin-6 in patients with chronic heart failure. *Int J Cardiol*. (2004) 94:283–7. doi: 10.1016/j.ijcard.2003.06.001
74. Yamaoka M, Yamaguchi S, Okuyama M, Tomoike H. Anti-inflammatory cytokine profile in human heart failure: behavior of interleukin-10 in association with tumor necrosis factor-alpha. *Jpn Circ J*. (1999) 63:951–6. doi: 10.1253/jcj.63.951
75. Winkelman C. Inactivity and inflammation: selected cytokines as biologic mediators in muscle dysfunction during critical illness. *AACN Clin Issues*. (2004) 15:74–82. doi: 10.1097/00044067-200401000-00006
76. Kasapis C, Thompson PD. The effects of physical activity on serum C-reactive protein and inflammatory markers: a systematic review. *J Am Coll Cardiol*. (2005) 45:1563–9. doi: 10.1016/j.jacc.2004.12.077
77. Nieman DC, Konrad M, Henson DA, Kennerly K, Shanely RA, Wallner-Liebmann SJ. Variance in the acute inflammatory response to prolonged cycling is linked to exercise intensity. *J Interferon Cytokine Res*. (2012) 32:12–7. doi: 10.1089/jir.2011.0038
78. Nieman DC, Henson DA, Smith LL, Utter AC, Vinci DM, Davis JM, et al. Cytokine changes after a marathon race. *J Appl Physiol*. (2001) 91:109–14. doi: 10.1152/jappl.2001.91.1.109
79. Peake JM, Suzuki K, Hordern M, Wilson G, Nosaka K, Coombes JS. Plasma cytokine changes in relation to exercise intensity and muscle damage. *Eur J Appl Physiol*. (2005) 95:514–21. doi: 10.1007/s00421-005-0035-2
80. de Gonzalo-Calvo D, Davalos A, Montero A, Garcia-Gonzalez A, Tyshkovska I, Gonzalez-Medina A, et al. Circulating inflammatory miRNA signature in response to different doses of aerobic exercise. *J Appl Physiol*. (2015) 119:124–34. doi: 10.1152/japplphysiol.00077.2015
81. Gannon GA, Rhind SG, Suzui M, Shek PN, Shephard RJ. Circulating levels of peripheral blood leucocytes and cytokines following competitive cycling. *Can J Appl Physiol*. (1997) 22:133–47. doi: 10.1139/h97-011
82. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *J Clin Invest*. (2003) 111:1805–12. doi: 10.1172/JCI200318921
83. Anand IS, Latini R, Florea VG, Kuskowski MA, Rector T, Masson S, et al. C-reactive protein in heart failure: prognostic value and the effect of valsartan. *Circulation*. (2005) 112:1428–34. doi: 10.1161/CIRCULATIONAHA.104.508465
84. Kavsak PA, MacRae AR, Newman AM, Lustig V, Palomaki GE, Ko DT, et al. Elevated C-reactive protein in acute coronary syndrome presentation is an independent predictor of long-term mortality and heart failure. *Clin Biochem*. (2007) 40:326–9. doi: 10.1016/j.clinbiochem.2006.10.025
85. Osman R, L'Allier PL, Elgharib N, Tardif JC. Critical appraisal of C-reactive protein throughout the spectrum of cardiovascular disease. *Vasc Health Risk Manag*. (2006) 2:221–37. doi: 10.2147/vhrm.2006.2.3.221
86. Yin WH, Chen JW, Jen HL, Chiang MC, Huang WP, Feng AN, et al. Independent prognostic value of elevated high-sensitivity C-reactive protein in chronic heart failure. *Am Heart J*. (2004) 147:931–8. doi: 10.1016/j.ahj.2003.11.021
87. Canada JM, Fronk DT, Cei LF, Carbone S, Erdle CO, Abouzaki NA, et al. Usefulness of C-reactive protein plasma levels to predict exercise intolerance in patients with chronic systolic heart failure. *Am J Cardiol*. (2016) 117:116–20. doi: 10.1016/j.amjcard.2015.10.020
88. Fedewa MV, Hathaway ED, Ward-Ritacco CL. Effect of exercise training on C reactive protein: a systematic review and meta-analysis of randomised and non-randomised controlled trials. *Br J Sports Med*. (2017) 51:670–676. doi: 10.1136/bjsports-2016-095999
89. Bruunsgaard H, Ladelund S, Pedersen AN, Schroll M, Jorgensen T, Pedersen BK. Predicting death from tumour necrosis factor-alpha and interleukin-6 in 80-year-old people. *Clin Exp Immunol*. (2003) 132:24–31. doi: 10.1046/j.1365-2249.2003.02137.x
90. Dominguez-Rodriguez A, Abreu-Gonzalez P, Garcia-Gonzalez M, Ferrer J. Prognostic value of interleukin-8 as a predictor of heart failure in patients with myocardial infarction and percutaneous intervention. *Int J Cardiol*. (2006) 111:158–60. doi: 10.1016/j.ijcard.2005.05.063
91. Goldhammer E, Tanchilevitch A, Maor I, Beniamini Y, Rosenschein U, Sagiv M. Exercise training modulates cytokines activity in coronary heart disease patients. *Int J Cardiol*. (2005) 100:93–9. doi: 10.1016/j.ijcard.2004.08.073
92. Modur V, Li Y, Zimmerman GA, Prescott SM, McIntyre TM. Retrograde inflammatory signaling from neutrophils to endothelial cells by soluble interleukin-6 receptor alpha. *J Clin Invest*. (1997) 100:2752–6. doi: 10.1172/JCI119821

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Cardiovascular Medicine

SYSTEMATIC REVIEW
published: 08 February 2022
doi: 10.3389/fcvm.2021.753117

Effects of Aerobic, Resistance, and Combined Exercise Training on Psychiatric Symptom Severity and Related Health Measures in Adults Living With Schizophrenia: A Systematic Review and Meta-Analysis

Shannon S. D. Bredin [1,2†], Kai L. Kaufman [1,3†], Maddison I. Chow [1,3†], Donna J. Lang [4], Nana Wu [1,3], David D. Kim [5] and Darren E. R. Warburton [1,3]*

[1] Physical Activity Promotion and Chronic Disease Prevention Unit, University of British Columbia, Vancouver, BC, Canada, [2] Laboratory for Knowledge Mobilization, University of British Columbia, Vancouver, BC, Canada, [3] Cardiovascular Physiology and Rehabilitation Laboratory, University of British Columbia, Vancouver, BC, Canada, [4] Department of Radiology, University of British Columbia, Vancouver, BC, Canada, [5] Department of Anesthesiology, Pharmacology and Therapeutics, University of British Columbia, Vancouver, BC, Canada

OPEN ACCESS

Edited by:
Junjie Xiao,
Shanghai University, China

Reviewed by:
Sanjoy Ghosh,
University of British Columbia Okanagan, Canada
Richard Yang Cao,
Shanghai Xuhui Central Hospital, China

***Correspondence:**
Darren E. R. Warburton
darren.warburton@ubc.ca

[†] These authors have contributed equally to this work

Specialty section:
This article was submitted to General Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

Received: 04 August 2021
Accepted: 20 December 2021
Published: 08 February 2022

Citation:
Bredin SSD, Kaufman KL, Chow MI, Lang DJ, Wu N, Kim DD and Warburton DER (2022) Effects of Aerobic, Resistance, and Combined Exercise Training on Psychiatric Symptom Severity and Related Health Measures in Adults Living With Schizophrenia: A Systematic Review and Meta-Analysis. Front. Cardiovasc. Med. 8:753117. doi: 10.3389/fcvm.2021.753117

Previous research has demonstrated the efficacy, effectiveness, and safety of exercise training in persons living with schizophrenia. However, the optimal exercise training program remains unclear. The aim of this paper was to conduct a systematic review and meta-analysis of the effects of aerobic, resistance, and combined aerobic and resistance training on health-related physical fitness and positive and negative symptoms in persons living with schizophrenia. Six electronic databases were searched systematically from their inception to December 2020 [MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, SPORTDiscus, and Cumulative Index to Nursing and Allied Health Literature (CINAHL)] to identify literature examining the effects of exercise training on psychiatric symptoms and health-related physical fitness indicators in persons living with schizophrenia. A total of 22 studies (n = 913) were included in this review, and 12 studies (n = 554) included within the meta-analysis reported the effects of exercise training (aerobic, resistance, and combined aerobic and resistance) in persons living with schizophrenia. Aerobic training had a significant decrease on Positive and Negative Syndrome Scale (PANSS) negative scores (ES −2.28, 95% CI −3.57 to −1.00; p = 0.0005) and PANSS general scores (ES −2.51, 95% CI −3.47 to −1.55; p < 0.00001). Resistance training did not lead to significant effects on PANSS total scores. Combined aerobic and resistance training did not lead to significant changes in body mass index, PANSS positive scores, or PANSS total scores. However, grouping together the results from all exercise training modalities (including aerobic training, resistance training, and combined aerobic and resistance training) revealed significant effects on body mass index (ES 1.86, 95% CI 0.84 to 2.88; p = 0.0003), maximal/peak oxygen consumption

(ES 2.54, 95% CI 1.47 to 3.62; $p = < 0.00001$), body weight (ES 6.58, 95% CI 2.94 to 10.22; $p = 0.0004$), PANSS negative scores (ES −1.90, 95% CI −2.70 to −1.10; $p < 0.00001$), and Scale for the Assessment of Negative Symptoms (SANS) total (ES −14.90, 95% CI −22.07 to −7.74; $p < 0.0001$). Collectively, these findings support the importance of exercise participation (aerobic and resistance training) in persons living with schizophrenia.

Keywords: health benefits, schizophrenia, psychiatric symptoms, exercise training, aerobic training, resistance training

INTRODUCTION

Schizophrenia is a severe mental illness characterized by a combination of psychiatric symptoms, with typical onset occurring in early adulthood. Psychiatric symptoms include positive, negative, and cognitive symptoms, which can have significant effects on daily living, social interactions, and functional capacity in persons living with schizophrenia (1, 2). Positive symptoms can be described as excessive or an exaggeration of normal function, which may include hallucinations, bizarre behaviors, and delusions (1). Negative symptoms can be characterized as a decrease in normal function and typically includes symptoms such as apathy, social withdrawal, and lethargy (1). Furthermore, additional symptoms may be associated with the impairment of cognitive functioning and include behaviors such as a deficit of executive functioning with disorganized speech and short-term memory (1). Schizophrenia affects ∼1% of the population worldwide (3), with no significant differences in prevalence rates between males and females (4). In comparison to the general population, schizophrenia can increase the risk of comorbidity and premature mortality (5), reducing lifespan by ∼25 years (6, 7). Cardiovascular disease is considered to be the major contributor to the increased risk for premature mortality (5, 8).

Antipsychotic medications are typically considered as a preferred method of treatment for schizophrenia; however, evidence has revealed associated adverse side effects, causing significant concern for long-term health (9, 10). First generation antipsychotics typically have an increased efficacy in treating positive symptoms; yet, they often have reduced efficacy in treating negative symptoms (10). Additionally, first-generation antipsychotic medications can cause side effects such as extrapyramidal symptoms, including dystonia, bradykinesia, and tardive dyskinesia (11). Second-generation antipsychotics were first introduced to primarily increase the efficacy of reducing negative symptoms and incidences of neurological side effects. Therefore, second-generation antipsychotics are commonly utilized to treat psychiatric symptoms in schizophrenia (9, 11, 12). While second-generation antipsychotics have significant benefits for persons living with schizophrenia, the associated side effects must be considered by healthcare professionals (9, 12). Second-generation antipsychotics (such as clozapine) have been associated with increased risks of adverse cardiometabolic effects such as significant weight gain, hyperglycaemia, dyslipidemia, and cardiovascular disease (12–14). Recently, Kim et al. (8) also revealed that the exposure to clozapine was associated with reduced cardiovascular fitness in persons living with chronic schizophrenia.

The increased rates of morbidity among this population are not solely caused by the effects of antipsychotics (12, 13). Persons living with schizophrenia have a higher prevalence of unhealthy lifestyle behavior choices placing them at an increased risk of morbidity and premature mortality (6, 14, 15). For instance, schizophrenia has been associated with a greater prevalence of cigarette smoking, with a reported rate of 90% of individuals engaging in this behavior (14). Furthermore, poor diet and alcohol consumption and substance use is associated with an increased risk of morbidity among this population (6, 14, 16, 17). Additionally, individuals living with schizophrenia have higher rates of sedentary behavior and physical inactivity, with 70–75% of individuals categorized as physically inactive, and a 1.5 to 2 times greater risk of being classified as overweight when compared to the general population (14, 18). A meta-analysis revealed that persons living with schizophrenia exhibit significantly lower maximal/peak oxygen consumption (VO_2max/peak) in comparison to apparently healthy controls (19).

In consideration of the increased health risks commonly linked to schizophrenia, the use of exercise and/or regular physical activity has been investigated as a potential adjunct therapy (20–22). The role of regular physical activity and exercise participation on reducing the risk for premature all-cause mortality and diverse chronic medical conditions (such as cardiometabolic disease and hypertension) is well established (23). Increasing evidence has shown that regular physical activity and/or exercise participation can improve quality of life, increase functional capacity, improve cardiorespiratory fitness, and increase muscular strength in persons living with major mental illness (21, 24–26). Also, regular physical activity and/or exercise can improve symptom severity, reduce depression, improve cognition, and trigger hippocampal growth (27). In schizophrenia, regular exercise and physical activity participation may also help to counteract some of the side effects associated with antipsychotic medications (14). For instance, psychiatric symptoms, particularly negative symptoms, can be difficult to effectively manage with the use of antipsychotic medication and can greatly influence rates of non-compliance to treatment (14, 20, 21, 28, 29). The engagement in physical activity/exercise can be advantageous in alleviating these symptoms and lead to a

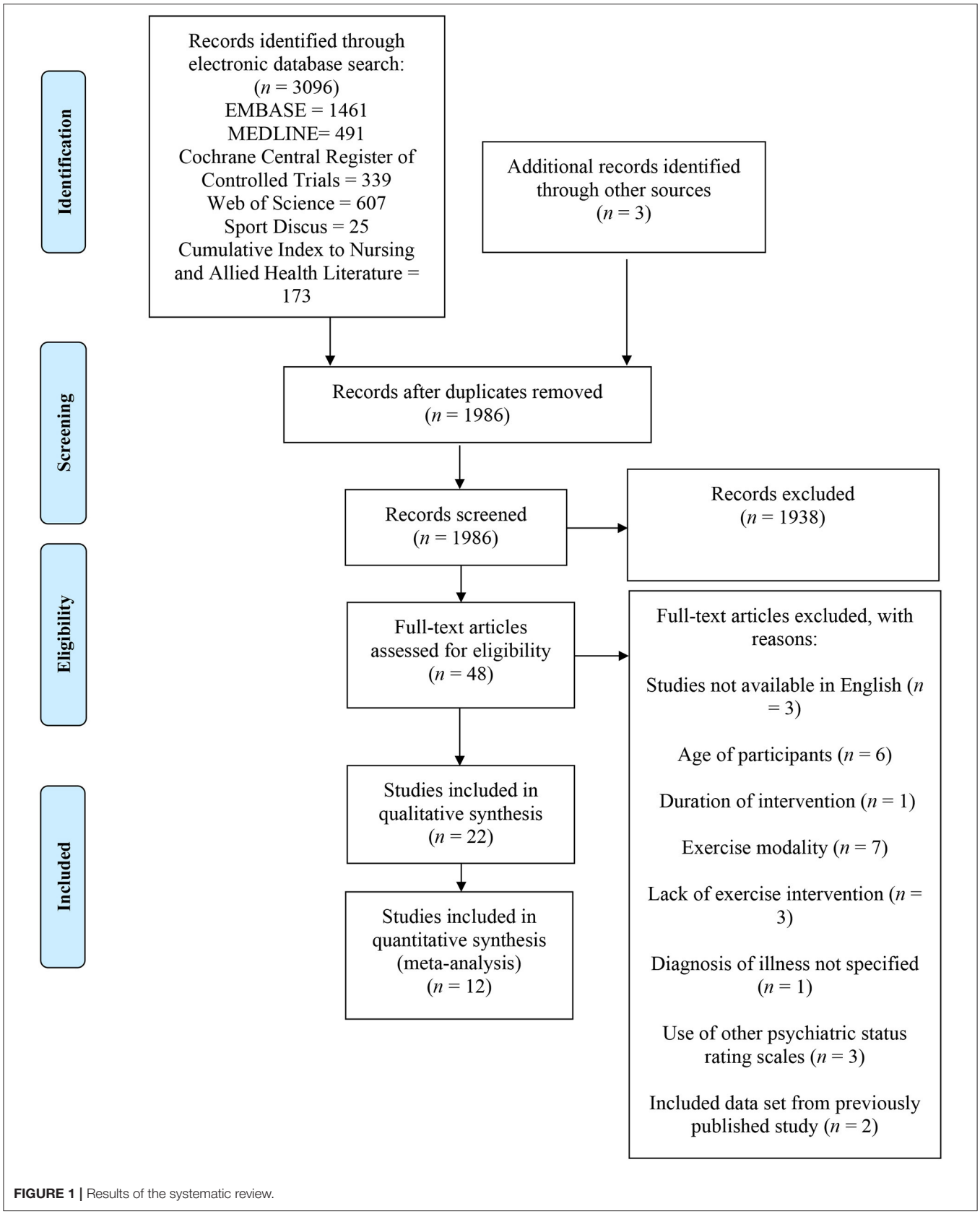


FIGURE 1 | Results of the systematic review.

reduction in dosage of antipsychotic medications (30, 31). The benefits of physical activity/exercise participation may be even greater in patients with treatment-resistant psychosis (27).

To date, studies have examined various exercise modalities, such as aerobic, resistance, and a combination of aerobic and resistance training as an adjunct treatment for persons living with schizophrenia (21, 32). Exercise interventions have examined various health-related physical fitness indicators [such as body weight, body mass index (BMI), and VO_2max/peak] in response to diverse exercise modalities (15, 20–22, 25, 27, 29, 33–40). However, to the best of our knowledge, no meta-analysis has explored the optimal training exercise program in persons living with schizophrenia. Therefore, this systematic review and meta-analysis was designed to examine the effectiveness of aerobic, resistance, and combined aerobic and resistance training on improving psychiatric symptoms and health-related physical fitness indicators in persons living with schizophrenia.

MATERIALS AND METHODS

This systematic review and meta-analysis adheres to the guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (**Figure 1**).

Search Strategy

A preliminary search of the literature was conducted to determine established reviews on the topic of interest prior to performing the systematic review. We conducted the systematic search utilizing the following electronic databases (from their inception to December 2020) to identify relevant studies: EMBASE (Ovid Interface), MEDLINE (Ovid Interface), Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, SPORTDiscus, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). Search strategies were tailored for each electronic database. The reviewers conducting the search were not blinded to studies identified. **Table 1** provides an example of the literature search strategy and search terms. Additional studies were retrieved through reference lists and through the authors' knowledge.

TABLE 1 | Results of the literature search strategy: MEDLINE (Ovid).

#	Search terms	Results
1	exp schizophrenia/ or schizophrenia.mp.	148,490
2	psychosis.mp.	40,821
3	1 or 2	171,975
4	exp exercise/ or exercise.mp	432,398
5	aerobic exercise.mp.	10,439
6	aerobic training.mp.	2,692
7	weight lifting.mp or exp weight lifting/	5,329
8	resistance training.mp. or exp resistance training/	14,795
9	physical activity.mp.	121,398
10	physical exertion.mp. or exp physical exertion/	58,138
11	4 or 5 or 6 or 7 or 8 or 9 or 10	517,276
12	Panss.mp.	4,709
13	BPRS.mp.	2,366
14	Psychiatric Status Rating Scales.mp or exp Psychiatric Status Rating Scales/	85,406
15	Symptom*.mp.	1,243,058
16	(Positive and Negative Syndrome Scale).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	4,454
17	Brief Psychiatric Rating Scale.mp. or ex Brief Psychiatric Rating Scale/	3,995
18	12 or 13 or 14 or 15 or 17	1,294,706
19	3 and 11 and 18	491

Exp, explode; mp, title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms; Asterisk (*), match all terms beginning with a word root.

Study Selection

Eligible studies for this systematic review met the following inclusion criteria: the study population included individuals between the ages of 18–65 years of either sex, living with a major mental illness, including schizophrenia, first episode psychosis, schizoaffective disorder, schizophreniform disorder, bipolar disorder, and psychotic disorder not otherwise specified. Participants were also required to have received or were currently receiving treatment for their condition and were prescribed antipsychotic medication. Acceptable exercise modalities included aerobic, resistance, or a combination of both aerobic and resistance training with the goal of reducing psychiatric symptoms and improving health-related physical fitness indicators in persons living with schizophrenia. The exercise interventions were required to have been a minimum duration of six weeks in length or longer. The key outcome was to evaluate the positive and negative symptoms in persons living with schizophrenia using valid psychiatric status rating scales, including the Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale (BPRS), Scale for the Assessment of Positive Symptoms (SAPS), and/or Scale for the Assessment of Negative Symptoms (SANS). The secondary outcomes included health-related physical fitness indicators (body weight, BMI, and VO_2max/peak). There were no limitations placed on study design. Comparisons were made between pre and post scores within each group to determine the effectiveness of the exercise intervention. Furthermore, when feasible, pre and post scores were analyzed between the exercise intervention group and a control group.

We excluded studies that included the following: studies that examined the effectiveness of high intensity interval training and/or mind-body exercises (such as yoga and tai chi) and studies that were not published in English. Studies that utilized symptom scales not identified within the inclusion criteria were also deemed ineligible for this systematic review. Two of the authors (K.L.K. and M.I.C.) independently conducted the search using the six outlined electronic databases and systematically scanned all identified study titles, abstracts, and keywords. In addition, both authors independently examined the full articles of the remaining studies ensuring that all inclusion criteria were met. All excluded studies were removed and the reasons for

exclusion were documented. Uncertainties regarding inclusion were resolved by consensus, or by discussion with third, fourth, and fifth reviewers (S.S.D.B., D.E.R.W., and D.D.K.). The review process was guided directly by a professor with expert knowledge of systematic reviews (S.S.D.B.).

Data Extraction and Quality Assessment

Two reviewers (K.L.K. and M.I.C.) independently extracted the relevant data from the selected articles using a standardized template. Authors were contacted directly to provide clarifications on data that was not included within the publication. Data extracted from the studies included: study purpose, study design, number of participants (*N*), mean age ± standard deviation and age range, sex distribution, diagnosis, mean time since diagnosis, medications, intervention, program duration, baseline health measures, outcome health measures, within group differences, between group differences, symptom severity, outcome symptom severity, within group differences, between group differences, limitations, adherence rates to program, rates of dropout, reasons for dropout, hospitalization duration, location of participant recruitment, and take home message/recommendations. Reviewers were not blinded to publication authors or journals during the extraction process.

Using the Downs and Black Quality Index (41), two of the authors (K.L.K. and M.I.C.) independently assessed the methodological quality of the included studies in alignment with the items established in the valid and reliable tool. Any discrepancies were assessed by another reviewer (N.W.). The checklist evaluation includes a total of 27 questions, with a maximum score of 32, assessing the following subscales: (i) reporting, (ii) external validity, (iii) internal validity, bias, (iv) internal validity, confounding, and (v) power. The maximal score signifies the highest level of methodological quality.

Data Synthesis and Analysis

A meta-analysis was performed utilizing the Review Manager program (RevMan version 5.1, Cochrane Collaboration) to synthesize and analyze the extracted data from the included studies. Results of the meta-analysis were reported as mean effect size and 95% confidence interval (CI) and were displayed using forest plot figures. The degree of heterogeneity across the studies was quantified using the I-squared test and chi-squared test, with 95% CI. Fixed effect models were utilized to illustrate data with lower degrees of heterogeneity (<50%), whereas random effects models were chosen when a significant degree of heterogeneity was present. When feasible, sensitivity analyses were completed by sequentially eliminating individual studies to determine if the results were greatly influenced by a particular study. When appropriate, subgroup analyses were examined between exercise intervention duration, frequency, and intensity. An assessment of publication bias was conducted for this meta-analysis using funnel plots. All studies included in the meta-analysis included an intervention and control group, with some of the control groups engaging in an additional form of exercise.

TABLE 2 | Downs and black quality index assessment for methodological quality.

References	Reporting (/11)	External validity (/3)	Bias (/7)	Confounding (/6)	Power (/5)	Total (/32)
Acil et al. (43)	7	2	4	4	5	22
Beebe et al. (33)	8	1	5	5	2	21
Bredin et al. (22)	9	2	5	5	3	24
Browne et al. (15)	6	1	4	2	5	18
Curcic et al. (34)	8	2	4	4	5	23
Dodd et al. (35)	9	2	4	3	4	22
Firth et al. (29)	8	3	4	3	4	22
Heggelund et al. (25)	10	1	4	4	3	22
Kern et al. (36)	10	2	7	5	5	29
Korman et al. (40)	10	3	5	3	5	26
Loh et al. (44)	10	2	6	5	5	28
Malchow et al. (45)	9	2	5	4	5	25
Maurus et al. (38)	11	2	5	5	2	25
Pajonk et al. (46)	9	3	6	6	4	28
Ryu et al. (47)	9	2	5	5	5	26
Scheewe et al. (20)	11	2	5	5	5	28
Senormanci et al. (42)	9	3	4	3	5	24
Shimada et al. (48)	9	1	5	6	5	26
Silva et al. (21)	9	2	6	5	5	27
Su et al. (37)	10	2	5	5	5	27
Svatkova et al. (39)	10	2	6	4	5	27
Woodward et al. (27)	10	2	4	6	4	26

RESULTS

Study Selections and Characteristics

A search of six electronic databases was conducted for this systematic review. Additional studies were included based on the authors' knowledge. After removing duplicates, titles, abstracts, and keywords were screened to identify potential studies. Full articles were then reviewed to determine if eligibility criteria were met (**Figure 1**). A total of 26 studies were excluded with reasons from this systematic review. In total, 22 studies published from 2005 (33) to 2020 (42) were deemed eligible through our inclusion criteria and examined the effects of exercise training for persons living with schizophrenia. The included studies consisted of aerobic training ($n = 12$), resistance training ($n = 3$), and combined aerobic and resistance training ($n = 7$). The results of the Downs and Black Quality Index assessment were consistent with good quality scores for the included studies (**Table 2**). The mean score was 24.8 out of 32, with a range of scores between 18 and 29. A meta-analysis was conducted using 12 of the included studies (20, 21, 25, 29, 34, 37–39, 42–44, 48). The summary of the quantitative results by modality of exercise and outcome are outlined in **Table 3**. Funnel plots were used to assess the publication bias for each outcome within the meta-analysis. It was determined that all figures were relatively symmetrical around the effect size, indicating that there was no publication bias present within the meta-analysis. Studies not included in the meta-analysis were excluded for the following reasons: lack of control group ($n = 5$) (15, 22, 27, 35, 40), missing data ($n = 3$) (33, 45, 46), and insufficient data to conduct a meta-analysis ($n = 2$) (36, 47).

Participant characteristics, interventions, baseline and outcome health measures, baseline and outcome psychiatric symptom severity scores, and intervention adherence rates are outlined in **Supplementary Tables 1–3**. The exercise interventions of the included studies investigated different exercise modalities (aerobic, resistance, or combined aerobic and resistance training), program durations, exercise intensities, and exercise frequencies. An included study implemented both a resistance exercise group and a combined exercise group in comparison to a control group and therefore, data for this study was reported as two independent trials. To evaluate symptom severity scores, 17 of the included studies utilized the PANSS. Of these studies, 11 reported PANSS positive scores, 11 reported PANSS negative scores, and seven reported PANSS general scores; while 14 reported PANSS total scores. Additionally, three studies used the BPRS, and four studies utilized the SANS and/or the SAPS. In addition, many of the included studies examined the effectiveness of various exercise modalities on improving health-related physical fitness measures, such as body mass index ($n = 11$), VO_2max/peak ($n = 9$), and body weight ($n = 6$).

TABLE 3 | Summary of quantitative results by modality of exercise and outcome.

Modality of exercise	Examined outcome	Number of studies	Results
Aerobic Training	PANSS Positive	4	Slightly favors exercise group Not statistically significant
Aerobic Training	PANSS Negative	4	Favors exercise group Statistically significant
Aerobic Training	PANSS General	3	Favors exercise group Statistically significant
Resistance Training	PANSS Total	3	Slightly favors exercise group Not statistically significant
Combined (Aerobic and Resistance Training)	Body Mass Index	3	Favors control group Statistically significant
Combined (Aerobic and Resistance Training)	PANSS Positive	3	Slightly favors exercise group Not statistically significant
Combined (Aerobic and Resistance Training)	PANSS Total	4	Slightly favors control group Not statistically significant
All Exercise Training Modalities	Body Mass Index	4 (5 trials)	Favors control group Statistically significant
All Exercise Training Modalities	Maximal Oxygen Consumption	4	Favors exercise group Statistically significant
All Exercise Training Modalities	Body Weight	2 (3 trials)	Favors control group Statistically significant
All Exercise Training Modalities	PANSS Positive	8 (9 trials)	Favors exercise group Not statistically significant
All Exercise Training Modalities	PANSS Negative	8 (9 trials)	Favors exercise group Statistically significant
All Exercise Training Modalities	PANSS General	6 (7 trials)	Favors exercise group Not statistically significant
All Exercise Training Modalities	PANSS Total	8 (9 trials)	Favors exercise group Not statistically significant
All Exercise Training Modalities	SANS	3	Favors exercise group Statistically significant

Participants and Exercise Intervention

A combined total of 814 participants living with severe mental illness and 83 healthy controls were included in this systematic review. The participant sample size ranged from 8 to 104, with participants' diagnoses including schizophrenia, schizoaffective disorder, schizophreniform disorder, bipolar disorder, first episode psychosis, or psychotic disorder not otherwise specified. All participants (excluding healthy controls) were currently receiving antipsychotic medication as treatment. It is important to note that two studies included participants living with treatment-resistant schizophrenia (27, 35). In total, the exercise intervention duration ranged between 8 and 26 weeks in length, and incorporated between one and five sessions per week, with the majority including three exercise sessions per week (11 studies) or twice per week (eight studies). In addition, the exercise sessions ranged between 30 and 60 min. Exercise intensity was reported in terms of percentage of maximal aerobic power (VO_2max) or VO_2peak, maximum heart rate, heart rate reserve, rating of perceived exertion, talk test, or percentage of 1-repetition maximum. The intensity of exercise ranged between 40 and 80% VO_2max or VO_2peak, 55 and 75% maximum heart rate, 30 and 75% heart rate reserve, and 60 and 85% 1 repetition maximum. Exercise equipment for aerobic and resistance training included treadmill, cycle ergometer, elliptical,

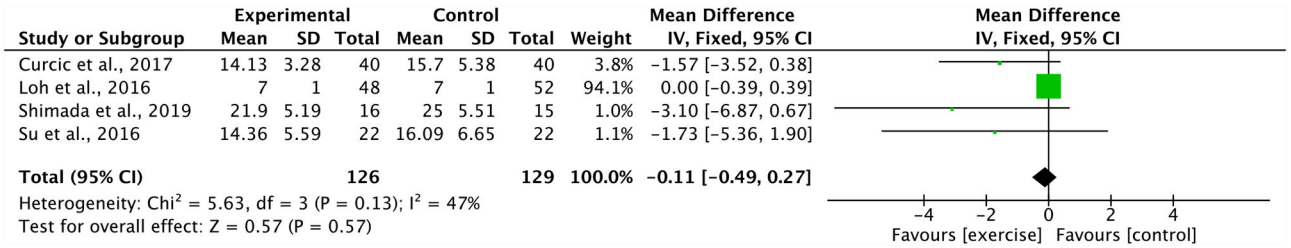


FIGURE 2 | The effects of aerobic training on PANSS positive scores.

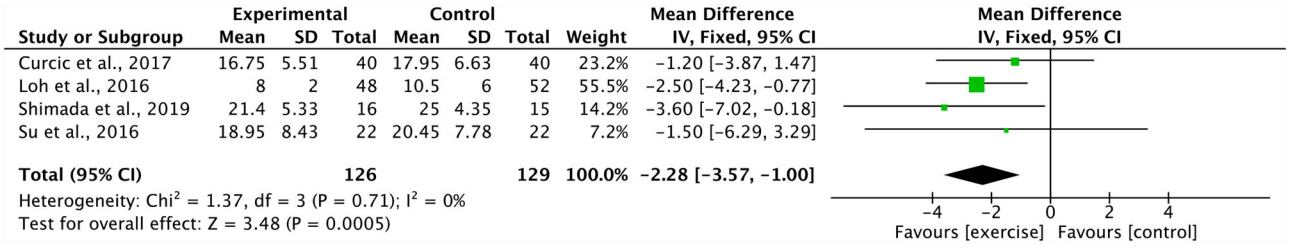


FIGURE 3 | The effects of aerobic training on PANSS negative scores.

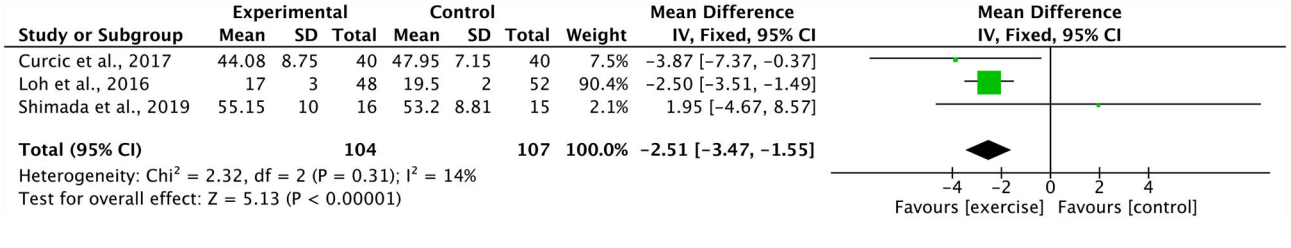


FIGURE 4 | The effects of aerobic training on PANSS general scores.

recumbent bike, rowing machine, cross trainer, resistance bands, dumbbells, and various small training equipment.

Aerobic Training

Four studies combined in a meta-analysis found no significant effect of aerobic training on PANSS positive scores (Effect Size, ES −0.11, 95% CI −0.49 to 0.27; $p = 0.57$) (34, 37, 44, 48). Across these studies, there was a moderate degree of heterogeneity (I^2: 47%; $p = 0.13$) (**Figure 2**). The sensitivity analysis greatly influenced the results, yielding a significant mean effect (ES −1.86, 95% CI −3.43 to −0.30; $p = 0.02$) with a low degree of heterogeneity (I^2: 0%; $p = 0.78$) (44). Additionally, these four studies were further analyzed in a meta-analysis which identified a significant decrease in PANSS negative scores within the aerobic training group (ES −2.28, 95% CI −3.57 to −1.00; $p = 0.0005$) (34, 37, 44, 48). The degree of heterogeneity was low for these studies (I^2: 0%; $p = 0.71$) (**Figure 3**). Further, three studies were pooled, revealing a significant reduction on effect of PANSS general scores, favoring the aerobic training group (ES −2.51, 95% CI −3.47 to −1.55; $p < 0.00001$) (34, 44, 48) (**Figure 4**). A low degree of heterogeneity was detected across the studies (I^2: 14%; $p = 0.31$). Due to insufficient study data, we were unable to conduct a meta-analysis on VO_2max/peak; however, there is growing evidence from randomized trials (49) to support the potential for significant changes in aerobic capacity after exercise interventions in persons living with schizophrenia.

Resistance Training

Three studies were included in a meta-analysis revealing no significant effect of resistance training on PANSS total scores (ES −0.87, 95% CI −3.52 to 1.78; $p = 0.52$) (21, 25, 38). The degree of heterogeneity was low (I^2: 0%; $p = 0.45$) (**Figure 5**). A sensitivity analysis revealed a shift in the results, changing the mean effect size to positive, however, it did not change the overall significance of the effect (21).

Combined Aerobic and Resistance Training

A meta-analysis pooling three studies identified no significant effect of combined aerobic and resistance training on body mass

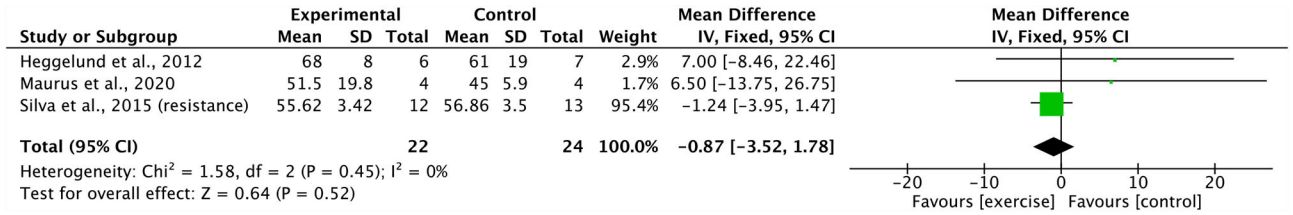


FIGURE 5 | The effects of resistance training on PANSS total scores.

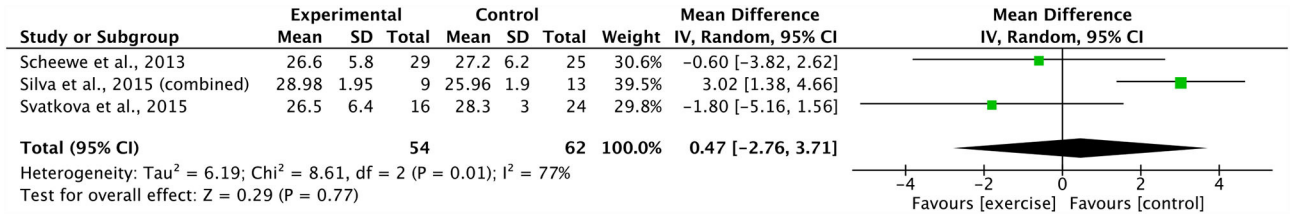


FIGURE 6 | The effects of combined aerobic and resistance training on body mass index scores.

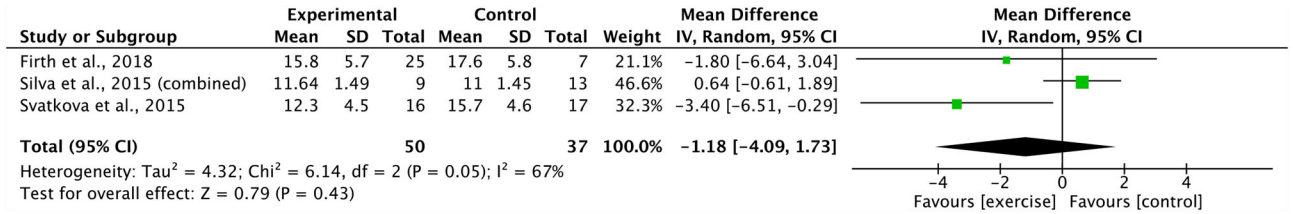


FIGURE 7 | The effects of combined aerobic and resistance training on PANSS positive scores.

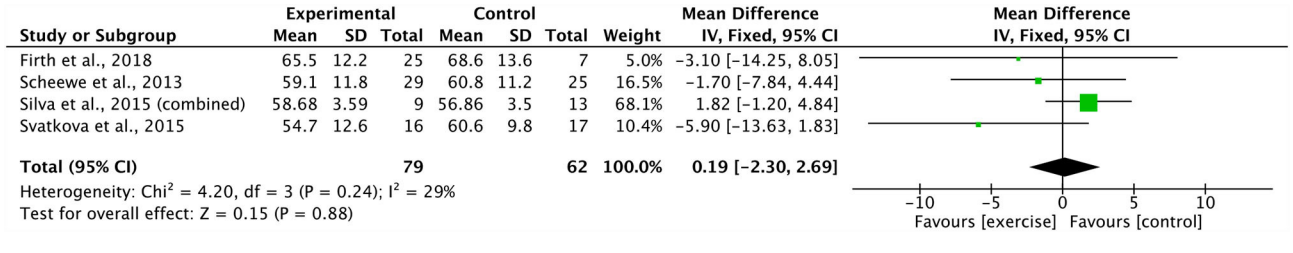


FIGURE 8 | The effects of combined aerobic and resistance training on PANSS total scores.

index (ES 0.47, 95% CI −2.76 to 3.71; $p = 0.77$) (20, 21, 39). There was a substantial degree of heterogeneity across these studies (I^2: 77%; $p = 0.01$) (**Figure 6**). Sensitivity analysis revealed shifts in the results; however, there was no effect on the overall significance. In addition, three studies were grouped, revealing a non-significant effect of combined aerobic and resistance training on PANSS positive scores (ES −1.18 95% CI −4.09 to 1.73; $p = 0.43$) (21, 29, 39). The degree of heterogeneity across the studies was substantial (I^2: 67%; $p = 0.05$) (**Figure 7**). The sensitivity analysis revealed significant shifts and changed the overall significance of the results (ES −2.93, 95% CI −5.55 to −0.32; $p = 0.03$) (21). The degree of heterogeneity was low (I^2: 0%; $p = 0.59$). Finally, four studies were pooled, illustrating a non-significant effect of combined aerobic and resistance training on PANSS total scores (ES 0.19, 95% CI −2.30 to 2.69; $p = 0.88$) (20, 21, 29, 39). Heterogeneity was low within these studies (I^2: 29%; $p = 0.24$) (**Figure 8**). Conducting a sensitivity analysis shifted the mean effect to be negative, but did not affect the overall significance (21).

All Exercise Training Modalities Included

Four studies (five trials) were pooled in a meta-analysis displaying a significant effect of all exercise training modalities (aerobic, resistance, and combined training) on body mass index

(ES 1.86, 95% CI 0.84 to 2.88; $p = 0.0003$) (20, 21, 38, 39). There was a moderate degree of heterogeneity across the trials (I^2: 42%; $p = 0.14$). In addition, four studies were combined, showing a significant increase in VO_2max/peak of all exercise training modalities (ES 2.54, 95% CI 1.47 to 3.62; $p < 0.00001$), favoring the exercise group (20, 34, 37, 39). The heterogeneity of the combined studies was low (I^2: 0%; $p = 0.78$). Two studies (three trials) were combined revealing a significant effect of all exercise training modalities on body weight (ES 6.58, 95% CI 2.94 to 10.22; $p = 0.0004$) (21, 25). These combined trials showed a low degree of heterogeneity (I^2: 0%; $p = 0.40$). Furthermore, eight studies (nine trials) were pooled, yielding a non-significant effect on PANSS positive scores for all exercise training modalities (ES −0.81, 95% CI −1.74 to 0.13; $p = 0.09$) (21, 29, 34, 37–39, 44, 48). A moderate degree of heterogeneity was identified within these trials (I^2: 57%; $p = 0.02$). A sensitivity analysis slightly influenced the results, indicating a significant effect on PANSS positive scores (ES −1.20, 95% CI −2.32 to −0.08; $p = 0.04$) with a moderate degree of heterogeneity (I^2: 58%; $p = 0.02$) (44). The subgroup differences between intervention duration (>12 weeks and ≤12 weeks) and frequency (<3 sessions per week and ≥3 sessions per week) within all exercise training modalities (aerobic, resistance, and combined training) on PANSS positive scores, were not statistically significant ($p = 0.16$; $p = 0.80$). In addition, using the same eight studies (nine trials), all exercise training modalities had a significant effect on PANSS negative scores (ES −1.90, 95% CI −2.70 to −1.10; $p < 0.00001$) (21, 29, 34, 37–39, 44, 48). There was low heterogeneity among these studies (I^2: 18%; $p = 0.28$). The subgroup differences between intervention duration (>12 weeks and ≤12 weeks), frequency (<3 sessions per week and ≥3 sessions per week), and intensity (moderate; moderate-vigorous) within all exercise training modalities (aerobic, resistance, and combined training) on PANSS negative scores, were not statistically significant ($p = 0.16$; $p = 0.09$; $p = 0.11$). A total of six studies (seven trials) were included in the meta-analysis demonstrating no significant effect of all exercise training modalities on PANSS general scores (ES −0.02, 95% CI −2.50 to 2.45; $p = 0.99$) (21, 29, 34, 38, 44, 48). In addition, there was a considerable degree of heterogeneity across these studies (I^2: 87%; $p =< 0.00001$). Furthermore, a sensitivity analysis had little effect on results and did not impact the significance of this effect. Eight studies (nine trials) were pooled in a meta-analysis demonstrating a non-significant effect of all exercise training modalities on PANSS total scores (ES −2.01, 95% CI −5.13 to 1.10; $p = 0.21$) (20, 21, 25, 29, 34, 38, 39, 48). The degree of heterogeneity across these studies was moderate (I^2: 54%; $p = 0.02$). Sensitivity analysis showed a considerable shift, yielding a significant mean effect (ES −2.73, 95% CI −4.74 to −0.71; $p = 0.008$) (21). These trials showed a low degree of heterogeneity (I^2: 35%; $p = 0.15$). The subgroup differences between intervention duration (>12 weeks and ≤12 weeks), frequency (<3 sessions per week and ≥3 sessions per week), and intensity (moderate; moderate-vigorous) within all exercise training modalities (aerobic, resistance, and combined training) on PANSS total scores, were not statistically significant ($p = 0.41$; $p = 0.29$; $p = 0.10$). Finally, three studies were grouped in a meta-analysis and displayed a significant decrease in SANS total scores in all exercise training modalities (ES −14.90, 95% CI −22.07 to −7.74; $p < 0.0001$). The heterogeneity across these studies was low (I^2: 0%; $p = 0.46$).

DISCUSSION

This systematic review consisted of 22 studies, with a total of 12 studies included in the meta-analysis to examine the effectiveness of aerobic, resistance, and combined aerobic and resistance training on improving psychiatric symptoms and health-related physical fitness indicators in persons living with schizophrenia. The findings from our meta-analysis reveal significant effects of exercise training on psychiatric symptoms and health-related physical fitness measures (such as body weight, BMI, and VO_2max/peak). These findings further support the importance of exercise training as an adjunct therapy for persons living with schizophrenia.

Aerobic Training

An increasing number of studies have investigated the effects of aerobic training on the improvement of health measures and the reduction of psychiatric symptoms in persons living with schizophrenia. Walking has been identified as a preferred method of treatment in individuals living with schizophrenia due to high accessibility and increased levels of motivation (15, 50). In our meta-analysis, four studies included walking/brisk walking demonstrating reductions in PANSS positive, negative, and total scores (34, 44, 48), or BPRS positive and negative scores (36). Exercise duration ranged from 90 to 180 min per week, with two-to-four sessions per week, implemented over a duration of 12 weeks. Two studies began the exercise intervention with relatively short exercise durations and gradually increased to 150 min per week (36, 44). However, Loh et al. (44) acknowledged that participants in the walking group reported greater levels of motivation due to the increased amount of social support provided. Thus, while the results from these moderate-intensity walking studies have demonstrated a relative decrease in positive and negative symptoms, more research is warranted to demonstrate a significant change in symptoms. Similarly, these findings were supported by a recent review (51) suggesting that while the recommendations for optimal aerobic training dosage is still unclear, a duration of 30–40 min, three days per week, over 10–12 weeks resulted in increased health benefits. Importantly, this dosage is well below international physical activity guideline recommendations for apparently healthy individuals, but consistent with other clinical populations that have exhibited low aerobic capacities and high levels of physical inactivity and sedentary behavior (52, 53).

A recent systematic review and meta-analysis revealed significant improvements in both PANSS positive and negative scores for individuals living with schizophrenia within the aerobic exercise intervention group (54). Similarly, our systematic review revealed that aerobic training had a significant influence on PANSS negative scores; however, we did not find a significant change in PANSS positive scores. Due to the limited studies included within our current paper, these findings should be interpreted with caution. There was a

moderate degree of heterogeneity across the studies within the PANSS positive scores; however, low heterogeneity was found among these studies for PANSS negative scores. The aerobic studies included in the systematic review by Sabe and colleagues also revealed improvements in VO_2max/peak scores, suggesting a possible relationship between aerobic capacity and decreased PANSS negative scores (54). In our current work, two included studies demonstrated improvements in VO_2max/peak (34, 37). Due to the lack of studies, we were not able to conduct a meta-analysis on this outcome. However, there is growing evidence from randomized trials to support the potential for significant changes in aerobic capacity after exercise interventions in persons living with schizophrenia (34, 49). Furthermore, other studies (not employing control groups) have also demonstrated significant (and clinically relevant) improvements in VO_2max/peak and other markers of aerobic fitness and exercise tolerance (22, 35). This is further supported by a clinical overview and meta-analysis by Vancampfort et al. (19) that reported lower cardiorespiratory fitness levels in persons living with schizophrenia in comparison to apparently healthy controls. The authors provided recommendations for aerobic training to help optimize health benefits (19). These recommendations outlined the importance of administering a risk stratification, assessments for cardiorespiratory fitness, attainable exercise interventions based on fitness level, and support strategies to ensure adherence to programs (19). Further, it is important for clinicians to consider psychiatric symptoms (specifically negative symptoms), elevated BMI scores, reported presence of pain, and comorbidities as factors that can influence the ability to perform and adhere to aerobic training and thus increase health benefits (19). This supports the earlier recommendations of our team (22).

Current literature suggests that aerobic exercise has a significant effect on PANSS general scores by reducing associated symptoms such as depression and anxiety (34, 55). These results are consistent with our findings in this systematic review. Further, findings by Pelham et al. (55) indicates that there is a negative correlation associated between aerobic fitness levels and rates of depression. This suggests that increasing levels of aerobic fitness results in lower levels of depression, leading to lower levels of PANSS general scores (55). This is supported by the findings of Woodward and colleagues that demonstrate a 12-week aerobic or weight-bearing exercise program can improve symptom severity, reduce depression, improve cognition, and trigger hippocampal growth (27).

Resistance Training

Despite the clear health benefits of engaging in exercise that taxes the musculoskeletal system (56, 57), few studies have examined the effect(s) of resistance training on psychiatric symptoms. Therefore, there is a paucity of evidence surrounding the benefits of resistance training in persons living with schizophrenia (21, 25). The meta-analysis revealed no significant findings with respect to PANSS total scores. Although it has been suggested that resistance training may have a beneficial effect on improving psychiatric symptoms in patients living with schizophrenia (21), a pilot study by Heggelund et al. (25) reported an increase in PANSS total scores following a resistance training intervention. These authors suggested that the findings may be attributed to the natural course of the illness commonly seen in persons living with schizophrenia. This is an important point to consider when comparisons are made to changes seen in other groups (e.g., apparently healthy controls and other clinical populations). Additionally, the authors acknowledged that an 8-week intervention may be too short in duration for participants to adapt to the exercise intervention to produce greater reductions in symptom severity. Moreover, a study by Silva et al. (21) reported significant improvements in PANSS positive, negative, and total scores following a 20-week resistance training intervention.

Although there was insufficient data to conduct a meta-analysis, two studies investigated BMI scores in response to resistance training, revealing equivocal findings. Specifically, Silva et al. (21) revealed minor reductions in BMI scores following a 20-week intervention. In comparison, following a 12-week resistance training intervention, Maurus et al. (38) documented a slight increase in BMI scores. These divergent findings are not unanticipated owing to differences in exercise training programs, treatment patterns, and clinical characteristics of persons living with schizophrenia.

Resistance training reduces all-cause mortality by increasing musculoskeletal fitness and functional independence in the general population (56–58). Therefore, considering the increased risk of secondary complications (such as cardiometabolic disease) and premature mortality, further investigation is warranted to fully examine the effects of resistance training on psychiatric symptoms and health outcomes in schizophrenia (18, 25, 59).

Although further research is clearly warranted, the findings from this systematic review support the implementation of resistance training in persons living with schizophrenia. The optimal dosage, intensity, and type of resistance training remains to be determined. However, there is preliminary evidence supporting two-to-three sessions of resistance training carried out over a period of 12 weeks or more. This is similar to what is seen with the rehabilitation of other chronic medical conditions with low baseline fitness (e.g., chronic heart failure) (60–62).

Combined Aerobic and Resistance Training

Combined aerobic and resistance training has been shown to decrease cardiovascular disease risk factors and increase VO_2max in overweight and obese populations when compared to aerobic or resistance training interventions (63, 64). Evidence has revealed that incorporating resistance training into an aerobic exercise intervention may act as a form of therapeutic treatment, as individuals living with schizophrenia receive the benefits of both aerobic and resistance training. In addition, findings suggest that combined training may help to improve body composition and lean body mass in persons living with schizophrenia (21, 26). All participants across three studies included in the meta-analysis reported BMI scores that were categorized as overweight (20, 21, 39). Although the mean effect size was not significant, there was a significant degree of heterogeneity that should be considered when interpreting these findings (**Figure 5**). It is

important to note that a contributing study consisted of a small sample size of solely male participants (21), which may not be an accurate representation of the general clinical population. Considerable limitations such as small sample sizes (21), low compliance rates, high drop-out rates, and symptom severity (20) may be contributing factors to these findings and the associated heterogeneity.

A systematic review by Martin et al., (64) determined that an exercise program involving both aerobic and resistance training led to improvements in PANSS negative and total scores. An additional systematic review by Firth et al. (65) found improvements in psychiatric symptoms (PANSS positive, negative, and total scores) that were only detected through the implementation of programs that included aerobic training. Our systematic review had preliminary evidence to support this conclusion; however, our meta-analysis did not reveal a statistically significant benefit for PANSS total scores. Conducting a sensitivity analysis showed that removing the only study with a positive ES (21) shifted the findings to favor combined training on PANSS total scores. However, these changes did not lead to significant findings. Furthermore, positive symptoms were favored within the combined training groups; however, sensitivity analysis was required to remove the only positive ES in order establish statistical significance in these findings. It is also important to note that the degree of heterogeneity in the meta-analysis was statistically significant across the studies assessing PANSS positive scores; therefore, these findings should be interpreted with caution. There is preliminary evidence to support the efficacy of combined training on psychiatric symptoms. Additional studies are clearly warranted to further investigate the effectiveness of combined training on improving psychiatric symptoms and health outcomes in schizophrenia.

Limitations

We aimed to evaluate the optimal exercise training program for improving health-related physical fitness and other health indicators in persons living with schizophrenia. However, we acknowledge certain limitations within this systematic review and meta-analysis. First, only 12 out of the 22 included studies were randomized controlled trials or quasi-experimental designs, with a large majority of the remaining articles being pilot or feasibility studies. Further, our findings reflected studies that included relatively small sample sizes, making it challenging to ensure the included sample population was an accurate representation of the clinical population of interest. While some studies reported specific levels of antipsychotic medications, the potential confounding influence of antipsychotic medications were not considered in this review. In addition, not all authors responded to requests made for further information or additional data.

Data from studies that did not implement a control group were not included within the meta-analysis. Therefore, comparisons between the intervention of interest and a control were analyzed. However, many of the control groups within the included studies participated in an alternative form of physical activity. As a result, it is difficult to determine whether the reported changes in health measures and psychiatric symptom scores are a result of the implemented exercise intervention. Due to the limited number of studies selected within this systematic review, there was minimal data available to interpret many of the outcomes. This created a challenge when independently conducting meta-analyses within each exercise modality. To support a greater number of outcomes, meta-analyses were conducted combining all exercise training modalities. Additionally, there were only two studies that included persons with treatment-resistant schizophrenia; however, because these studies did not include a control group, a meta-analysis could not be performed. Increasingly, control groups are not being employed owing to the overwhelming health benefits seen with exercise training in persons living with schizophrenia. In addition, due to the limited number of studies included within the meta-analysis, it was not feasible to conduct subgroup analyses for duration, frequency, and intensity within each exercise modality group (aerobic, resistance, and combined aerobic and resistance training). Therefore, subgroup analyses were only conducted for all exercise training modalities for PANSS positive, PANSS negative, and PANSS total. Finally, it should be noted that the degree of heterogeneity within this meta-analysis ranges from low to considerable, with the majority being low.

Future Directions

Future studies should carefully examine the risks and adherence rates between modalities of exercise training to outline evidence-based recommendations for exercise training interventions that consider patient interests (such as motivational and support strategies to maximize health benefits associated with exercise training). Moreover, while varying degrees of symptom severities were taken into consideration for this systematic review, further investigation is needed to determine which modality of exercise training is optimal for individuals who may experience severe ratings of psychiatric symptoms and/or may be treatment resistant. Finally, additional studies are warranted to clearly examine the ideal dosages (frequency, intensity, type, and time) of aerobic, resistance, and combined training to achieve optimal health benefits in persons living with schizophrenia. This research is important in the context of recent findings that demonstrate an exacerbation of symptoms following exercise training in individuals living with schizophrenia receiving certain antipsychotic treatment regimens (66).

CONCLUSION

Our findings suggest that different modalities of exercise may play an important role in reducing psychiatric symptoms and improving health-related physical fitness outcomes in persons living with schizophrenia. These findings are directly aligned with previous research that highlights the importance of incorporating exercise as an adjunct treatment to improve health and wellbeing in this population (30, 65). More studies are needed to determine which type of exercise has increased efficacy in reducing psychiatric symptoms and various health measures. There is growing evidence that 90 min of weekly moderate-to-vigorous intensity exercise aerobic or combined aerobic and resistance exercise can lead to a significant reduction

in symptoms in persons living with schizophrenia, with the potential for health benefits at relatively low volumes and intensities of exercise.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

SSDB, KLK, MIC, DJL, and DERW: conceptualization. SSDB, KLK, MIC, DJL, NW, DDK, and DERW: methodology, writing—review, and editing. SSDB, KLK, MIC, and DERW: formal analysis, investigation, and writing—original draft preparation. SSDB, KLK, MIC, NW, and DERW: data curation. SSDB and DERW: supervision, project administration, funding acquisition, and resources. All authors contributed to the article and approved the submitted version.

FUNDING

SSDB was supported by the Canadian Institutes of Health Research, MITACs and the Social Sciences and Humanities Research Council of Canada. DERW was funded by the Canadian Institutes of Health Research, MITACs, the Social Sciences and Humanities Research Council, the NIB Trust Fund, and the Natural Sciences and Engineering Research Council of Canada and supported by a CIHR New Investigator Award and a Michael Smith Foundation for Health Research Clinical Scholar Award. DJL has received operating funds from the Canadian Institutes for Health Research, the BC Mind Foundation, and the Provincial Health Services Authority of BC in conjunction with the B.C. Mental Health and Addictions Research Institute.

ACKNOWLEDGMENTS

We would like to acknowledge all of the trainees, staff, and faculty that assisted with this project. We would also like to acknowledge the patients living with schizophrenia that have helped inform our practice and research over the years.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.753117/full#supplementary-material

REFERENCES

1. Tandon R, Gaebel W, Barch DM, Bustillo J, Gur RE, Heckers S, et al. Definition and description of schizophrenia in the DSM-5. *Schizophr Res.* (2013) 150:3–10. doi: 10.1016/j.schres.2013.05.028
2. Harvey PD, Strassnig M. Predicting the severity of everyday functional disability in people with schizophrenia: cognitive deficits, functional capacity, symptoms, and health status. *World Psychiatry.* (2012) 11:73–9. doi: 10.1016/j.wpsyc.2012.05.004
3. Lavretsky, H. History of Schizophrenia As a Psychiatric disorder. In: Mueser KT, Jeste DV, editors. *Clinical Handbook of Schizophrenia*. New York, NY: The Guilford Press (2008). p. 3–13.
4. Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. *PLoS Med.* (2005) 2:e141. doi: 10.1371/journal.pmed.0020141
5. Laursen TM, Munk-Olsen T, Vestergaard M. Life expectancy and cardiovascular mortality in persons with schizophrenia. *Curr Opin Psychiatry.* (2012) 25:83–8. doi: 10.1097/YCO.0b013e32835035ca
6. Brown S, Inskip H, Barraclough B. Causes of the excess mortality of schizophrenia. *Br J Psychiatry.* (2000) 177:212–7. doi: 10.1192/bjp.177.3.212
7. Strassnig M, Brar JS, Ganguli R. Low cardiorespiratory fitness and physical functional capacity in obese patients with schizophrenia. *Schizophr Res.* (2011) 126:103–9. doi: 10.1016/j.schres.2010.10.025
8. Kim DD, Lang DJ, Procyshyn RM, Woodward ML, Kaufman K, White RF, et al. Reduced cardiovascular fitness associated with exposure to clozapine in individuals with chronic schizophrenia. *Psychiatry Res.* (2018) 262:28–33. doi: 10.1016/j.psychres.2018.01.029
9. Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Lobos CA, et al. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. *Schizophr Res.* (2010) 123:225–33. doi: 10.1016/j.schres.2010.07.012
10. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet.* (2009) 373:31–41. doi: 10.1016/S0140-6736(08)61764-X
11. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Eng J Med.* (2005) 353:1209–23. doi: 10.1056/NEJMoa051688
12. Nasrallah HA. Atypical antipsychotic-induced metabolic side effects: insights from receptor-binding profiles. *Mol Psychiatry.* (2008) 13:27–35. doi: 10.1038/sj.mp.4002066
13. Hennekens CH, Hennekens AR, Hollar D, Casey DE. Schizophrenia and increased risks of cardiovascular disease. *Am Heart J.* (2005) 150:1115–21. doi: 10.1016/j.ahj.2005.02.007
14. Vancampfort D, Knapen J, Probst M, van Winkel R, Deckx S, Maurissen K, et al. Considering a frame of reference for physical activity research related to the cardiometabolic risk profile in schizophrenia. *Psychiatry Res.* (2010) 177:271–9. doi: 10.1016/j.psychres.2010.03.011
15. Browne J, Penn DL, Battaglini CL, Ludwig K. Work out by walking: a pilot exercise program for individuals with schizophrenia spectrum disorders. *J Nerv Ment Dis.* (2016) 204:651–7. doi: 10.1097/NMD.0000000000000556
16. Ussher M, Stanbury L, Cheeseman V, Faulkner G. Physical activity preferences and perceived barriers to activity among persons with severe mental illness in the United Kingdom. *Psychiatr Serv.* (2007) 58:405–8. doi: 10.1176/ps.2007.58.3.405
17. Taylor CI, Tompsett C, Sanders R, Cobley S. The effectiveness of structured exercise programmes on psychological and physiological outcomes for patients with psychotic disorders: a systematic review and meta-analysis. *Int J Sport Exerc Psychol.* (2020) 18:336–61. doi: 10.1080/1612197X.2018.1519838
18. De Hert M, Schreurs V, Vancampfort D, Van Winkel R. Metabolic syndrome in people with schizophrenia: a review. *World psychiatry.* (2009) 8:15. doi: 10.1002/j.2051-5545.2009.tb00199.x
19. Vancampfort D, Rosenbaum S, Probst M, Soundy A, Mitchell AJ, De Hert M, et al. Promotion of cardiorespiratory fitness in schizophrenia: a

clinical overview and meta-analysis. *Acta Psychiatr Scand.* (2015) 132:131–43. doi: 10.1111/acps.12407
20. Scheewe T, Backx F, Takken T, Jörg F, Van Strater A, Kroes A, et al. Exercise therapy improves mental and physical health in schizophrenia: a randomised controlled trial. *Acta Psychiatr Scand.* (2013) 127:464–73. doi: 10.1111/acps.12029
21. Silva BA, Cassilhas RC, Attux C, Cordeiro Q, Gadelha AL, Telles BA, et al. A 20-week program of resistance or concurrent exercise improves symptoms of schizophrenia: results of a blind, randomized controlled trial. *Braz J Psychiatry.* (2015) 37:271–9. doi: 10.1590/1516-4446-2014-1595
22. Bredin SS, Warburton DE, Lang DJ. The health benefits and challenges of exercise training in persons living with schizophrenia: a pilot study. *Brain Sci.* (2013) 3:821–48. doi: 10.3390/brainsci3020821
23. Warburton DER, Bredin SSD. Health benefits of physical activity: a systematic review of current systematic reviews. *Curr Opin Cardiol.* (2017) 32:541–56. doi: 10.1097/HCO.0000000000000437
24. Heggelund J, Nilsberg GE, Hoff J, Morken G, Helgerud J. Effects of high aerobic intensity training in patients with schizophrenia - a controlled trial. *Nord J Psychiatry.* (2011) 65:269–75. doi: 10.3109/08039488.2011.560278
25. Heggelund J, Morken G, Helgerud J, Nilsberg GE, Hoff J. Therapeutic effects of maximal strength training on walking efficiency in patients with schizophrenia - a pilot study. *BMC Res Notes.* (2012) 5:344. doi: 10.1186/1756-0500-5-344
26. Marzolini S, Jensen B, Melville P. Feasibility and effects of a group-based resistance and aerobic exercise program for individuals with severe schizophrenia: a multidisciplinary approach. *Ment Health Phys Act.* (2009) 2:29–36. doi: 10.1016/j.mhpa.2008.11.001
27. Woodward ML, Gicas KM, Warburton DE, White RF, Rauscher A, Leonova O, et al. Hippocampal volume and vasculature before and after exercise in treatment-resistant schizophrenia. *Schizophr Res.* (2018) 202:158–65. doi: 10.1016/j.schres.2018.06.054
28. Acosta FJ, Bosch E, Sarmiento G, Juanes N, Caballero-Hidalgo A, Mayans T. Evaluation of noncompliance in schizophrenia patients using electronic monitoring (MEMS®) and its relationship to sociodemographic, clinical and psychopathological variables. *Schizophr Res.* (2009) 107:213–7. doi: 10.1016/j.schres.2008.09.007
29. Firth J, Carney R, Elliott R, French P, Parker S, McIntyre R, et al. Exercise as an intervention for first-episode psychosis: a feasibility study. *Early Interv Psychiatry.* (2018) 12:307–15. doi: 10.1111/eip.12329
30. Vancampfort D, Knapen J, Probst M, Scheewe T, Remans S, De Hert M, et al. systematic review of correlates of physical activity in patients with schizophrenia. *Acta Psychiatr Scand.* (2012) 125:352–62. doi: 10.1111/j.1600-0447.2011.01814.x
31. Birt J. Management of weight gain associated with antipsychotics. *Ann Clin Psychiatry.* (2003) 15:49–58. doi: 10.1023/A:1023280610379
32. Vancampfort D, Rosenbaum S, Schuch FB, Ward PB, Probst M, Stubbs B. Prevalence and predictors of treatment dropout from physical activity interventions in schizophrenia: a meta-analysis. *Gen Hosp Psychiatry.* (2016) 39:15–23. doi: 10.1016/j.genhosppsych.2015.11.008
33. Beebe LH, Tian L, Morris N, Goodwin A, Allen SS, Kuldau J. Effects of exercise on mental and physical health parameters of persons with schizophrenia. *Issues Ment Health Nurs.* (2005) 26:661–76. doi: 10.1080/01612840590959551
34. Curcic D, Stojmenovic T, Djukic-Dejanovic S, Dikic N, Vesic-Vukasinovic M, Radivojevic N, et al. Positive impact of prescribed physical activity on symptoms of schizophrenia: randomized clinical trial. *Psychiatr Danub.* (2017) 29:459–65. doi: 10.24869/psyd.2017.459
35. Dodd KJ, Duffy S, Stewart JA, Impey J, Taylor N. A small group aerobic exercise programme that reduces body weight is feasible in adults with severe chronic schizophrenia: a pilot study. *Disabil Rehabil.* (2011) 33:1222–9. doi: 10.3109/09638288.2010.526162
36. Kern RS, Reddy LF, Cohen AN, Young AS, Green MF. Effects of aerobic exercise on cardiorespiratory fitness and social functioning in veterans 40 to 65 years old with schizophrenia. *Psychiatry Res.* (2020) 291:113258. doi: 10.1016/j.psychres.2020.113258
37. Su C-Y, Wang P-W, Lin Y-J, Tang T-C, Liu M-F, Chen M-D. The effects of aerobic exercise on cognition in schizophrenia: a 3-month follow-up study. *Psychiatry Res.* (2016) 244:394–402. doi: 10.1016/j.psychres.2016.08.011
38. Maurus I, Mantel C, Keller-Varady K, Schmitt A, Lembeck M, Roh A, et al. Resistance training in patients with schizophrenia: concept and proof of principle trial. *J Psychiatr Res.* (2020) 120:72–82. doi: 10.1016/j.jpsychires.2019.09.015
39. Svatkova A, Mandl RC, Scheewe TW, Cahn W, Kahn RS, Hulshoff Pol HE. Physical exercise keeps the brain connected: biking increases white matter integrity in patients with schizophrenia and healthy controls. *Schizophr Bull.* (2015) 41:869–78. doi: 10.1093/schbul/sbv033
40. Korman NH, Shah S, Suetani S, Kendall K, Rosenbaum S, Dark F, et al. Evaluating the feasibility of a pilot exercise intervention implemented within a residential rehabilitation unit for people with severe mental illness: GO HEART: (group occupational health exercise and rehabilitation treatment). *Front Psychiatry.* (2018) 9:343. doi: 10.3389/fpsyt.2018.00343
41. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Commun Health.* (1998) 52:377–84. doi: 10.1136/jech.52.6.377
42. Senormanci G, Korkmaz N, Senormanci O, Ugur S, Topsac M, Gultekin O. Effects of exercise on resilience, insight and functionality in patients with chronic schizophrenia in a psychiatric nursing home setting: a randomized controlled trial. *Issues Ment Health Nurs.* (2020) 42:690–8. doi: 10.1080/01612840.2020.1847221
43. Acil A, Dogan S, Dogan O. The effects of physical exercises to mental state and quality of life in patients with schizophrenia. *J Psychiatr Ment Health Nurs.* (2008) 15:808–15. doi: 10.1111/j.1365-2850.2008.01317.x
44. Loh SY, Abdullah A, Abu Bakar AK, Thambu M, Nik Jaafar NR. Structured walking and chronic institutionalized schizophrenia inmates: a pilot RCT study on quality of life. *Glob J Health Sci.* (2016) 8:238–48. doi: 10.5539/gjhs.v8n1p238
45. Malchow B, Keller K, Hasan A, Dörfler S, Schneider-Axmann T, Hillmer-Vogel U, et al. Effects of endurance training combined with cognitive remediation on everyday functioning, symptoms, and cognition in multiepisode schizophrenia patients. *Schizophr Bull.* (2015) 41:847–58. doi: 10.1093/schbul/sbv020
46. Pajonk FG, Wobrock T, Gruber O, Scherk H, Berner D, Kaizl I, et al. Hippocampal plasticity in response to exercise in schizophrenia. *Arch Gen Psychiatry.* (2010) 67:133–43. doi: 10.1001/archgenpsychiatry.2009.193
47. Ryu J, Jung JH, Kim J, Kim CH, Lee HB, Kim DH, et al. Outdoor cycling improves clinical symptoms, cognition and objectively measured physical activity in patients with schizophrenia: a randomized controlled trial. *J Psychiatr Res.* (2020) 120:144–53. doi: 10.1016/j.jpsychires.2019.10.015
48. Shimada T, Ito S, Makabe A, Yamanushi A, Takenaka A, Kobayashi M. Aerobic exercise and cognitive functioning in schizophrenia: a pilot randomized controlled trial. *Psychiatry Res.* (2019) 282:112638. doi: 10.1016/j.psychres.2019.112638
49. Kimhy D, Vakhrusheva J, Bartels MN, Armstrong HF, Ballon JS, Khan S, et al. The impact of aerobic exercise on brain-derived neurotrophic factor and neurocognition in individuals with schizophrenia: a single-blind, randomized clinical trial. *Schizophr Bull.* (2015) 41:859–68. doi: 10.1093/schbul/sbv022
50. Soundy A, Muhamed A, Stubbs B, Probst M, Vancampfort D. The benefits of walking for individuals with schizophrenia spectrum disorders: a systematic review. *Int J Ther Rehabil.* (2014) 21:410–20. doi: 10.12968/ijtr.2014.21.9.410
51. Kim M, Jeon J. The effect of exercise on physical and mental health for adults with schizophrenia: a review of clinical aerobic exercise. *Ethiop J Health Dev.* (2020) 34:35–43.
52. Warburton DER, Bredin SSD. Health benefits of physical activity: a strengths-based approach. *J Clin Med.* (2019) 8:2044. doi: 10.3390/jcm8122044
53. Warburton DE, Bredin SS. Reflections on physical activity and health: what should we recommend? *Can J Cardiol.* (2016) 32:495–504. doi: 10.1016/j.cjca.2016.01.024
54. Sabe M, Kaiser S, Sentissi O. Physical exercise for negative symptoms of schizophrenia: Systematic review of randomized controlled trials and meta-analysis. *Gen Hosp Psychiatry.* (2020) 62:13–20. doi: 10.1016/j.genhosppsych.2019.11.002
55. Pelham TW, Campagna PD, Ritvo PG, Birnie WA. The effects of exercise therapy on clients in a psychiatric rehabilitation program. *Psychosoc Rehabilitation J.* (1993) 16:75. doi: 10.1037/h0095650

56. Warburton DE, Gledhill N, Quinney A. The effects of changes in musculoskeletal fitness on health. *Can J Appl Physiol.* (2001) 26:161–216. doi: 10.1139/h01-012
57. Warburton DE, Gledhill N, Quinney A. Musculoskeletal fitness and health. *Can J Appl Physiol.* (2001) 26:217–37. doi: 10.1139/h01-013
58. Warburton DER, Whitney Nicol C, Bredin SSD. Health benefits of physical activity: the evidence. *CMAJ.* (2006) 174:801–9. doi: 10.1503/cmaj.051351
59. Strassnig MT, Signorile JF, Potiaumpai M, Romero MA, Gonzalez C, Czaja S, et al. High velocity circuit resistance training improves cognition, psychiatric symptoms and neuromuscular performance in overweight outpatients with severe mental illness. *Psychiatry Res.* (2015) 229:295–301. doi: 10.1016/j.psychres.2015.07.007
60. Price KJ, Gordon BA, Bird SR, Benson AC. A review of guidelines for cardiac rehabilitation exercise programmes: is there an international consensus? *Eur J Prev Cardiol.* (2016) 23:1715–33. doi: 10.1177/2047487316657669
61. Stone JA, Campbell NR, Genest J, Harris S, Pipe A, Warburton DER. Health behaviour interventions and cardiovascular disease risk factor modifications. In: Stone JA, editor. *Canadian Guidelines for Cardiac Rehabilitation and Cardiovascular Disease Prevention*. 3rd ed. Winnipeg, MB: Canadian Association of Cardiac Rehabilitation (2009). p. 251–340.
62. Schwaab B, Bjarnason-Wehrens B, Meng K, Albus C, Salzwedel A, Schmid JP, et al. Cardiac rehabilitation in german speaking countries of Europe-evidence-based guidelines from Germany, Austria and Switzerland LLKardReha-DACH-Part 2. *J Clin Med.* (2021) 10:2192. doi: 10.3390/jcm10102192
63. Ho SS, Dhaliwal SS, Hills AP, Pal S. The effect of 12 weeks of aerobic, resistance or combination exercise training on cardiovascular risk factors in the overweight and obese in a randomized trial. *BMC Public Health.* (2012) 12:1–10. doi: 10.1186/1471-2458-12-704
64. Martin H, Beard S, Clissold N, Andraos K, Currey L. Combined aerobic and resistance exercise interventions for individuals with schizophrenia: a systematic review. *Ment Health Phys Act.* (2017) 12:147–55. doi: 10.1016/j.mhpa.2017.04.003
65. Firth J, Cotter J, Elliott R, French P, Yung AR. A systematic review and meta-analysis of exercise interventions in schizophrenia patients. *Psychol Med.* (2015) 45:1343–61. doi: 10.1017/S0033291714003110
66. Kim DD, Lang DJ, Warburton DER, Barr AM, White RF, Honer WG, et al. Exercise and worsening of extrapyramidal symptoms during treatment with long-acting injectable antipsychotics. *Pharmacy.* (2021) 9:123. doi: 10.3390/pharmacy9030123

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Cardiovascular Medicine

REVIEW
published: 21 February 2022
doi: 10.3389/fcvm.2022.753652

A Contemporary Review of the Effects of Exercise Training on Cardiac Structure and Function and Cardiovascular Risk Profile: Insights From Imaging

*Waleed Alhumaid[1], Stephanie D. Small[2], Amy A. Kirkham[2], Harald Becher[1], Edith Pituskin[3], Carla M. Prado[4], Richard B. Thompson[5], Mark J. Haykowsky[3] and D. Ian Paterson[1]**

[1] Division of Cardiology, Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, AB, Canada, [2] Faculty of Kinesiology, University of Toronto, Toronto, ON, Canada, [3] Faculty of Nursing, College of Health Sciences, University of Alberta, Edmonton, AB, Canada, [4] Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, AB, Canada, [5] Department of Biomedical Engineering, University of Alberta, Edmonton, AB, Canada

Exercise is a commonly prescribed therapy for patients with established cardiovascular disease or those at high risk for *de novo* disease. Exercise-based, multidisciplinary programs have been associated with improved clinical outcomes post myocardial infarction and is now recommended for patients with cancer at elevated risk for cardiovascular complications. Imaging studies have documented numerous beneficial effects of exercise on cardiac structure and function, vascular function and more recently on the cardiovascular risk profile. In this contemporary review, we will discuss the effects of exercise training on imaging-derived cardiovascular outcomes. For cardiac imaging *via* echocardiography or magnetic resonance, we will review the effects of exercise on left ventricular function and remodeling in patients with established or at risk for cardiac disease (myocardial infarction, heart failure, cancer survivors), and the potential utility of exercise stress to assess cardiac reserve. Exercise training also has salient effects on vascular function and health including the attenuation of age-associated arterial stiffness and thickening as assessed by Doppler ultrasound. Finally, we will review recent data on the relationship between exercise training and regional adipose tissue deposition, an emerging marker of cardiovascular risk. Imaging provides comprehensive and accurate quantification of cardiac, vascular and cardiometabolic health, and may allow refinement of risk stratification in select patient populations. Future studies are needed to evaluate the clinical utility of novel imaging metrics following exercise training.

Keywords: cardiovascular disease, exercise training, imaging, left ventricular function, vascular function, body composition

OPEN ACCESS

Edited by:
Jian Yang,
Fudan University, China

Reviewed by:
Owais Bhat,
Virginia Commonwealth University, United States
Sebastian Kelle,
Deutsches Herzzentrum Berlin, Germany

***Correspondence:**
D. Ian Paterson
ip3@ualberta.ca

Specialty section:
This article was submitted to General Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

Received: *05 August 2021*
Accepted: *17 January 2022*
Published: *21 February 2022*

Citation:
Alhumaid W, Small SD, Kirkham AA, Becher H, Pituskin E, Prado CM, Thompson RB, Haykowsky MJ and Paterson DI (2022) A Contemporary Review of the Effects of Exercise Training on Cardiac Structure and Function and Cardiovascular Risk Profile: Insights From Imaging. Front. Cardiovasc. Med. 9:753652. doi: 10.3389/fcvm.2022.753652

INTRODUCTION

Regular physical exercise provides many benefits to the cardiovascular system and overall health at all stages of life. As such, aerobic exercise (e.g., walking, cycling) and more recently resistance exercise (e.g., weightlifting), have been an integral component of clinical guidelines, and the cornerstone of cardiac rehabilitation for patients with or at risk for cardiovascular disease including coronary artery disease (CAD), heart failure, and cancer (1–4).

The most common form of exercise for primary and secondary prevention of cardiovascular disease is aerobic training, which improves oxygen delivery (i.e. cardiac output) during physical effort, and resistance training, which increases skeletal muscle mass and strength. Patients with established cardiovascular disease are commonly referred to cardiac rehabilitation, which typically involves a 6–24-week program of supervised, moderate-intensity (50–75% of maximal heart rate or 40–60% of heart rate reserve) continuous aerobic exercise, supplemental resistance training and other health interventions. High-intensity interval training (brief periods of 85–100% maximal heart rate or 80–90% heart rate reserve alternated with rest or low intensity) is a time efficient aerobic exercise alternative for lower risk patients and appears to offer similar health benefits (5). Exercise training interventions have been shown to exert direct and indirect beneficial effects on the cardiovascular risk profile. Aerobic and resistance training prevent or reduce insulin resistance and diabetes mellitus type II (6), and have favorable effects on blood pressure, lipid profile, vascular inflammation, body composition, and overall cardiac function in patients with established cardiac disease as well as healthy individuals (7–9). Dietary counseling for optimal nutritional study also plays an integral role in most rehabilitation programs and targeted nutrition interventions can improve body composition, metabolic and cardiovascular health (10).

Imaging provides a valuable modality to quantify the effects of exercise training and multimodal rehabilitation as it enables an evaluation of the physiological and morphological adaptations of the heart and vasculature. Imaging is frequently used to characterize the impact of exercise training interventions on cardiac function and remodeling, two prognostic measures that help to guide the therapeutic management of patients with cardiac disease. Echocardiography and magnetic resonance imaging (MRI) are the primary imaging modalities used to evaluate the cardiovascular effects of exercise based on their accuracy, versatility, and safety profile for repeat testing. In assessing the heart, these modalities are principally used to provide information on ventricular size, mass, and function as well as hemodynamic and flow quantification. Cardiac MRI also allows the evaluation of myocardial tissue characterization, including macro- and microscopic fibrosis using quantitative mapping sequences and contrast enhanced imaging (**Figure 1**). In assessing the vasculature, these modalities are primarily used to evaluate vascular function, stiffness, and structure. These imaging modalities are increasingly applied in real time to evaluate dynamic changes in cardiovascular function during exercise to unmask occult dysfunction that may not be identified at rest (11, 12). Furthermore, our group has also used MRI to evaluate relevant extra-cardiac sequelae of cardiac disease such as lung water content in patients with potential heart failure, regional adipose tissue deposition as a metric of cardiovascular risk, and skeletal muscle volume and function impairments (13–15).

In this review article, we will review the potential benefits of exercise on left ventricular (LV) function and remodeling, vascular function and structure, and body composition in adult patients with or at risk for cardiovascular disease and discuss the application and utility of imaging to characterize these changes.

Exercise Training Effects on Cardiac Structure and Function in Healthy Individuals

Before examining the role of exercise training in patients with cardiovascular disease, it is important to understand its effects in healthy individuals. Public health recommendations for the general population are to include 150 min per week of moderate-intensity aerobic exercise or 75 min if the intensity is classified as vigorous (16). Sustained (e.g., several hours) endurance exercise has been linked to increased circulating biomarkers of myocardial stress including cardiac troponin T and N-terminal-pro-B-type natriuretic peptide (NT-pro-BNP) (17). However, it has been postulated that BNP and NT-pro-BNP elevation in this setting may have cytoprotective and growth regulatory effects and thus be indicative of physiological stress rather myocardial damage (17).

Soluble suppression of tumorigenicity 2 (sST2) is an emerging prognostic biomarker that has been associated with myocardial fibrosis, inflammation, and function and is an independent predictor of long-term mortality (18). High-intensity and duration exercise such as a marathon race has been linked to increased levels of sST2 (19). This association might explain the increased incidence of myocardial scar on cardiac MRI late gadolinium enhancement imaging among athletes who practice intense endurance training compared to the general population (20). Although, the clinical significance of this finding in athletes is unclear and further studies are needed. Cardiac imaging, in particular echocardiography and MRI, have a vital role in examining geometric changes that may occur in athlete's hearts. Aerobic exercise training has been associated with LV dilation and hypertrophy, right ventricular and/or biatrial dilatation (21, 22). Therefore, to differentiate between exercise-induced physiological cardiac remodeling and cardiomyopathy, a recent meta-analysis of 27 studies defined normal reference values of biventricular size and function estimated by cardiac MRI in competitive athletes. Compared to the general population, competitive athletes generally have higher resting biventricular end-diastolic and end-systolic volumes, and stroke volume (22, 23). However, an important caveat is that most patients with cardiovascular disease will not complete the volume of aerobic exercise necessary to induce physiological remodeling.

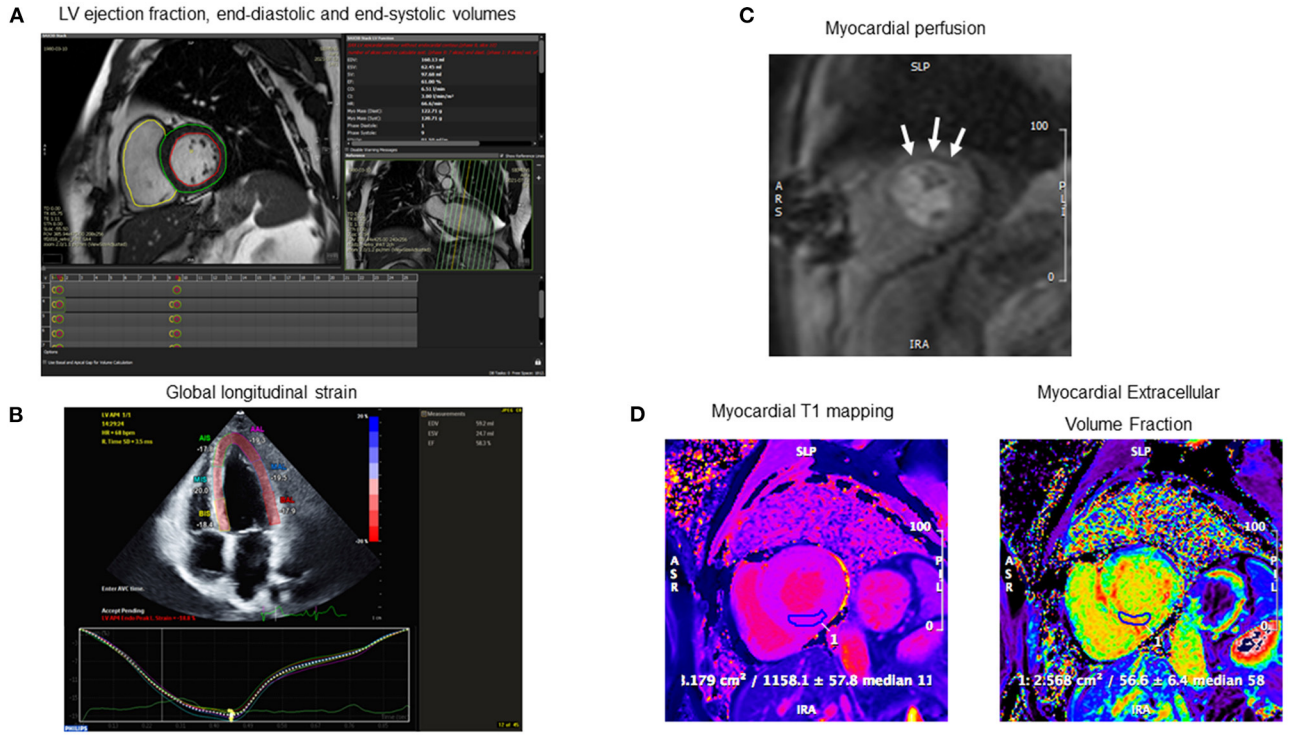


FIGURE 1 | Examples of cardiac imaging metrics to assess the effects of exercise training in patients with or at risk for cardiovascular disease. **(A)** Left ventricular volumetric analysis of short-axis steady state free precession (SSFP) images acquired from cardiac MRI. **(B)** Global longitudinal strain acquired transthoracic echocardiogram. **(C)** Myocardial perfusion acquired from first-pass gadolinium enhanced imaging on vasodilator stress cardiac MRI. Note anterolateral perfusion defect (white arrows). **(D)** Myocardial tissue characterization on cardiac MRI with native T1 mapping (left) and extracellular volume fraction (ECV) (right). Note the elevated myocardial T1 (1,158 ms) and ECV (57%) consistent with cardiac amyloidosis.

Influence of Sex and Age on the Effects of Exercise Training on Cardiac Function

Sex

Ventricular volumes and mass are lower in females compared to males however cardiac function is comparable between sexes (23). Compared to men, women of comparable training status and age, typically have 5–15% lower peak VO2 after adjustment for body weight and lean body mass (24). A primary determinant of lower peak VO2 among women is lower peak exercise cardiac output relative to men (25). Given that women demonstrate a similar heart rate during exercise as men (26, 27), lower stroke volume is the primary contributor to the attenuated cardiac output response during exercise (28, 29). Additionally, sex differences exist for myocardial remodeling after injury and cardiovascular overload (e.g., training responses) (30). A recent meta-analysis of 26 studies ($n = 468$ healthy individuals) found similar LV hypertrophy adaptations to endurance training among men and women, but that LV end-diastolic, end-systolic and stroke volumes increased more in men (31). In addition, women appear to experience greater improvements in arteriovenous oxygen difference with endurance training compared to men (32–34). The sex differences literature on exercise training responses is primarily limited to healthy adults, as the studies of patients with heart failure have been predominantly performed in men (35). Several research gaps also exist regarding potential sex differences in the vascular adaptations to endurance training (36).

Estrogen levels have been shown to play an important role in attenuation of pathologic pressure-overload LV hypertrophy but may not affect exercise-related physiological hypertrophy in rodents (37, 38). Therefore, while menopausal status may be a determinant of pathological hypertrophy between the sexes, other factors may explain differences in cardiac adaptations to exercise training (30, 39). In younger, premenopausal women, the adaptations to endurance training are more likely related to peripheral determinants as opposed to LV adaptations, as seen in men (27, 36, 40, 41). Older, post-menopausal women experience similar peripheral adaptations to endurance training but appear to have a smaller increase in peak VO2 and blood volume compared to premenopausal women (32). Spina et al. demonstrated that among older (60–70 years) women, 9–12 months of endurance training increased peak VO_2 and arteriovenous oxygen difference, but LV end-diastolic and stroke volumes did not change (40). Nio et al. compared training responses to 12 weeks of endurance training among pre- vs. post-menopausal women and found that post-menopausal women experienced a smaller increase in peak VO_2 and blood volume, but no differences in cardiac output, heart rate, or LV volumes compared to premenopausal women (32).

Age

Ventricular volumes decrease with age but systolic function is unchanged with aging (23). Cardiovascular function among older adults tends to be impaired relative to younger adults owing to a number of age-related changes including worsening cardiac mechanics, decreased responsiveness to ß-adrenergic stimulation and increased vascular and aortic stiffness (36, 42–45). Among healthy, sedentary adults, there is a rate of decline in peak VO_2 of an average of 5–10% per decade due to both structural and functional changes in central and peripheral determinants (27, 36, 40, 46). However, endurance training can attenuate the rate of age-related decline in peak VO_2. While endurance training increases peak VO_2 in older men and women, the magnitude of adaptation is less in older women relative younger controls (32, 47). The attenuated training adaptations appear to be related to lower improvements to cardiac output, stroke volume, and LV function among older vs. younger adults (27, 46). Older women experience similar improvements to peak VO_2 in response to endurance training as older men, but there appears to be a sex difference in the responsible mechanisms. Prospective studies have demonstrated that older men are more likely to experience central adaptations such as improvements in cardiac output, stroke volume, and LV systolic function after 9–12 months of endurance training (48, 49). Conversely, older women are more likely to experience peripheral adaptations such as increased arteriovenous oxygen difference with minimal concurrent improvements in stroke volume (32, 33, 40, 49). Regular aerobic exercise appears to attenuate the age-related aortic stiffening among healthy men and women (36, 46) (**Table 1**).

EXERCISE TRAINING EFFECTS ON CARDIAC STRUCTURE AND FUNCTION IN PATIENTS WITH ESTABLISHED CARDIOVASCULAR DISEASE

Cardiac Remodeling in Cardiovascular Disease States: Clinical Significance

Left ventricular remodeling after myocardial injury is defined as a structural adaptation in chamber size and shape, arising from complex biochemical and cellular changes. This deleterious cascade leads to varying degrees of LV dilatation, hypertrophy and extra-cellular collagen deposition, manifesting clinically as myocardial stiffness, and/or LV dysfunction (75). The extent of remodeling is often used as a surrogate for cardiac disease progression and is an emerging therapeutic target in heart failure. Therapeutic interventions, including cardiac rehabilitation, have been used to attenuate cardiac remodeling, typically defined as a $\geq$10% increase in LV end-diastolic or end-systolic volume in the post-myocardial infarction (MI) or heart failure setting (76). Cardiac imaging routinely provides data on remodeling-specific markers, such as LV volumes and ejection fraction (EF), which elucidate prognosis and guide the potential need for further intervention (76).

Studies of structured, exercise-based cardiac rehabilitation for patients with heart failure or post-MI have been associated with improved cardiac function and attenuation of ventricular remodeling in addition to a reduction in cardiovascular mortality (77, 78). Thus, these programs have been implemented as a class I recommendation in contemporary guidelines for patients with cardiac diseases (1–4). Cardiac imaging is commonly used to evaluate the effects of exercise training on LV size and function in conjunction with other therapeutic interventions such as pharmacotherapy, coronary revascularization and cardiac resynchronization.

Exercise Training Effects in Patients With Coronary Artery Disease

Echocardiography has been the predominant modality used to study the effects of exercise training on cardiac remodeling in patients with CAD. Pooled analyses of clinical trial data suggest that the timing and duration of the exercise intervention is important. For example, these studies have shown that the attenuation of cardiac remodeling occurs when exercise is initiated early, within 1 week of hospitalization in clinically stable, post-MI patients and is continued for at least 6 months (50, 51). These salient effects on LV remodeling post-MI have been described in patients with preserved LV function (52) as well as moderate systolic dysfunction (53). Randomized controlled trials of exercise training have demonstrated improvements in LVEF ranging from 5 to 15% (51, 54, 55). There is also preliminary evidence to suggest that exercise may improve diastolic function. A randomized controlled trial evaluating the effects of exercise on diastolic function post MI found that E wave and E/A ratio by Doppler echocardiography increased by 0.2 in the exercise group, suggesting enhanced LV filling and reduced LV wall stress (53).

Exercise training and cardiac rehabilitation are effective strategies for limiting morbidity and mortality inpatients with coronary artery disease (77, 78). The mechanisms underlying this reduction in mortality are likely multifactorial but include reductions in cardiovascular risk factors as well as improved myocardial perfusion, which can be attributed to increased coronary artery collateralization and vasorelaxation as well as reduced vascular oxidative stress (79, 80). Improved coronary artery collateralization secondary to exercise training has been demonstrate using Thallium scintigraphy and gated SPECT with technetium-99 m sestamibi (56–58, 81). Coronary autoregulation is influenced by the interplay between nitric oxide production by the endothelium and inactivation by reactive oxygen species. In patients with CAD, coronary vasomotor tone is disturbed due to an imbalance in nitric oxide metabolism, however, exercise training restores nitric oxide availability and is largely responsible for the improvement in myocardial perfusion (81).

In summary, imaging studies demonstrate that exercise training has favorable effects on LV remodeling, systolic and diastolic function as well as myocardial perfusion in patients with CAD (**Table 1**).

Exercise Training Effects in Patients With Heart Failure

In patients with heart failure and reduced ejection fraction (HFrEF) (LVEF $<$ 40%), exercise training has been shown to

TABLE 1 | Characteristics of the imaging studies reporting on the cardiac effects of exercise training.

References	Study design (sample size)	Study population (age, % male)	Imaging type	Aerobic exercise prescription	Resistance exercise prescription	Exercise program duration	Relevant results
Healthy adults							
Diaz-Canestro and Montero (31)	Meta-analysis of RCTs and non-RCTs ($n = 468$)	Healthy adults (age range 22–72, 61% male)	Predominantly echocardiography or MRI	F: 3–6 days/week I: 50–85% HRR/60–95% HR_{max}/60–100% VO_{2max} T: 20–180 min	None	3–12 months	Relative to men: ↓ LVEDV, LVESV, & SV ↔ LV mass
Nio et al. (32)	Single-arm prospective study ($n = 25$)	Healthy women (age range 45–58) 11 pre-menopausal & 14 post-menopausal	Echocardiography	F: 3 days/week I: HIIT: 90–95% HR_{max} × 4 intervals of 4 + 3 min recovery	None	12 weeks	Relative to post-menopausal: ↑ VO_{2peak} ↔ LVEF & LV volume
Stratton et al. (46)	Single-arm prospective study	Healthy men 11 young (age range 24–32) 13 older (age range 60–82)	Radionuclide ventriculography	F: 4–5 days/week I: increasing to 80–85% HR_{max} by 4th month T: 45 min	None	6 months	Relative to older men: ↔ VO_{2peak}, LVEDV & LVEF
Spina et al. (34)	Single-arm prospective study	15 healthy men (mean age 63) 16 healthy women (mean age 64)	Acetylene rebreather and Echocardiography	F: 5 days/week I: 60–70% to 75–85% HR_{max} T: 45 min	None	9–12 months	Relative to men: ↔ VO_{2peak} ↓ exercise SV ↑ exercise arteriovenous O2 difference
Coronary artery disease							
Haykowsky et al. (50)	Meta-regression of RCTs ($n = 647$)	Post-MI (mean age 55, "pre-dominantly" male)	Echocardiography, MRI or radionuclide ventriculography	F: 3–7 days/week I: ∼60–85% VO_{2peak}/80% HR_{max} T: 30–180 min	NR	1-6 weeks	Relative to control: ↑ LVEF ↓ LVEDV & LVESV with earlier initiation post-MI and increased program duration
Zhang et al. (51)	Meta-analysis of RCTs ($n = 1,137$)	Post-MI (mean age 58, 93% male)	Echocardiography, MRI or radionuclide ventriculography	F: 3–5 days/week I: 60–85% HRR/70–90% HR_{peak}/55–85% VO_{2peak} T: 20–60 min	None	NR	Relative to control: ↑ VO_{2peak} & LVEF ↓ LVD when initiated <29 days post-MI
McGregor et al. (52)	Longitudinal, controlled trial ($n = 56$)	Post-MI with preserved LVEF (mean age 56 ± 10, 100% male)	Echocardiography	F: 2 days/week I: 60–80% VO_{2peak} T: 40 min	F: 2 days/week I: based on RPE T: 1 set × 12 reps; 25–40 min	10 weeks	Relative to control: ↑ VO_{2peak} ↓ LVEDV & LVESV
Gaillauria et al. (53)	RCT ($n = 61$)	Post-MI with reduced LVEF (mean age 55 ± 3, 72% male)	Echocardiography	F: 3 days/week I: 60-70% VO_{2peak} T: 40 min	NR	6 months	Relative to control: ↑ VO_{2peak} & LVEF ↓ LVEDV & LVESV
Gaillauria et al. (54)	RCT ($n = 46$)	Post-acute ST elevation MI (mean age 54 ± 8, 87% male)	Echocardiography	F: 3 days/week I: 60–70% VO_{2peak} T: 30 min	NR	6 months	Relative to control: ↑ VO_{2peak} ↑ LVEF

(Continued)

TABLE 1 | Continued

References	Study design (sample size)	Study population (age, % male)	Imaging type	Aerobic exercise prescription	Resistance exercise prescription	Exercise program duration	Relevant results
Haddadzadeh et al. (55)	RCT ($n = 42$)	Post-coronary event (mean age 62 ± 9, 77% male)	Echocardiography	F: 3–5 days/week Center-based group I: 40–70% HRR T: 20–40 min Home-based group I: 40–70% HRR T: 20–40 min	None	12 weeks	Center and home-based groups relative to control: ↑ LVEF Center-based group relative to home-based group: ↔ LVEF
Belardinelli et al. (56)	RCT ($n = 46$)	CAD & reduced LVEF (mean age 57 ± 9, 91% male)	Dobutamine stress echocardiography followed by thallium myocardial scintigraphy	F: 3 days/week I: 60% VO_{2peak} T: 40 min	None	8 weeks	Relative to control: ↑ VO_{2peak} & contractile response to dobutamine and thallium activity
Belardinelli et al. (57)	RCT ($n = 30$)	CAD & reduced LVEF (mean age 55 ± 9, 100% male)	Dobutamine stress echocardiography followed by thallium myocardial scintigraphy	Dipyridamole (75 mg/day) given with exercise F: 3 days/week I: 60% VO_{2peak} T: 30 min	None	8 weeks	Relative to control: ↑ VO_{2peak}, coronary collateral score, thallium activity, LVEF, & WTSI
Gaillauria et al. (58)	RCT ($n = 50$)	Post-acute ST elevation MI (mean age 53 ± 9, 92% male)	Gated single-photon emission computed tomography imaging	F: 3 days/week I: 60–70% VO_{2peak} T: 40 min	None	6 months	Relative to control: ↑ VO_{2peak} ↓ resting & stress WMSI, resting & stress WTSI
Heart failure							
Chen et al. (59)	Meta-analysis of RCTs ($n = 813$)	Heart failure with reduced EF (age range 54–74, "pre-dominantly male")	Echocardiography or MRI	F: 2–5 days/week I: 60–80% VO_{2peak} T: 20–60 min	Too few studies for comparison	Most 3–6 months, range 2–14 months	Relative to control: ↑ LVEF ↓ LVEDV & LVESV with greater effect for ≥ 6 months training
Erbs et al. (60)	Retrospective analysis of RCT ($n = 73$)	Chronic heart failure as a result of dilative cardiomyopathy or ischemic heart disease (mean age 53 ± 3)	Echocardiography	F: 7 days/week I: 70% VO_{2peak} T: 20 min	F: 1 time/week I: Group training (walking, calisthenics, & non-competitive ball games) T: 60 min	6 months	Relative to control: ↑ VO_{2peak} ↓ LVEDD
Erbs et al. (61)	RCT ($n = 37$)	Chronic heart failure as a result of dilative cardiomyopathy or ischemic heart disease (mean age 61 ± 11, 100% male)	Echocardiography	F: 7 days/week I: 60% VO_{2peak} T: 20–30 min	F: 1 days/week I: Group training (walking, calisthenics, & non-competitive ball games) T: 60 min	12 weeks	Relative to control: ↑ VO_{2max} & LVEF ↓ LVEDV, LVESV, LVEDD, & LVESD

(Continued)

TABLE 1 | Continued

References	Study design (sample size)	Study population (age, % male)	Imaging type	Aerobic exercise prescription	Resistance exercise prescription	Exercise program duration	Relevant results
Tucker et al. (62)	Meta-analysis of RCTs (n = 1,078)	Heart failure with reduced EF (mean age 63, 77% male)	Echocardiography or MRI	F: 3–5 days/week HIIT group: I & T: 85–95% HR_{peak}/VO_{2peak} 3–6 min intervals + 2–3 min recovery (25–47 min total) MIT group: I & T: 40–70% HRR/77–90% HR_{max}/60–80% VO_{2peak} for 20–45 min	Too few studies for comparison	Most 3-6 months, range 1 month to 10 years	Relative to control: ↑ LVEF & VO_{2peak} with greater effect for ≥ 6 months training No difference in change in LVEF between HIIT & MIT groups ↔ LVEDV & LVESV
Pearson et al. (63)	Meta-analysis of RCTs and non-RCTs (n = 470)	Heart failure (any type) (age range 49–77, "pre-dominantly male")	Echocardiography	F: 2–7 days/week I: 40–80% HRR/45–70%HR_{max}/60–80% VO_{2peak} T: 20–60 min	F: 2–3 days/week I: 50–80% 1RM T: 2–3 sets × 8–10 reps	1–7 months	Relative to control: ↓ LV E/e'
Hambrecht et al. (64)	RCT (n = 73)	Heart failure with reduced EF (mean age 54 ± 9)	Echocardiography	F: 7 days/week I: 70% VO_{2peak} T: 20 min	F: 1 time/week I: Group training (walking, calisthenics, and non-competitive ball games) T: 60 min	6 months	Relative to control: ↑ LVEF ↓ LVEDD
Kitzman et al. (65)	RCT (n = 63)	Heart failure with preserved EF (mean age 70 ± 7, 24% male)	Echocardiography	F: 3 days/week I: 40–70% HRR T: 60 min	None	16 weeks	Relative to control: ↑ VO_{2peak} ↔ LVEDV, LVESV, LVEF, & LV E/A ratio
Haykowsky et al. (35)	RCT (n = 40)	Heart failure with preserved EF (mean age 69 ± 6, 12% male)	Echocardiography	F: 3 days/week I: 40–70% HRR T: 60 min	None	16 weeks	Relative to control: ↑ VO_{2peak} ↔ LVEDV
Mueller et al. (66)	RCT (n = 176)	Heart failure with preserved EF (age 70 ± 8, 33% males)	Echocardiography	HIIT group F: 3 days/week I: 4 × 4-min intervals @ 80–90% HRR T: 38 min MIT group F: 5 days/week I: 35–50% HRR T: 40 min	None	12 weeks	HIIT & MIT relative to control: ↑ VO_{2peak} ↔ LV E/e'
Fukuta et al. (67)	Meta-analysis of RCTs (n = 436)	Heart failure with preserved EF (mean age 66, 37% male)	Echocardiography or Doppler ultrasound	F: 2–3 days/week I: 70% HRR/60–75% HR_{max}/60–80% VO_{2peak} T: 20–60 min	None	3–6 months	Relative to control: ↑ VO_{2peak}, ↔ LVEF, E wave, & E/e'

(Continued)

TABLE 1 | Continued

References	Study design (sample size)	Study population (age, % male)	Imaging type	Aerobic exercise prescription	Resistance exercise prescription	Exercise program duration	Relevant results
Patients at risk for cardiovascular disease							
Leggio et al. (68)	Single-arm prospective study ($n = 116$)	Hypertensive (mean age 51 ± 8, 49% male)	Echocardiography	F: 3 days/week I: 70–85% VO_{2peak} T: 45 min	None	8 weeks	Relative to baseline: ↑ LV S' ↓ LV E/e' ↔ LVEF, LV mass
Molmen-Hansen et al. (69)	RCT ($n = 88$)	Hypertensive (mean age 52 ± 8, 56% male)	Echocardiography	F: 3 days/week HIIT group: I & T: 4 × 4-min @85–90% VO_{2max} T: 38 min MIT group: I: 70% VO_{2max} T: 47 min	None	12 weeks	HIIT and MIT relative to control: ↑ VO_{2max} HIIT relative to MIT: ↑ LVEF, LV e' & S' ↔ LV E & A wave, LV wall thickness
Sahin et al. (70)	RCT ($n = 30$)	Hypertensive (mean age 56 ± 9, 38% male)	Echocardiography	F: 3 days/week I: alternating 1-min low & high load T: 20 min	F: 3 days/week I: 75% 1-RM T: 6 exercises (3 upper/3 lower extremities), 3 sets × 10 reps	12 weeks	Relative to control: ↑ LV GLS & LA reservoir strain ↓ LV mass
Verboven et al. (71)	Systematic Review of RCTs and prospective studies ($n = 705$)	Type 2 diabetes (mean age range 46–61, sex not reported)	Echocardiography or MRI	F: 2–4 days/week I: HIIT: 90–95% HR_{max} MIT: 50–75% HR_{max}	F: 2–3 days/week I: 55–80% of maximum voluntary contraction ($n = 59$)	12 weeks−1 year	Relative to MIT: ↑ VO_{2peak}, LV E/A ↔ LV GLS, LVEF, LV mass
Cassidy et al. (72)	RCT ($n = 28$)	Type 2 diabetes (mean age 60 ± 9, 78% male)	MRI	F: 3 days/week I&T: 5 × 2–4-min @RPE 16–17 with 3-min recovery T: 33 min	None	12 weeks	Relative to control: ↑ LV mass, LVEDV, LVSV, LVEF, & LV E wave
Hollekim-Strand et al. (73)	Pilot RCT ($n = 47$)	Type 2 diabetes with LV diastolic dysfunction (mean age 56 ± 6, 64% male)	Echocardiography	HIIT group: F: 3 days/week I & T: 4 × 4-min @90–95% HR_{max} for 40 min MIT group: F & I: NR T: >10 min bouts, 210 min/week	None	12 weeks	HIIT relative to MIT: ↑ $VO_{2peak,}$ LV e', LV S' ↔ LV E/e'
Murray et al. (74)	Systematic review of RCTs and non-RCTs ($n = 221$)	Breast cancer (during chemotherapy) (mean age 49, 0% males)	Echocardiography	F: 3 days/week I: 70% HRR/50–95% HR_{max}/60–100% VO_{2peak} T: 15–60 min	F: 3 days/week I: NR T: 60 min in combination with aerobic training	1–16 weeks	Relative to control: ↑ VO_{2peak} ↔ LV GLS & LVEF

A, peak mitral inflow during atrial systole; E, early diastolic transmitral velocity; e', early diastolic mitral annular velocity; EDD, end-diastolic diameter; EDV, end-diastolic volume; EF, ejection fraction; ESD, end-systolic diameter; ESV, end-systolic volume; F, frequency; GLS, global longitudinal strain; HIIT, high intensity interval training; HR_{max}, max heart rate; HRR, heart rate reserve; I= intensity; LA: left atrial; LV, left ventricular; MIT, moderate intensity training; MRI, magnetic resonance imaging; MVC, maximal voluntary contraction; RCTs, randomized controlled trials; RPE, rate of perceived exertion; T, time/duration; S', systolic mitral annulus tissue velocity; SBP, systolic blood pressure; VO_{2peak}, peak volume of oxygen consumption with exercise; VO_{2max}, max volume of oxygen consumption with exercise; WMSI, wall motion score index; WTSI, wall thickening score index; 1-RM, 1-rep max.

reverse LV remodeling, with favorable effects on ejection fraction, stroke volume, and end-diastolic and end-systolic diameters (59–62).

However, similar to patients with CAD, the length of training program needed to have measurable positive effects was 6 months or longer (59, 60, 62). In one recent meta-analysis, LVEF was observed to improve with a mean difference of 6.3% in trials of ≥ 6 months duration vs. 2.3% for studies of shorter duration (62). Similarly, clinical trials of patients with reduced ejection fraction (LVEF < 35%) found that exercise training of 3 months duration or less did not impact relevant circulating cardiac biomarkers: NT-pro-BNP, high sensitivity C-reactive protein, and cardiac troponin (82). Regarding the type of exercise, the meta-analysis reported that high intensity interval training (HIIT) or combined aerobic and resistance training was not superior to moderate intensity continuous training for improvement in LVEF (62). Diastolic function also likely improves with exercise training. A meta-analysis of patients with HFrEF found that aerobic training induced a mean difference of −2.85 in E/E' ratio (early diastolic filling over diastolic tissue velocity) relative to controls, suggesting improved myocardial relaxation (63). However, this exercise-induced improvement in cardiac function is possibly explained by changes to vascular tone rather than direct cardiac effects. Using echocardiography and right-heart catheterization, Hambrecht et al. showed that 6 months of training in patients with HFrEF lowered total peripheral resistance, which strongly correlated to concurrent increased stroke volume (64). In studies of patients with heart failure and preserved ejection fraction (HFpEF) (LVEF ≥ 50%), exercise training did not result in any significant changes in LV volume, systolic function and diastolic function but did lead to a mild improvement in cardiorespiratory fitness [improves peak oxygen uptake (VO_2) by ∼2 ml/kg/min] (65). Furthermore, measurements of carotid artery distensibility and brachial artery flow mediated dilatation were also unaffected by aerobic training in this study (65). However, exercise trained patients with HFpEF exhibit increased arterial-venous oxygen difference after 4 months, consistent with improved skeletal muscle oxygen uptake and/or extraction by active muscles (35). A recent randomized controlled trial of HIIT, moderate intensity intermittent training or guideline-based control in 180 patients with HFpEF confirmed no improvement in echo-derived diastolic function (E/E') and left atrial volume or cardiorespiratory fitness (peak VO_2) after 12 months of training (66). An earlier meta-analysis also reported no change in cardiac imaging parameters and minor improvement in exercise performance in patients with HFpEF (67) (**Table 1**).

EXERCISE TRAINING EFFECTS ON CARDIAC STRUCTURE AND FUNCTION IN PATIENTS AT RISK FOR CARDIOVASCULAR DISEASE

Patients With Hypertension

Uncontrolled systemic hypertension may lead to LV hypertrophy and ultimately to heart failure (83). Moderate-intensity aerobic exercise training is recommended in patients with hypertension has been associated with 2-3 mmHg reductions in both systolic and diastolic blood pressure (84). Single-site imaging studies of exercise training in hypertensive patients also suggest associated improvement in cardiac function. An observational study of 116 patients undergoing 8 weeks of moderate-to-high intensity aerobic training (70–85% of peak heart rate) found no change in LVEF or LV wall thickness however tissue Doppler echocardiography and strain imaging suggested a post-intervention improvement in systolic and diastolic function (68). In a randomized study of 88 patients with hypertension, Molmen-Hansen et al. showed that high-intensity interval training (>90% maximal heart rate) improved 24-h ambulatory blood pressure, increased LVEF from 58 to 65%, increased E' from 8.06 to 9.26 cm/s, but with no change in LV wall thickness (69). A recent study of 30 hypertensive patients participating in 10 weeks of cardiac rehabilitation improved blood pressure control, decreased LV mass from 104 to 97 g/m^2 and improved LV global longitudinal strain from 19.8 to 20.7% (70). Interestingly, a meta-analysis of 16 studies of normotensive and hypertensive patients showed that isometric resistance training lowered systolic blood pressure in both groups, however potential associated effects on cardiac structure and function have not been elucidated (85) (**Table 1**).

Patients With Diabetes Mellitus

Diabetes mellitus is an independent risk factor for the development of atherosclerosis and heart failure. Diabetic cardiomyopathy is characterized by two distinct phenotypes, LV dilatation with systolic dysfunction or concentric LV hypertrophy with diastolic dysfunction (86). Glycemic control has been shown to influence cardiac function in individuals with diabetes (87), however, even individuals with well-controlled diabetes (defined by HbA1c < 7.5%) have subclinical myocardial dysfunction demonstrated by a significantly reduced longitudinal strain reserve on stress echocardiography (88). A systematic review of exercise training in individuals with diabetes suggested an improvement in diastolic function (E/A) but no consistent effect on systolic function or LV remodeling on echocardiography or MRI (71). Nevertheless, this apparent effect of exercise training is likely important because diastolic dysfunction with preserved LVEF is a common phenotype in patients with diabetic cardiomyopathy (86).

Two studies have suggested that high-intensity intermittent exercise may be superior to moderate-intensity exercise in reversing diabetes-associated myocardial impairment, with demonstrated improvement in systolic and diastolic function (72, 73). However, high-intensity training also increases LV wall mass and end-diastolic volume, presumably due to changes in loading conditions (72) (**Table 1**).

Patients With Cancer

Cancer therapy-related cardiac dysfunction (CTRCD) is an important clinical consideration for patients receiving anthracycline and/or trastuzumab-based adjuvant treatment. Early recognition and management of CTRCD is important as it has the potential to delay cancer treatment and directly impact cardiovascular morbidity and mortality. Cardiac imaging plays

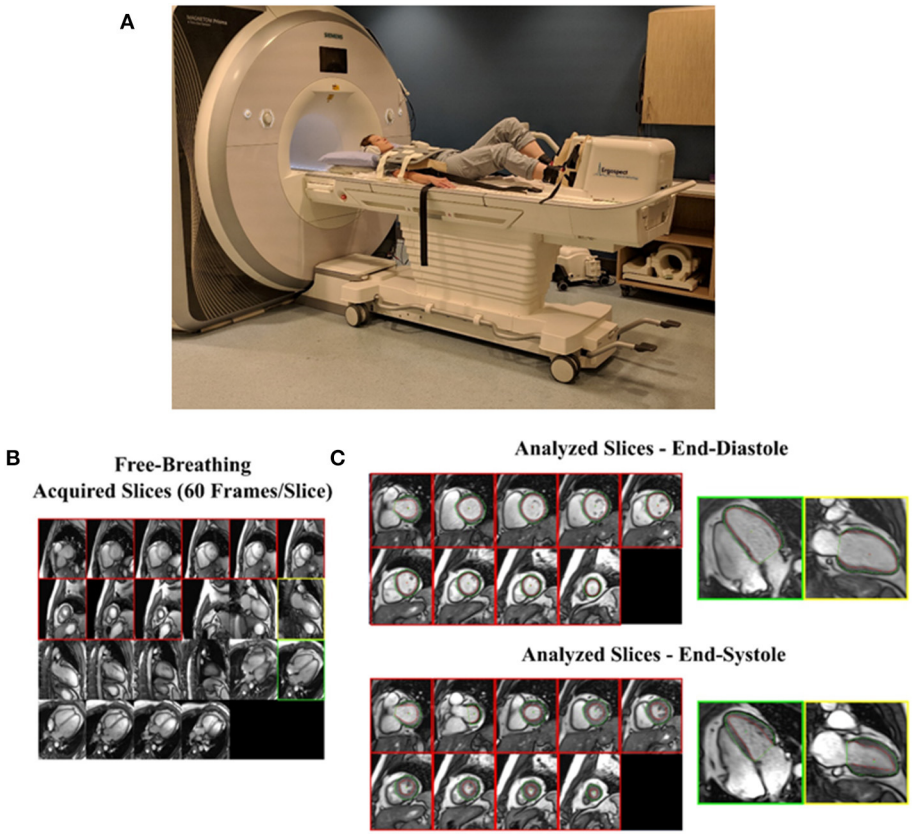


FIGURE 2 | Real-time imaging of cardiac function during exercise using cardiac MRI. **(A)** Healthy volunteer in supine position outside of magnet bore using MRI conditional stepper device to achieve maximal aerobic activity. **(B)** All short-axis and long-axis slices are viewed simultaneously to select those for volumetric analysis. Short-axis slices with myocardium and a single 2- and 4-chamber view are chosen. **(C)** A full cardiac cycle for each selected slice is extracted from which end-diastolic and end-systolic images are identified and endocardial (red) and epicardial (green) borders are traced. Modified from Kirkham et al. (97).

a critical role in the early detection and monitoring of CTRCD. This adverse complication is most commonly assessed by measuring LVEF by echocardiography, multi-gated blood pool imaging or cardiac MRI (89). Left ventricular global longitudinal strain is also recommended as a sensitive metric to. detect early LV dysfunction (89).

While pre-clinical models suggest that aerobic exercise training prevents cancer therapy-related cardiotoxicity, this has not translated to the clinical setting in the available research to-date. A recent meta-analysis of 8 studies (221 patients) of exercise training in patients with breast cancer receiving trastuzumab and/or anthracyclines showed no consistent benefit in the prevention of LV dilatation or worsening systolic function as assessed by echocardiography or cardiac MRI (74). However, exercise did improve cardio-respiratory fitness as measured by peak VO_2 (**Table 1**).

CARDIAC IMAGING WITH EXERCISE STRESS

Cardiac reserve function is defined as the difference in cardiac function from rest to peak exercise captured by echocardiography or cardiac MRI. Its potential importance stems from its ability to detect stress-induced myocardial dysfunction and evaluate exercise-related changes to chronotropy, inotropy, lusitropy, and vasodilation in patients with normal resting parameters (90).

In patients with HFpEF, a number of metrics have been studied with exercise imaging including LVEF, LV global longitudinal strain, E/E' ratio, mitral annular systolic velocity, and tricuspid regurgitation maximal velocity (91–93). Resting echocardiography, electrocardiogram, and serum biomarkers such as NT-pro-BNP often fail to identify patients with HFpEF, whereas a stress echocardiogram has been shown to be more sensitive for this diagnosis (93). Exercise echocardiography can be performed using a treadmill or a cycle ergometer. The latter having the advantage of imaging being performed in a semi-supine position and therefore does not require patient transfer and allows for image acquisition at incremental workloads.

Exercise stress imaging with cardiac MRI offers the advance of enhanced accuracy and reproducible quantification of cardiac volumes and biventricular function relative to other imaging modalities (94, 95). The exercise modes employed with cardiac MRI include a supine cycle ergometer or stepper device attached to the scan table to allowing real-time image acquisition while the patient is exercising, instantaneous with achievement of

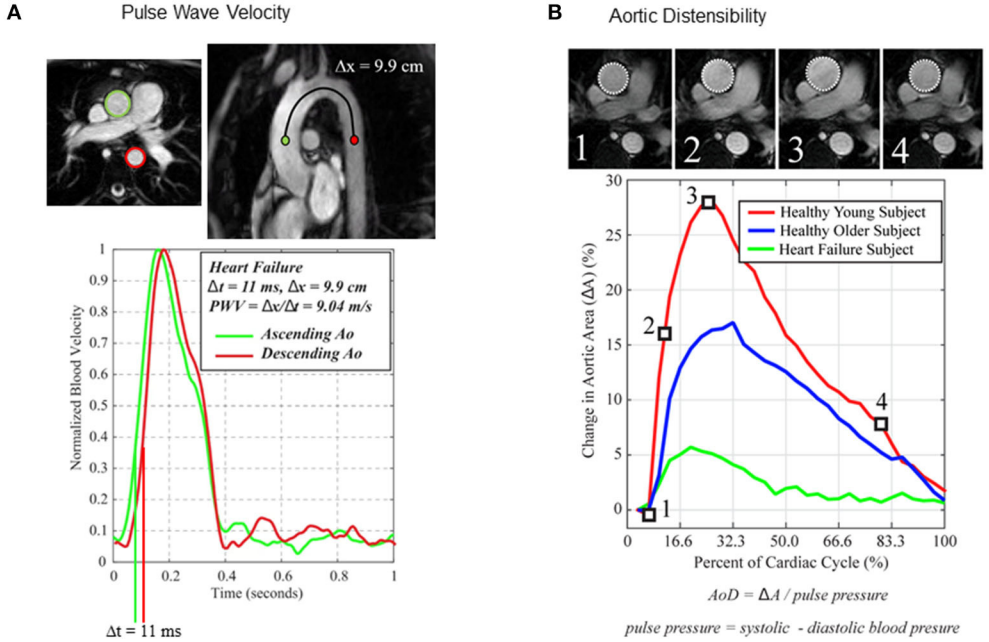


FIGURE 3 | Imaging techniques used to assess the effects of exercise training in patients with or at risk for cardiovascular disease. **(A)** MRI derived arterial stiffness. Pulse wave velocity (PWV) estimated from MRI derived phase velocity imaging of the thoracic aorta in an older patient with heart failure. Adapted from Thompson et al. (101). **(B)** Thoracic aorta distensibility (AoD) on SSFP cines. Comparison of aortic distensibility between a young healthy individual, an older healthy individual and an older patient with heart failure.

peak exercise or by exercise performed outside of the bore with quick transfer of patients to the MRI table for image acquisition (96, 97). Exercise-related increased respiratory rates and cardiac translation introduce both patient-related difficulties in breath-holds and ECG signal, which are required for the standard cardiac MRI acquisition methods (97). Our group recently validated a real-time, free-breathing approach that remedies these exercise-related issues in patients with cardiovascular risk factors and/or cancer (97) (**Figure 2**).

EXERCISE TRAINING EFFECTS ON VASCULAR HEALTH

Imaging Metrics of Vascular Structure and Function

Age, cardiometabolic disease and toxic exposures (e.g., smoking, chemotherapy) each affect the arterial wall matrix, reduce elasticity and thus increase the potential for arterial stiffening and impaired blood flow (98). Endothelial dysfunction is also common in patients with and at risk for atherosclerotic disease and can increase arterial tone and stiffness due to impaired vascular smooth muscle function (98). Arterial stiffness is typically derived from the assessment of pulse wave velocity (PWV) in a vessel segment and is measured non-invasively using tonometry or cuff-based technologies as well as by imaging on Doppler ultrasound or MRI-derived phase velocity imaging (99). These imaging modalities also allow for complementary information on arterial wall thickness (B-mode or M-mode ultrasound) (100) and aortic distensibility (MRI cine imaging) (101) (**Figure 3**). Measures of arterial stiffness are clinically relevant as they predict future cardiovascular events (102–104) incident hypertension (105) and heart failure (106). Hence, therapies directed at attenuating vascular dysfunction are desirable. Aerobic exercise training is known to improve cardiovascular risk factors modulating arterial stiffness (4) and some studies also suggest direct effects on improving vascular function (107, 108).

EXERCISE TRAINING EFFECTS ON VASCULAR FUNCTION IN PATIENTS WITH ESTABLISHED CARDIOVASCULAR DISEASE

Patients With Coronary Artery Disease

Aerobic exercise training has been linked to reduced arterial stiffness in patients with CAD. A systematic review of 5 studies of arterial stiffness in patients with CAD found that aerobic training was associated with lower PWV measures on Doppler ultrasound (109). One study suggested that the magnitude of benefit was greater for participants who trained for 20 weeks compared to 12 weeks, change in PWV −1.0 vs. −0.6 m/s, respectively (110). However, these

studies were non-randomized, small (range 20–119 participants) and did not control for potential confounders. In contrast, a randomized-controlled trial of 12 months of combined aerobic and resistance training in 137 patients with CAD and diabetes mellitus found no effect of exercise on IMT measures (111). Although, subgroup analysis suggested improved IMT measures in patients without carotid plaques at baseline (**Table 2**).

Patients With Heart Failure

Vascular function is believed to play an integral role in the development and progression of heart failure, particularly with preserved ejection fraction (117). Indeed, carotid artery distensibility derived from B-mode ultrasound is significantly reduced in patients with HFpEF compared to healthy controls and is also directly related to cardiorespiratory fitness (peak VO_2) (118). In a cross-sectional study of 143 patients attending cardiac rehabilitation, a significant correlation between indices of arterial stiffness and cardiorespiratory exercise tolerance was found in patients with preserved ejection fraction but not in patients with reduced ejection fraction (119). However, a randomized, controlled trial of 16 weeks of combined aerobic and resistance training for patients with HFpEF found no improvement in carotid artery distensibility or in brachial artery flow mediated dilatation despite improvement in cardiorespiratory fitness (65). While vascular function appears to be an important determinant of exercise tolerance in patients with HFpEF, it does not appear to be improved by exercising training (**Table 2**).

EXERCISE TRAINING EFFECTS ON VASCULAR FUNCTION IN PATIENTS AT RISK FOR CARDIOVASCULAR DISEASE

Early studies suggested that 3 months of aerobic exercise training in patients with cardiovascular risk factors (hypertension, diabetes mellitus and dyslipidemia) reduced arterial PWV (108). However, these salient effects on arterial stiffness were an early response to exercise as they were not sustained at 6 months of aerobic training (112). Similarly, meta-analyses of predominantly aerobic exercise training in individuals with hypertension or diabetes found no improvement in the non-invasive assessment of arterial stiffness (113, 114). However, subgroup analysis in hypertensive patients suggested improvement with interventions of longer duration (113). Data on exercise training and arterial stiffness in patients with cancer is lacking however one recent study of 12 weeks of circuit resistance training reported significant improvement in cardiorespiratory fitness (VO_2 max + 4.3 ml/kg/min) and PWV (−0.9 m/s) in 51 patients (115). A recent meta-analysis of exercise training in patients with breast or prostate cancer (163 total patients) reported that aerobic exercise improved vascular endothelial function on ultrasound (116) (**Table 2**).

EXERCISE TRAINING EFFECTS ON CARDIAC AND EXTRA-CARDIAC TISSUE STRUCTURE AND COMPOSITION

Late gadolinium enhancement sequences on cardiac MRI are frequently utilized to identify and quantify myocardial scar (replacement fibrosis) arising from acute ischemic injury (120). Follow-up studies of patients with acute MI, have shown that infarct size decreases by 16% on late gadolinium enhancement imaging (121). However, the effect of exercise training on infarct size has not been well-elucidated. Quantitative mapping MRI sequences also allow the characterization of both myocardial and extra-cardiac tissues to provide valuable insight into whole-body cardiovascular health profile. Elevated myocardial T_1 times and extracellular volume metrics have been validated as indicators of edema in acute disease and interstitial reactive fibrosis in chronic conditions and are increasingly used as risk markers in patients at risk for or with established cardiovascular disease (122, 123). For example, Reinstadler et al. showed that in patients with ST elevation myocardial infarction, native T_1 values in remote, non-infarcted myocardium independently predicted adverse cardiovascular outcomes at 6 months (124). Similarly, Vita et al. showed that in patients with non-ischemic dilated cardiomyopathy, elevated myocardial extracellular volume predicts long-term heart failure outcomes (125). Increased myocardial T_1 and extracellular volume have also been reported in cancer survivors with previous exposure to anthracycline-based chemotherapy (126, 127). Kirkham et al., reported that native myocardial T_1 was elevated compared to controls and correlated with cardiorespiratory fitness among anthracycline-treated breast cancer survivors, suggesting that this metric of myocardial microarchitecture has important functional implications (128). A recent non-randomized study of 27 patients with breast cancer undergoing 4 months of exercise training during anthracycline-based chemotherapy found no effect of exercise on native myocardial T_1 but not report on extracellular volume fraction (129). To our knowledge, there have been no reports on the effects of exercise training on myocardial T_1 and extracellular volume fraction (i.e., myocardial reactive fibrosis ± edema) in patients with established cardiovascular disease or with cardiovascular risk factors.

It is now well-established that the location of fat deposition is much more closely linked to cardiovascular disease risk than the total quantity of fat (130). For instance, subcutaneous fat (located under the skin) accounts for 80–95% of total body fat but has relatively benign cardiometabolic consequences (130). When the finite limit of the expansion capacity of subcutaneous fat is reached, or in the presence of toxic exposures (e.g., smoking or chemotherapy), fat deposition occurs in ectopic "overflow" sites instead, including around the visceral organs (visceral), in skeletal muscle (intermuscular), in liver cells, or around the heart (epicardial) (130). Ectopic fat only accounts for 5–15% of total body fat but has much worse cardiometabolic consequences. For example, visceral and intermuscular fat deposition are independent predictors for cardiometabolic disease including hypertension, dyslipidemia, insulin resistance and atherogenesis

TABLE 2 | Characteristics of the imaging studies reporting on the vascular effects of exercise training.

References	Study design (sample size)	Study population (age, % male)	Imaging type	Aerobic exercise prescription	Resistance exercise prescription	Exercise program duration	Relevant results
Coronary artery disease							
Oliveira et al. (109)	Systematic review of prospective studies ($n = 271$)	CAD (mean age range 48–67, sex not reported)	Carotid-femoral or carotid-brachial Doppler ultrasound	F: 1–3 days/week I: 40–85% HRR/anaerobic threshold T: 15–50 min	Too few studies for comparison	6–20 weeks	Relative to control: ↓ PWV
Laskey et al. (110)	Prospective, single-arm trial ($n = 48$)	Clinically stable CAD (mean age 61 ± 11, 54% male)	Doppler ultrasound	F: 3 days/week I: 40–85% HRR T: 15–50 min	None	20 weeks	Relative to control: ↓ central aortic systolic pressure & PWV
Byrkjeland et al. (111)	RCT ($n = 137$)	Type 2 diabetes and CAD (mean age 63 ± 8, 84% male)	Ultrasonography	F: 3 days/week I: not reported T: 33 min	F: 3 days/week I: not reported T: 17 min	12 months	Relative to control: ↔ carotid intima-media thickness
Heart failure							
Kitzman et al. (65)	RCT ($n = 63$)	Heart failure with preserved ejection fraction	Ultrasonography, Doppler echocardiography	F: 3 days/week I: 40–70% HRR T: 60 min	None	16 weeks	Relative to control: ↑ VO_{2peak} ↔ carotid artery distensibility & FMD
Patients at risk for cardiovascular disease							
Madden et al. (108)	RCT ($n = 36$)	Type 2 diabetes, hypertension and hypercholesterolemia (mean age 71 ± 1, 52% male)	Doppler ultrasound	F: 3×/wk I: 60–75% HRR T: 60 min	None	12 weeks	Relative to control: ↓ femoral and radial PWV ↔ VO_{2peak}
Madden et al. (112)	RCT ($n = 52$)	Type 2 diabetes, hypertension and hypercholesterolemia (mean age 69 ± 1, 58% male)	Doppler ultrasound	F: 3×/wk I: 60–75% HRR T: 60 min	None	6 months	Relative to control: ↓ femoral and radial PWV ↑VO_{2peak}
Montero et al. (113)	Meta-analysis of RCTs & non-RCTs ($n = 472$)	Pre-hypertensive (age range 44–70, <50% males)	Doppler ultrasound	F: 3–6/wk I: 60–75% HRR/60–85%HR_{max}/50–75% VO_{2max} T: 25–60 min	None	1–7 months	Relative to control: ↔ measures of arterial stiffness (PMV, distensibility)
Way et al. (114)	Meta-analysis of RCTs & non-RCTs ($n = 783$)	Type 2 diabetes (mean age 57 ± 17, 51% male)	Doppler ultrasound	F: 3×/wk I: 60–75% HRR/60–90% HR_{max}/50–85% VO_{2peak}/65–75% VO_{2max} T: 25–60 min	F: 2–3×/wk I: 50–70% 1–RM/60–80% MVC T: 2–3 sets × 10–15 reps, 25–60 min	12–24 weeks	Relative to control: ↓ endothelial-independent dilation ↔ PWV & FMD
Jones et al. (115)	RCT ($n = 51$)	Breast cancer survivors (mean age 56 ± 7, 0% male)	Doppler ultrasound	F: 2××/wk I: 50–70% HR_{max} T: 60 min	F: 2×/wk I: 60% 1-RM T: 12 resistance-based exercises, 1 set × 10–12 reps	12 weeks	Relative to control: ↓ PWV ↑VO_{2max}
Beaudry et al. (116)	Meta-analysis of RCTs ($n = 163$)	Cancer survivors (mean age 57 ± 7, 54% male)	Ultrasonography	F: 3×/wk I: 55–75% VO_{2peak} T: 20–45 min	None	3–6 months	Relative to control: ↑ FMD & VO_{2peak}

CAD, coronary artery disease; F, frequency; FMD, flow mediated dilation; HR_{max}, max heart rate; HRR, heart rate reserve; I, intensity; LV, left ventricular; MVC, maximal voluntary contraction; NMD, nitric-flow mediated dilation; PWV, pulse wave velocity; RCTs, randomized control trials; T, time/duration; VO_{2peak}, peak volume of oxygen consumption with exercise; VO_{2max}, max volume of oxygen consumption with exercise; 1-RM, 1-rep max.

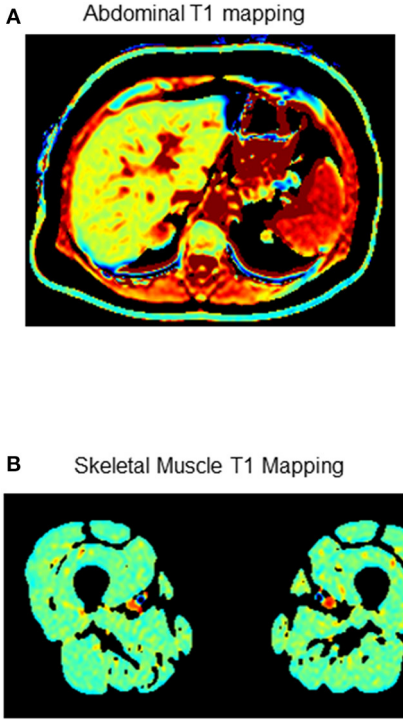


FIGURE 4 | Examples of MRI T1 mapping sequences to assess the extra-cardiac effects of exercise training in patients with or at risk for cardiovascular disease. **(A)** Abdominal fat density **(B)** Skeletal muscle fat compartments. Dark signal = fat.

and are predictive of cardiovascular mortality (131, 132). Furthermore, our group has shown that thigh intermuscular fat is a strong independent predictor of cardiorespiratory fitness level in male and female patients with HFpEF, breast cancer survivors, and females with cardiovascular risk factors (15, 133, 134). We have shown that visceral and intermuscular fat volume at the time of a breast cancer diagnosis predicts later cardiac events (135) and also significantly and rapidly increase with trastuzumab-based chemotherapy treatment (14).

Imaging modalities used to quantify body composition in clinical practice and research include computed tomography, dual energy X-ray absorptiometry and MRI (**Figure 4**). MRI is uniquely suited to accurately and safely (without ionizing radiation) quantify fat in all of these locations as well as complementary information on cardiac structure and function in a single assessment.

Exercise training and caloric restriction (i.e., reduced daily calorie intake) are the primary interventions used to improve body composition. A meta-analysis comparing the effects of exercise training to caloric restriction in patients with obesity found that both interventions independently reduce visceral fat with a potential trend toward greater reduction with exercise (136). In patients with CAD undergoing cardiac rehabilitation, bioelectrical impedance-derived measures of visceral fat have been shown to improve, but with a greater magnitude of benefit with a greater volume of exercise training (137). Similarly, in a small study of patients with chronic heart failure, 5 months of cardiac rehabilitation also appears to reduce visceral adipose tissue (138). Data on the effects of exercise training in patients with hypertension is limited. However, one study of 156 hypertensive patients randomized to 12 months of exercise training or usual care found 30% reduction in visceral fat area on B-mode ultrasound compared to no effect with antihypertensive pharmacotherapy alone (139). Meta-analyses of the effect of exercise training on visceral fat in both overweight adults and patients with type 2 diabetes mellitus suggest that aerobic exercise training (but not resistance training) appears to provide the greatest benefits (140) (**Table 3**).

Our group is conducting a randomized-controlled trial of a multi-modal intervention including combined aerobic and resistance exercise training and dietary counseling (with no caloric restriction) on LV function in patients receiving cardiotoxic breast cancer treatment and includes quantification of ectopic fat as a secondary outcome measure (141). In a recent randomized controlled trial where exercise was performed shortly after the completion of breast cancer treatment, whole-body, and visceral fat volume were significantly reduced by 16-weeks of combined aerobic and resistance training (142). Therefore, another strategy to reduce cardiovascular risk in this population may be to perform an exercise intervention after treatment completion.

SUMMARY AND FUTURE DIRECTIONS

Exercise training is a cornerstone treatment for patients with cardiovascular disease due its demonstrated impact on risk profile and clinical outcomes. Ultrasound or MR imaging for quantification of changes to the cardiac and extra-cardiac phenotype of patients, provide valuable whole-body information about the cardiovascular risk profile and have an excellent safety profile to allow for repeat testing.

The choice of imaging modality to evaluate changes in cardiovascular structure and function is an important consideration. In general, echocardiography is the most readily available modality and offers a comprehensive assessment of ventricular volumes, mass and function. It can also more easily be used to evaluate cardiac function in real time during exercise on a semi-recumbent bicycle. Cardiac MRI is considered the gold standard imaging test for ventricular volumes, mass and function due to high reproducibility. As mentioned previously, it also allows assessment of cardiac and extra cardiac tissue characterization which has increasingly been linked to prognosis in patients with or at risk for cardiovascular disease. Therefore, cardiac MRI should likely be used to study the effects of exercise training in higher risk patient groups when available.

There is strong evidence supporting a beneficial effect of exercise training, particularly >6 months duration, on cardiac function and remodeling in patients with CAD or heart failure (**Table 4**). Imaging studies on the effects of exercise training for vascular function in patients with or at risk for cardiovascular disease have shown either modest or no improvement in arterial

TABLE 3 | Characteristics of the studies reporting on the extra-cardiac effects of exercise training.

References	Study design (sample size)	Study population (age, % male)	Imaging type	Aerobic exercise prescription	Resistance exercise prescription	Exercise program duration	Relevant results
Obesity							
Verheggen et al. (136)	Meta-analysis & Systematic Review of prospective studies ($n = 4,815$)	Obese patients Exercise group: $N = 2404$ (mean age range 21–73) Low calorie group: $N = 2411$ (mean age range 30–66, 33% male)	Computed tomography, MRI or DEXA	F: 1–7 days/week I: 40–90% VO_{2peak}/HR_{max} T: 15–90 min	None	6–20 weeks	Both groups: ↓ weight & VAT Exercise relative to diet group: ↓ weight loss, trend ↑ VAT loss
Coronary artery disease							
Mirman et al. (137)	Prospective, two-arm trial ($n = 715$)	Clinically stable CAD Traditional cardiac rehab: $N = 516$ (median age 69, 74% male) Intensive cardiac rehab: $N = 199$ (median age 64, 78% male)	Bioelectrical impedance analysis	Traditional program: F: 2–3 days/week I: <70–85% HR_{max} T: 45–60 min Intensive program: F: 2 days/week I: <70–85% HR_{max} T: 240 min	F: 2–3 days/week I: not reported T: 15–30 min	Traditional: 8–12 weeks Intensive: 9 weeks	↓ weight, VAT & ↑ lean mass but greater effect in intensive program
Heart failure							
Takagawa et al. (138)	Prospective, single arm study ($n = 19$)	Chronic heart failure (any type)	Bioelectrical impedance analysis	F: 3–5 days/week I: anaerobic threshold−1 min T: 40–50 min	None	5 months	↓ weight & VAT ↔ lean mass
Patients at risk for cardiovascular disease							
Fang et al. (139)	RCT ($n = 156$)	Hypertensives (mean age 46 ± 8, 58% male)	B-mode ultrasound	F: 3 days/week I: 65% HR_{max} T: 60 min	None	12 months	↓ BMI and VAT only in exercise group
Sabag et al. (140)	Meta-analysis ($n = 1,383$)	Type 2 diabetes (mean age range 45–69, 37% male)	Computed tomography or MRI	F: 2–7 days/week I: 50–70% VO_{2peak}, 60–90% HR_{max} T: 20–120 min	F: 3–5 days/week I: 40–80% 1-RM T: not reported	4 weeks−12 months	Aerobic training: ↓ VAT Resistance or combined training: ↔ VAT

BMI, body mass index; CAD, coronary artery disease; DEXA, dual-energy x-ray absorptiometry; F, frequency; HR_{max}, max heart rate; I, intensity; MRI, magnetic resonance imaging; RCTs, randomized control trials; T, time/duration; VAT, visceral adipose tissue; VO_{2peak}, peak volume of oxygen consumption with exercise; 1-RM, 1-rep max.

TABLE 4 | Overview of the exercise training effects of on cardiovascular imaging metrics in patients with or at risk for cardiovascular disease.

	CAD	HFrEF	HFpEF	Hypertension	Diabetes mellitus	Cancer
Systolic function	+	+	0	+/–	+/–	0
LV remodeling	+	+	0	+/–	+/–	0
Vascular function	+/–	0	0	0	0	?
Myocardial reactive fibrosis	?	?	?	?	?	?
Body composition	+	+/–	+/–	+/–	+	+/–

+, beneficial effect.
+/–, possible beneficial effect, more studies needed.
0, no effect.
?, no or limited available data.
CAD, coronary artery disease; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; LV, left ventricular.

stiffness. Furthermore, these studies are limited by the small number of participants, non-randomized design and lack of controlling for confounders.

Ectopic fat deposition, particularly, visceral and intermuscular fat are important indicators of cardiovascular risk that can be reduced by exercise training in numerous patient populations. MRI-acquired myocardial tissue characterization using T_1 mapping sequences also provide incremental prognostic information however, the effect of exercise training on this parameter has not well-studied. MRI and/or ultrasound is well-suited for multiparametric evaluation of exercise training interventions and is easily translatable to the clinical setting to help guide patient management. Incorporation of MRI-derived lung water quantification could also help to identify cardiogenic causes of exercise intolerance and evaluate exercise training in patients with subclinical pulmonary edema (13, 143). Exercise cardiac reserve is another attractive approach to evaluating cardiogenic causes of exercise intolerance and detecting subclinical disease, and related studies are underway in the cancer setting (144, 145).

Targeted nutrition interventions can also positively impact cardiovascular health and should be further explored in combination with exercise interventions (146). Dietary patterns and specific nutrients can have independent, synergistic, or additive effects on reducing cardiovascular disease risk (147). Furthermore, nutrition interventions also have a therapeutic role for certain cardiovascular diseases (148). In addition to providing calories and macronutrients, specific nutrients can reduce oxidative damage, increase pro-inflammatory mediators and decrease anti-inflammatory mediators, while also promoting optimal body composition (e.g., decreasing ectopic fat, increase protein synthesis and reducing degradation) (148, 149).

Preclinical models of cardiovascular disease have been used extensively to study the cardioprotective effects of exercise training. Aerobic training has been shown to attenuate cardiac injury in animal models of myocardial infarction (150), ischemic heart failure (151), and preclinical disease (71, 152, 153). These models provide significant insight on the salient effects of exercise in cardiovascular disease and allow extensive histological and biochemical characterization of cardiovascular structure and function in a controlled setting. By comparison, resistance training protocols have been understudied in animal models of cardiovascular disease, in part due to a lack of standardized protocols. Nevertheless, beneficial cardiac and vascular adaptations with resistance training have been reported in small animal models of cardiovascular disease (154). Future preclinical work in exercise training requires refinement and standardization of training protocols to improve study comparisons and to better simulate exercise programs in the clinical setting (155). In conclusion, ultrasound and magnetic resonance-based imaging provides detailed information on the cardiac and extra-cardiac effects of exercise training. Imaging studies provide moderate or good evidence for exercise training to mitigate or improve cardiac remodeling and function in patients with or at risk for cardiovascular disease. Similar work on vascular function suggests a benefit in patients with CAD although these studies were non-randomized and included small numbers of patients. There is no clear benefit of exercise training in vascular function in patients with heart failure, hypertension or diabetes mellitus. There is little data on the effects of exercise training on replacement or reactive myocardial fibrosis. Future work on imaging studies of exercise training should also evaluate the complementary role of nutrition interventions given their importance in cardiac rehabilitation.

AUTHOR CONTRIBUTIONS

WA and DIP proposed the review subject matter and drafted the manuscript. All authors made critical revisions to the manuscript, contributed to the article, and approved the submitted version.

FUNDING

MH was supported by the Faculty of Nursing Research Chair in aging and quality of life at the University of Alberta, EP was supported by a Tier 2 Canada Research Chair, and CP was supported by a Campus Alberta Innovates Program Chair in Nutrition, Food, and Health as well as a Canadian Institutes of Health Research new investigator award.

REFERENCES

1. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* (2021) 42:1289–367. doi: 10.15829/1560-4071-2021-4418
2. Bozkurt B, Fonarow GC, Goldberg LR, Guglin M, Josephson RA, Forman DE, et al. ACC's heart failure and transplant section and leadership council. Cardiac rehabilitation for patients with heart failure: JACC expert panel. *J Am Coll Cardiol.* (2021) 77:1454–69. doi: 10.1016/j.jacc.2021.01.030
3. Gilchrist SC, Barac A, Ades PA, Alfano CM, Franklin BA, Jones LW, et al. Cardio-Oncology rehabilitation to manage cardiovascular outcomes in cancer patients and survivors: a scientific statement from the American heart association. *Circulation.* (2019) 139:e997–1012. doi: 10.1161/CIR.0000000000000679
4. Balady GJ, Williams MA, Ades PA, Bittner V, Comoss P, Foody JM, et al. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update: a scientific statement from the American heart association exercise, cardiac rehabilitation, and prevention committee, the council on clinical cardiology; the councils on cardiovascular nursing, epidemiology and prevention, and nutrition, physical activity, and metabolism; and the American association of cardiovascular and pulmonary rehabilitation. *Circulation.* (2007) 115:2675–82. doi: 10.1161/CIRCULATIONAHA.106.180945
5. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American college of sports medicine. American college of sports medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc.* (2011) 43:1334–59. doi: 10.1249/MSS.0b013e318213fefb
6. Kriska AM, Saremi A, Hanson RL, Bennett PH, Kobes S, Williams DE, et al. Physical activity, obesity, and the incidence of type 2 diabetes in a high-risk population. *Am J Epidemiol.* (2003) 158:669–75. doi: 10.1093/aje/kwg191
7. Sarzynski MA, Burton J, Rankinen T, Blair SN, Church TS, Després JP, et al. The effects of exercise on the lipoprotein subclass profile: A meta-analysis of 10 interventions. *Atherosclerosis.* (2015) 243:364–72. doi: 10.1016/j.atherosclerosis.2015.10.018
8. Kokkinos P, Myers J. Exercise and physical activity: clinical outcomes and applications. *Circulation.* (2010) 122:1637–48. doi: 10.1161/CIRCULATIONAHA.110.948349
9. Mathieu P, Poirier P, Pibarot P, Lemieux I, Despres JP. Visceral obesity: the link among inflammation, hypertension, and cardiovascular disease. *Hypertension.* (2009) 53:577–84. doi: 10.1161/HYPERTENSIONAHA.108.110320
10. Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, Ruiz-Gutiérrez V, Covas MI, et al. Effects of a mediterranean-style diet on cardiovascular risk factors: a randomized trial. *Ann Intern Med.* (2006) 145:1–11. doi: 10.7326/0003-4819-145-1-200607040-00004
11. Foulkes S, Claessen G, Howden EJ, Daly RM, Fraser SF, La Gerche A. The utility of cardiac reserve for the early detection of cancer treatment-related cardiac dysfunction: a comprehensive overview. *Front Cardiovasc Med.* (2020) 7:32. doi: 10.3389/fcvm.2020.00032
12. Pandey A, Khera R, Park B, Haykowsky M, Borlaug BA, Lewis GD, et al. Relative impairments in hemodynamic exercise reserve parameters in heart failure with preserved ejection fraction: a study-level pooled analysis. *JACC Heart Fail.* (2018) 6:117–126. doi: 10.1016/j.jchf.2017.10.014
13. Thompson RB, Chow K, Pagano JJ, Sekowski V, Michelakis ED, Tymchak W, et al. Quantification of lung water in heart failure using cardiovascular magnetic resonance imaging. *J Cardiovasc Magn Reson.* (2019) 21:58. doi: 10.1186/s12968-019-0567-y
14. Kirkham AA, Pituskin E, Thompson RB, Mackey JR, Koshman SL, Jassal D, et al. Cardiac and cardiometabolic phenotyping of trastuzumab-mediated cardiotoxicity: a secondary analysis of the MANTICORE trial. *Eur Heart J Cardiovasc Pharmacother.* (2021) pvab016. doi: 10.1093/ehjcvp/pvab016. [Epub ahead of print].
15. Beaudry RI, Kirkham AA, Thompson RB, Grenier JG, Mackey JR, Haykowsky MJ. Exercise intolerance in anthracycline-treated breast cancer survivors: the role of skeletal muscle bioenergetics, oxygenation, and composition. *Oncologist.* (2020) 25:e852–60. doi: 10.1634/theoncologist.2019-0777
16. American Heart Association editorial staff. *American Heart Association Recommendations for Physical Activity in Adults and Kids.* (2018). Available online at: https://www.heart.org/en/healthy-living/fitness/fitness-basics/aha-recs-for-physical-activity-in-adults (accessed August 2, 2021).
17. Scharhag J, Herrmann M, Urhausen A, Haschke M, Herrmann W, Kindermann W. Independent elevations of N-terminal pro–brain natriuretic peptide and cardiac troponins in endurance athletes after prolonged strenuous exercise. *Am Heart J.* (2005) 150:1128–34. doi: 10.1016/j.ahj.2005.01.051
18. Dieplinger B, Egger M, Haltmayer M, Kleber ME, Scharnagl H, Silbernagel G, et al. Increased soluble ST2 predicts long-term mortality in patients with stable coronary artery disease: results from the ludwigshafen risk and cardiovascular health study. *Clin Chem.* (2014) 60:530–40. doi: 10.1373/clinchem.2013.209858
19. Aengevaeren VL, VAN Kimmenade RRJ, Hopman MTE, VAN Royen N, Snider JV, Januzzi JL, et al. Exercise-induced changes in soluble ST2 concentrations in marathon runners. *Med Sci Sports Exerc.* (2019) 51:405–10. doi: 10.1249/MSS.0000000000001806
20. Zhang CD, Xu SL, Wang XY, Tao LY, Zhao W, Gao W. Prevalence of myocardial fibrosis in intensive endurance training athletes: a systematic review and meta-analysis. *Front Cardiovasc Med.* (2020) 7:585692. doi: 10.3389/fcvm.2020.585692
21. La Gerche A, Taylor AJ, Prior DL. Athlete's heart: the potential for multimodality imaging to address the critical remaining questions. *JACC Cardiovasc Imaging.* (2009) 2:350–63. doi: 10.1016/j.jcmg.2008.12.011
22. D'Ascenzi F, Anselmi F, Piu P, Fiorentini C, Carbone SF, Volterrani L, et al. Cardiac magnetic resonance normal reference values of biventricular size and function in male athlete's heart. *JACC Cardiovasc Imaging.* (2019) 12:1755–65. doi: 10.1016/j.jcmg.2018.09.021
23. Kawel-Boehm N, Hetzel SJ, Ambale-Venkatesh B, Captur G, Francois CJ, Jerosch-Herold M, et al. Reference ranges ("normal values") for cardiovascular magnetic resonance (CMR) in adults and children: 2020 update. *J Cardiovasc Magn Reson.* (2020) 22:87. doi: 10.1186/s12968-020-00683-3
24. Charkoudian N, Joyner MJ. Physiologic considerations for exercise performance in women. *Clin Chest Med.* (2004) 25:247–55. doi: 10.1016/j.ccm.2004.01.001
25. Wiebe CG, Gledhill N, Warburton DE, Jamnik VK, Ferguson S. Exercise cardiac function in endurance-trained males versus females. *Clin J Sport Med.* (1998) 8:272–9. doi: 10.1097/00042752-199810000-00004
26. Fu Q, Levine BD. Cardiovascular response to exercise in women. *Med Sci Sports Exerc.* (2005) 37:1433–5. doi: 10.1249/01.mss.0000174886.08219.85
27. Ogawa T, Spina RJ, Martin WH III, Kohrt WM, Schechtman KB, Holloszy JO, et al. Effects of aging, sex, and physical training on cardiovascular responses to exercise. *Circulation.* (1992) 86:494–503. doi: 10.1161/01.CIR.86.2.494
28. Best SA, Okada Y, Galbreath MM, Jarvis SS, Bivens TB, Adams-Huet B, et al. Age and sex differences in muscle sympathetic nerve activity in relation to haemodynamics, blood volume and left ventricular size. *Exp Physiol.* (2014) 99:839–48. doi: 10.1113/expphysiol.2013.077248
29. Hutchinson PL, Cureton KJ, Outz H, Wilson G. Relationship of cardiac size to maximal oxygen uptake and body size in men and women. *Int J Sports Med.* (1991) 12:369–73. doi: 10.1055/s-2007-1024696
30. Piro M, della Bona R, Abbate A, Biasucci LM, Crea F. Sex-related differences in myocardial remodeling. *J Am Coll Cardiol.* (2010) 55:1057–65. doi: 10.1016/j.jacc.2009.09.065
31. Diaz-Canestro C, Montero D. The impact of sex on left ventricular cardiac adaptations to endurance training: a systematic review and meta-analysis. *Sports Med.* (2020) 50:1501–13. doi: 10.1007/s40279-020-01294-9
32. Nio AQX, Rogers S, Mynors-Wallis R, Meah VL, Black JM, Stembridge M, et al. The menopause alters aerobic adaptations to high-intensity interval training. *Med Sci Sports Exerc.* (2020) 52:2096–106. doi: 10.1249/MSS.0000000000002372

33. Murias JM, Kowalchuk JM, Paterson DH. Mechanisms for increases in VO2max with endurance training in older and young women. *Med Sci Sports Exerc.* (2010) 42:1891–8. doi: 10.1249/MSS.0b013e3181dd0bba
34. Spina RJ, Ogawa T, Kohrt WM, Martin WH, Holloszy JO, Ehsani AA. Differences in cardiovascular adaptations to endurance exercise training between older men and women. *J Appl Physiol.* (1993) 75:849–55. doi: 10.1152/jappl.1993.75.2.849
35. Haykowsky MJ, Brubaker PH, Stewart KP, Morgan TM, Eggebeen J, Kitzman DW. Effect of endurance training on the determinants of peak exercise oxygen consumption in elderly patients with stable compensated heart failure and preserved ejection fraction. *J Am Coll Cardiol.* (2012) 60:120–8. doi: 10.1016/j.jacc.2012.02.055
36. Seals DR, Nagy EE, Moreau KL. Aerobic exercise training and vascular function with ageing in healthy men and women. *J Physiol.* (2019) 597:4901–14. doi: 10.1113/JP277764
37. van Eickels M, Grohé C, Cleutjens JP, Janssen BJ, Wellens HJ, Doevendans PA. 17beta-estradiol attenuates the development of pressure-overload hypertrophy. *Circulation.* (2001) 104:1419–23. doi: 10.1161/hc3601.095577
38. Haines CD, Harvey PA, Leinwand LA. Estrogens mediate cardiac hypertrophy in a stimulus-dependent manner. *Endocrinology.* (2012) 153:4480–90. doi: 10.1210/en.2012-1353
39. Babiker FA, De Windt LJ, van Eickels M, Thijssen V, Bronsaer RJ, Grohé C, et al. 17beta-estradiol antagonizes cardiomyocyte hypertrophy by autocrine/paracrine stimulation of a guanylyl cyclase A receptor-cyclic guanosine monophosphate-dependent protein kinase pathway. *Circulation.* (2004) 109:269–76. doi: 10.1161/01.CIR.0000105682.85732.BD
40. Spina RJ, Ogawa T, Miller TR, Kohrt WM, Ehsani AA. Effect of exercise training on left ventricular performance in older women free of cardiopulmonary disease. *Am J Cardiol.* (1993) 71:99–104. doi: 10.1016/0002-9149(93)90718-R
41. Barnes JN, Fu Q. Sex-Specific ventricular and vascular adaptations to exercise. *Adv Exp Med Biol.* (2018) 1065:329–46. doi: 10.1007/978-3-319-77932-4_21
42. Spina RJ, Miller TR, Bogenhagen WH, Schechtman KB, Ehsani AA. Gender-related differences in left ventricular filling dynamics in older subjects after endurance exercise training. *J Gerontol A Biol Sci Med Sci.* (1996) 51:B232–7. doi: 10.1093/gerona/51A.3.B232
43. Lakatta EG. Cardiovascular regulatory mechanisms in advanced age. *Physiol Rev.* (1993) 73:413–67. doi: 10.1152/physrev.1993.73.2.413
44. Lakatta EG, Gerstenblith G, Angell CS, Shock NW, Weisfeldt ML. Diminished inotropic response of aged myocardium to catecholamines. *Circ Res.* (1975) 36:262–9. doi: 10.1161/01.RES.36.2.262
45. Lakatta EG, Yin FC. Myocardial aging: functional alterations and related cellular mechanisms. *Am J Physiol.* (1982) 242:H927–41. doi: 10.1152/ajpheart.1982.242.6.H927
46. Stratton JR, Levy WC, Schwartz RS, Abrass IB, Cerqueira MD. Beta-adrenergic effects on left ventricular filling: influence of aging and exercise training. *J Appl Physiol.* (1994) 77:2522–9. doi: 10.1152/jappl.1994.77.6.2522
47. Spina RJ. Cardiovascular adaptations to endurance exercise training in older men and women. *Exerc Sport Sci Rev.* (1999) 27:317–32. doi: 10.1249/00003677-199900270-00012
48. Levy WC, Cerqueira MD, Abrass IB, Schwartz RS, Stratton JR. Endurance exercise training augments diastolic filling at rest and during exercise in healthy young and older men. *Circulation.* (1993) 88:116–26. doi: 10.1161/01.CIR.88.1.116
49. Ehsani AA, Ogawa T, Miller TR, Spina RJ, Jilka SM. Exercise training improves left ventricular systolic function in older men. *Circulation.* (1991) 83:96–103. doi: 10.1161/01.CIR.83.1.96
50. Haykowsky M, Scott J, Esch B, Schopflocher D, Myers J, Paterson I, et al. A meta-analysis of the effects of exercise training on left ventricular remodeling following myocardial infarction: start early and go longer for greatest exercise benefits on remodeling. *Trials.* (2011) 12:92. doi: 10.1186/1745-6215-12-92
51. Zhang YM, Lu Y, Tang Y, Yang D, Wu HF, Bian ZP, et al. The effects of different initiation time of exercise training on left ventricular remodeling and cardiopulmonary rehabilitation in patients with left ventricular dysfunction after myocardial infarction. *Disabil Rehabil.* (2016) 38:268–76. doi: 10.3109/09638288.2015.1036174
52. McGregor G, Gaze D, Oxborough D, O'Driscol J Shave R. Reverse left ventricular remodelling: effect of cardiac rehabilitation exercise training in myocardial infarction patients with preserved ejection fraction. *Eur J Phys Rehabil Med.* (2016) 52:370–8.
53. Giallauria F, Cirillo P, Lucci R, Pacileo M, De Lorenzo A, D'Agostino M, et al. Left ventricular remodelling in patients with moderate systolic dysfunction after myocardial infarction: favourable effects of exercise training and predictive role of N-terminal pro-brain natriuretic peptide. *Eur J Cardiovasc Prev Rehabil.* (2008) 15:113–8. doi: 10.1097/HJR.0b013e3282f00990
54. Giallauria F, Acampa W, Ricci F, Vitelli A, Torella G, Lucci R, et al. Exercise training early after acute myocardial infarction reduces stress-induced hypoperfusion and improves left ventricular function. *Eur J Nucl Med Mol Imaging.* (2013) 40:315–24. doi: 10.1007/s00259-012-2302-x
55. Haddadzadeh MH, Maiya AG, Padmakumar R, Shad B, Mirbolouk F. Effect of exercise-based cardiac rehabilitation on ejection fraction in coronary artery disease patients: a randomized controlled trial. *Heart Views.* (2011) 12:51–7. doi: 10.4103/1995-705X.86013
56. Belardinelli R, Georgiou D, Ginzton L, Cianci G, Purcaro A. Effects of moderate exercise training on thallium uptake and contractile response to low-dose dobutamine of dysfunctional myocardium in patients with ischemic cardiomyopathy. *Circulation.* (1998) 97:553–61. doi: 10.1161/01.CIR.97.6.553
57. Belardinelli R, Belardinelli L, Shryock J. Effects of dipyridamole on coronary collateralization and myocardial perfusion in patients with ischaemic cardiomyopathy. *Eur Heart J.* (2001) 22:1205–13. doi: 10.1053/euhj.2000.2446
58. Giallauria F, Acampa W, Ricci F, Vitelli A, Maresca L, Mancini M, et al. Effects of exercise training started within 2 weeks after acute myocardial infarction on myocardial perfusion and left ventricular function: a gated SPECT imaging study. *Eur J Prev Cardiol.* (2012) 19:1410–9. doi: 10.1177/1741826711425427
59. Chen YM, Li ZB, Zhu M, Cao YM. Effects of exercise training on left ventricular remodelling in heart failure patients: an updated meta-analysis of randomised controlled trials. *Int J Clin Pract.* (2012) 66:782–91. doi: 10.1111/j.1742-1241.2012.02942.x
60. Erbs S, Linke A, Gielen S, Fiehn E, Walther C, Yu J, et al. Exercise training in patients with severe chronic heart failure: impact on left ventricular performance and cardiac size. A retrospective analysis of the leipzig heart failure training trial. *Eur J Cardiovasc Prev Rehabil.* (2003) 10:336–44. doi: 10.1097/01.hjr.0000099031.38268.27
61. Erbs S, Höllriegel R, Linke A, Beck EB, Adams V, Gielen S, et al. Exercise training in patients with advanced chronic heart failure (NYHA IIIb) promotes restoration of peripheral vasomotor function, induction of endogenous regeneration, and improvement of left ventricular function. *Circ Heart Fail.* (2010) 3:486–94. doi: 10.1161/CIRCHEARTFAILURE.109.868992
62. Tucker WJ, Beaudry RI, Liang Y, Clark AM, Tomczak CR, Nelson MD, et al. Meta-analysis of exercise training on left ventricular ejection fraction in heart failure with reduced ejection fraction: a 10-year update. *Prog Cardiovasc Dis.* (2019) 62:163–71. doi: 10.1016/j.pcad.2018.08.006
63. Pearson MJ, Mungovan SF, Smart NA. Effect of exercise on diastolic function in heart failure patients: a systematic review and meta-analysis. *Heart Fail Rev.* (2017) 22:229–42. doi: 10.1007/s10741-017-9600-0
64. Hambrecht R, Gielen S, Linke A, Fiehn E, Yu J, Walther C, et al. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure: a randomized trial. *JAMA.* (2000) 283:3095–101. doi: 10.1001/jama.283.23.3095
65. Kitzman DW, Brubaker PH, Herrington DM, Morgan TM, Stewart KP, Hundley WG, et al. Effect of endurance exercise training on endothelial function and arterial stiffness in older patients with heart failure and preserved ejection fraction. *J Am Coll Cardiol.* (2013) 62:584–92. doi: 10.1016/j.jacc.2013.04.033
66. Mueller S, Winzer EB, Duvinage A, Gevaert AB, Edelmann F, Haller B, et al. Effect of high-intensity interval training, moderate continuous training, or guideline-based physical activity advice on peak oxygen consumption in patients with heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA.* (2021) 325:542–51. doi: 10.1001/jama.2020.26812

67. Fukuta H, Goto T, Wakami K, Kamiya T, Ohte N. Effects of exercise training on cardiac function, exercise capacity, and quality of life in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. *Heart Fail Rev*. (2019) 24:535–47. doi: 10.1007/s10741-019-09774-5
68. Leggio M, Mazza A, Cruciani G, Sgorbini L, Pugliese M, Bendini MG, et al. Effects of exercise training on systo-diastolic ventricular dysfunction in patients with hypertension: an echocardiographic study with tissue velocity and strain imaging evaluation. *Hypertens Res.* (2014) 37:649–54. doi: 10.1038/hr.2014.44
69. Molmen-Hansen HE, Stolen T, Tjonna AE, Aamot IL, Ekeberg IS, Tyldum GA, et al. Aerobic interval training reduces blood pressure and improves myocardial function in hypertensive patients. *Eur J Prev Cardiol.* (2012) 19:151–60. doi: 10.1177/1741826711400512
70. Sahin AA, Ozben B, Sunbul M, Yagci I, Sayar N, Cincin A, et al. The effect of cardiac rehabilitation on blood pressure, and on left atrial and ventricular functions in hypertensive patients. *J Clin Ultrasound.* (2021) 49:456–65. doi: 10.1002/jcu.22956
71. Verboven M, Van Ryckeghem L, Belkhouribchia J, Dendale P, Eijnde BO, Hansen D, et al. Effect of exercise intervention on cardiac function in type 2 diabetes mellitus: a systematic review. *Sports Med.* (2019) 49:255–68. doi: 10.1007/s40279-018-1003-4
72. Cassidy S, Thoma C, Hallsworth K, Parikh J, Hollingsworth KG, Taylor R, et al. High intensity intermittent exercise improves cardiac structure and function and reduces liver fat in patients with type 2 diabetes: a randomised controlled trial. *Diabetologia.* (2016) 59:56–66. doi: 10.1007/s00125-015-3741-2
73. Hollekim-Strand SM, Bjørgaas MR, Albrektsen G, Tjønna AE, Wisløff U, Ingul CB. High-intensity interval exercise effectively improves cardiac function in patients with type 2 diabetes mellitus and diastolic dysfunction: a randomized controlled trial. *J Am Coll Cardiol.* (2014) 64:1758–60. doi: 10.1016/j.jacc.2014.07.971
74. Murray J, Bennett H, Bezak E, Perry R. The role of exercise in the prevention of cancer therapy-related cardiac dysfunction in breast cancer patients undergoing chemotherapy: systematic review. *Eur J Prev Cardiol.* (2021) 9:zwab006. doi: 10.1093/eurjpc/zwab006
75. St John Sutton MG, Sharpe N. Left ventricular remodeling after myocardial infarction pathophysiology and therapy clinical cardiology: new frontiers. *Circulation.* (2000) 101:2981–8. doi: 10.1161/01.CIR.101.25.2981
76. Aimo A, Gaggin HK, Barison A, Emdin M, Januzzi JL Jr. Imaging, biomarker, and clinical predictors of cardiac remodeling in heart failure with reduced ejection fraction. *JACC Heart Fail.* (2019) 7:782–794. doi: 10.1016/j.jchf.2019.06.004
77. Taylor RS, Brown A, Ebrahim S, Jolliffe J, Noorani H, Rees K, et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *Am J Med.* (2004) 116:682–92. doi: 10.1016/j.amjmed.2004.01.009
78. Anderson L, Thompson DR, Oldridge N, Zwisler AD, Rees K, Martin N, et al. Exercise-based cardiac rehabilitation for coronary heart disease: cochrane systematic review and meta-analysis. *J Am Coll Cardiol.* (2016) 67:1–12. doi: 10.1016/j.jacc.2015.10.044
79. Prior BM, Yang HT, Terjung RL. What makes vessels grow with exercise training? *J Appl Physiol.* (2004) 97:1119–28. doi: 10.1152/japplphysiol.00035.2004
80. Adams V, Linke A, Krankel N, Erbs S, Gielen S, Möbius-Winkler S, et al. Impact of regular physical activity on the NAD(P)H oxidase and angiotensin receptor system in patients with coronary artery disease. *Circulation.* (2005) 111:555–62. doi: 10.1161/01.CIR.0000154560.88933.7E
81. Linke A, Erbs S, Hambrecht R. Exercise and the coronary circulation—alterations and adaptations in coronary artery disease. *Prog Cardiovasc Dis.* (2006) 48:270–84. doi: 10.1016/j.pcad.2005.10.001
82. Ahmad T, Fiuzat M, Mark DB, Neely B, Neely M, Kraus WE, et al. The effects of exercise on cardiovascular biomarkers in patients with chronic heart failure. *Am Heart J.* (2014) 167:193–202.e1. doi: 10.1016/j.ahj.2013.10.018
83. Kenchaiah S, Pfeffer MA. Cardiac remodeling in systemic hypertension. *Med Clin North Am.* (2004) 88:115–30. doi: 10.1016/S0025-7125(03)00168-8
84. Brook RD, Appel LJ, Rubenfire M, Ogedegbe G, Bisognano JD, Elliott WJ, et al. Beyond medications and diet: alternative approaches to lowering blood pressure: a scientific statement from the American heart association. *Hypertension*. (2013) 61:1360–80. doi: 10.1161/HYP.0b013e318293645f
85. López-Valenciano A, Ruiz-Pérez I, Ayala F, Sánchez-Meca J; Vera-Garcia FJ. Updated systematic review and meta-analysis on the role of isometric resistance training for resting blood pressure management in adults. *J Hypertens.* (2019) 37:1320–33. doi: 10.1097/HJH.0000000000002022
86. Seferović PM, Paulus WJ. Diabetic cardiomyopathy—fact or fiction? Clinical diabetic cardiomyopathy: a two-faced disease with restrictive and dilated phenotypes. *Eur Heart J.* (2015) 36:1718–27. doi: 10.1093/eurheartj/ehv134
87. Leung M, Wong VW, Hudson M, Yeung DY. Impact of improved glycemic control on cardiac function in type 2 diabetes mellitus. *Circ Cardiovasc Imaging*. (2016) 9:e003643. doi: 10.1161/CIRCIMAGING.115.003643
88. Van Ryckeghem L, Keytsman C, Verbaanderd E, Frederix I, Bakelants E, Petit T, et al. Asymptomatic type 2 diabetes mellitus display a reduced myocardial deformation but adequate response during exercise. *Eur J Appl Physiol.* (2021) 121:929–40. doi: 10.1007/s00421-020-04557-5
89. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American society of echocardiography and the European association of cardiovascular imaging. *J Am Soc Echocardiogr.* (2014) 27:911–39. doi: 10.1016/j.echo.2014.07.012
90. Holland DJ, Prasad SB, Marwick TH. Contribution of exercise echocardiography to the diagnosis of heart failure with preserved ejection fraction (HFpEF). *Heart.* (2010) 96:1024–8. doi: 10.1136/hrt.2009.183947
91. Donal E, Lund LH, Oger E, Reynaud A, Schnell F, Persson H, et al. Value of exercise echocardiography in heart failure with preserved ejection fraction: a substudy from the KaRen study. *Eur Heart J Cardiovasc Imaging.* (2016) 17:106–13. doi: 10.1093/ehjci/jev144
92. Borlaug BA, Olson TP, Lam CS, Flood KS, Lerman A, Johnson BD, et al. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. *J Am Coll Cardiol.* (2010) 56:845–54. doi: 10.1016/j.jacc.2010.03.077
93. Meluzín J, Sitar J, Krístek J, Prosecky R, Pesl M, Podrouzková H, et al. The role of exercise echocardiography in the diagnostics of heart failure with normal left ventricular ejection fraction. *Eur J Echocardiogr.* (2011) 12:591–602. doi: 10.1093/ejechocard/jer082
94. La Gerche A, Claessen G, Van de Bruaene A, Pattyn N, Van Cleemput J, Gewillig M, et al. Cardiac MRI: a new gold standard for ventricular volume quantification during high-intensity exercise. *Circ Cardiovasc Imaging.* (2013) 6:329–38. doi: 10.1161/CIRCIMAGING.112.980037
95. Jekic M, Foster EL, Ballinger MR, Raman SV, Simonetti OP. Cardiac function and myocardial perfusion immediately following maximal treadmill exercise inside the MRI room. *J Cardiovasc Magn Reson.* (2008) 10:3. doi: 10.1186/1532-429X-10-3
96. Le TT, Bryant JA, Ting AE, Ho PY, Su B, Teo RC, et al. Assessing exercise cardiac reserve using real-time cardiovascular magnetic resonance. *J Cardiovasc Magn Reson.* (2017) 19:7. doi: 10.1186/s12968-017-0322-1
97. Kirkham AA, Goonasekera MV, Mattiello BC, Grenier JG, Haykowsky MJ, Thompson RB. Reliability and reproducibility of cardiac MRI quantification of peak exercise function with long-axis views. *PLoS ONE.* (2021) 16:e0245912. doi: 10.1371/journal.pone.0245912
98. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol.* (2005) 25:932–43. doi: 10.1161/01.ATV.0000160548.78317.29
99. Townsend RR, Wilkinson IB, Schiffrin EL, Avolio AP, Chirinos JA, Cockcroft JR, et al. American heart association council on hypertension. Recommendations for improving and standardizing vascular research on arterial stiffness: a scientific statement from the American heart association. *Hypertension.* (2015) 66:698–722. doi: 10.1161/HYP.0000000000000033
100. Roman MJ, Naqvi TZ, Gardin JM, Gerhard-Herman M, Jaff M, Mohler E, et al. American society of echocardiography report. Clinical application of noninvasive vascular ultrasound in cardiovascular risk stratification: a report from the American society of echocardiography and the society for vascular medicine and biology. *Vasc Med.* (2006) 11:201–11. doi: 10.1177/1358863x06070511
101. Thompson RB, Tomczak CR, Haykowsky MJ. Evaluation of cardiac, vascular, and skeletal muscle function with MRI: novel physiological end

points in cardiac rehabilitation research. *Can J Cardiol.* (2016) 32:S388–96. doi: 10.1016/j.cjca.2016.07.006
102. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol.* (2010) 55:1318–27. doi: 10.1016/j.jacc.2009.10.061
103. Lorenz MW, Polak JF, Kavousi M, Mathiesen EB, Völzke H, Tuomainen TP, et al. Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. *Lancet*. (2012) 379:2053–62. doi: 10.1016/S0140-6736(12)60441-3
104. Willeit P, Tschiderer L, Allara E, Reuber K, Seekircher L, Gao L, et al. Carotid intima-media thickness progression as surrogate marker for cardiovascular risk: meta-analysis of 119 clinical trials involving 100 667 patients. *Circulation.* (2020) 142:621–42. doi: 10.1161/CIRCULATIONAHA.120.046361
105. Kaess BM, Rong J, Larson MG, Hamburg NM, Vita JA, Levy D, et al. Aortic stiffness, blood pressure progression, and incident hypertension. *JAMA.* (2012) 308:875–81. doi: 10.1001/2012.jama.10503
106. Chae CU, Pfeffer MA, Glynn RJ, Mitchell GF, Taylor JO, Hennekens CH. Increased pulse pressure and risk of heart failure in the elderly. *JAMA.* (1999) 281:634–9. doi: 10.1001/jama.281.7.634
107. Tanaka H, Dinenno FA, Monahan KD, Clevenger CM, DeSouza CA, Seals DR. Aging, habitual exercise, and dynamic arterial compliance. *Circulation.* (2000) 102:1270–5. doi: 10.1161/01.CIR.102.11.1270
108. Madden KM, Lockhart C, Cuff D, Potter TF, Meneilly GS. Short-term aerobic exercise reduces arterial stiffness in older adults with type 2 diabetes, hypertension, and hypercholesterolemia. *Diabetes Care.* (2009) 32:1531–5. doi: 10.2337/dc09-0149
109. Oliveira NL, Ribeiro F, Alves AJ, Campos L, Oliveira J. The effects of exercise training on arterial stiffness in coronary artery disease patients: a state-of-the-art review. *Clin Physiol Funct Imaging.* (2014) 34:254–62. doi: 10.1111/cpf.12093
110. Laskey W, Siddiqi S, Wells C, Lueker R. Improvement in arterial stiffness following cardiac rehabilitation. *Int J Cardiol.* (2013) 167:2734–8. doi: 10.1016/j.ijcard.2012.06.104
111. Byrkjeland R, Stensæth KH, Anderssen S, Njerve IU, Arnesen H, Seljeflot I, et al. Effects of exercise training on carotid intima-media thickness in patients with type 2 diabetes and coronary artery disease. Influence of carotid plaques. *Cardiovasc Diabetol.* (2016) 15:13. doi: 10.1186/s12933-016-0336-2
112. Madden KM, Lockhart C, Cuff D, Potter TF, Meneilly GS. Aerobic training-induced improvements in arterial stiffness are not sustained in older adults with multiple cardiovascular risk factors. *Hum Hypertens.* (2013) 27:335–9. doi: 10.1038/jhh.2012.38
113. Montero D, Roche E, Martinez-Rodriguez A. The impact of aerobic exercise training on arterial stiffness in pre- and hypertensive subjects: a systematic review and meta-analysis. *Int J Cardiol.* (2014) 13:361–8. doi: 10.1016/j.ijcard.2014.03.072
114. Way KL, Keating SE, Baker MK, Chuter VH, Johnson NA. The effect of exercise on vascular function and stiffness in type 2 diabetes: a systematic review and meta-analysis. *Curr Diabetes Rev.* (2016) 12:369–83. doi: 10.2174/1573399811666150817124601
115. Jones LM, Stoner L, Baldi JC, McLaren B. Circuit resistance training and cardiovascular health in breast cancer survivors. *Eur J Cancer Care.* (2020) 29:e13231. doi: 10.1111/ecc.13231
116. Beaudry RI, Liang Y, Boyton ST, Tucker WJ, Brothers RM, Daniel KM, et al. Meta-analysis of exercise training on vascular endothelial function in cancer survivors. *Integr Cancer Ther.* (2018) 17:192–9. doi: 10.1177/1534735418756193
117. Marti CN, Gheorghiade M, Kalogeropoulos AP, Georgiopoulou VV, Quyyumi AA, Butler J. Endothelial dysfunction, arterial stiffness, and heart failure. *J Am Coll Cardiol.* (2012) 60:1455–69. doi: 10.1016/j.jacc.2011.11.082
118. Kitzman DW, Herrington DM, Brubaker PH, Moore JB, Eggebeen J, Haykowsky MJ. Carotid arterial stiffness and its relationship to exercise intolerance in older patients with heart failure and preserved ejection fraction. *Hypertension.* (2013) 61:112–9. doi: 10.1161/HYPERTENSIONAHA.111.00163
119. Fujiwara K, Shimada K, Nishitani-Yokoyama M, Kunimoto M, Matsubara T, Matsumori R, et al. Arterial stiffness index and exercise tolerance in patients undergoing cardiac rehabilitation. *Int Heart J.* (2021) 62:230–7. doi: 10.1536/ihj.20-418
120. Bulluck H, Hammond-Haley M, Weinmann S, Martinez-Macias R, Hausenloy DJ. Myocardial infarct size by CMR in clinical cardioprotection studies: insights from randomized controlled trials. *JACC Cardiovasc Imaging.* (2017) 10:230–40. doi: 10.1016/j.jcmg.2017.01.008
121. Ingkanisorn WP, Rhoads KL, Aletras AH, Kellman P, Arai AE. Gadolinium delayed enhancement cardiovascular magnetic resonance correlates with clinical measures of myocardial infarction. *J Am Coll Cardiol.* (2004) 43:2253–9. doi: 10.1016/j.jacc.2004.02.046
122. Wong TC, Piehler K, Meier CG, Testa SM, Klock AM, Aneizi AA, et al. Association between extracellular matrix expansion quantified by cardiovascular magnetic resonance and short-term mortality. *Circulation.* (2012) 126:1206–16. doi: 10.1161/CIRCULATIONAHA.111.089409
123. Treibel TA, Fridman Y, Bering P, Sayeed A, Maanja M, Frojdh F, et al. Extracellular volume associates with outcomes more strongly than native or post-contrast myocardial T1. *JACC Cardiovasc Imaging.* (2020) 13:44–54. doi: 10.1016/j.jcmg.2019.03.017
124. Reinstadler SJ, Stiermaier T, Liebetrau J, Fuernau G, Eitel C, de Waha S, et al. Prognostic significance of remote myocardium alterations assessed by quantitative noncontrast T1 mapping in ST-segment elevation myocardial infarction. *JACC Cardiovasc Imaging.* (2018) 11:411–9. doi: 10.1016/j.jcmg.2017.03.015
125. Vita T, Gräni C, Abbasi SA, Neilan TG, Rowin E, Kaneko K, et al. Comparing CMR mapping methods and myocardial patterns toward heart failure outcomes in nonischemic dilated cardiomyopathy. *JACC Cardiovasc Imaging.* (2019) 12:1659–69. doi: 10.1016/j.jcmg.2018.08.021
126. Tham EB, Haykowsky MJ, Chow K, Spavor M, Kaneko S, Khoo NS, et al. Diffuse myocardial fibrosis by T 1-mapping in children with subclinical anthracycline cardiotoxicity: relationship to exercise capacity, cumulative dose and remodeling. *J Cardiovasc Magn Reson.* (2013) 15:48. doi: 10.1186/1532-429X-15-48
127. Jordan JH, Vasu S, Morgan TM, D'Agostino RB Jr, Meléndez GC, Hamilton CA, et al. Anthracycline-associated T1 mapping characteristics are elevated independent of the presence of cardiovascular comorbidities in cancer survivors. *Circ Cardiovasc Imaging.* (2016) 9:e004325. doi: 10.1161/CIRCIMAGING.115.004325
128. Kirkham AA, Goonasekera MV, Mattiello BC, Grenier JG, Haykowsky MJ, Thompson RB. Aerobic fitness is related to myocardial fibrosis post-anthracycline therapy. *Med Sci Sports Exerc.* (2021) 53:267–74. doi: 10.1249/MSS.0000000000002469
129. Costello BT, Roberts TJ, Howden EJ, Bigaran A, Foulkes SJ, Beaudry RI, et al. Exercise attenuates cardiotoxicity of anthracycline chemotherapy measured by global longitudinal strain. *JACC CardioOncol.* (2019) 1:298–301. doi: 10.1016/j.jaccao.2019.09.002
130. Despres JP. Body fat distribution and risk of cardiovascular disease: an update. *Circulation.* (2012) 126:1301–13. doi: 10.1161/CIRCULATIONAHA.111.067264
131. Hausman GJ, Basu U, Du M, Fernyhough-Culver M, Dodson MV. Intermuscular and intramuscular adipose tissues: bad vs. good adipose tissues. *Adipocyte.* (2014) 3:242–55. doi: 10.4161/adip.28546
132. Neeland IJ, Ross R, Després JP, Matsuzawa Y, Yamashita S, Shai I, et al. Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement. *Lancet Diabetes Endocrinol.* (2019) 7:715–25. doi: 10.1016/S2213-8587(19)30084-1
133. Haykowsky MJ, Nicklas BJ, Brubaker PH, Hundley WG, Brinkley TE, Upadhya B, et al. Regional adipose distribution and its relationship to exercise intolerance in older obese patients who have heart failure with preserved ejection fraction. *JACC Heart Fail.* (2018) 6:640–9. doi: 10.1016/j.jchf.2018.06.002
134. Ying W, Sharma K, Yanek LR, Vaidya D, Schär M, Markl M, et al. Visceral adiposity, muscle composition, and exercise tolerance in heart failure with preserved ejection fraction. *ESC Heart Failure.* (2021) 8:2535–45. doi: 10.1002/ehf2.13382
135. Cespedes Feliciano EM, Chen WY, Bradshaw PT, Prado CM, Alexeeff S, Albers KB, et al. Adipose tissue distribution and cardiovascular disease

risk among breast cancer survivors. *J Clin Oncol.* (2019) 37:2528–36. doi: 10.1200/JCO.19.00286
136. Verheggen RJ, Maessen MF, Green DJ, Hermus AR, Hopman MT, Thijssen DH. A systematic review and meta-analysis on the effects of exercise training versus hypocaloric diet: distinct effects on body weight and visceral adipose tissue. *Obes Rev.* (2016) 17:664–90. doi: 10.1111/obr.12406
137. Mirman AM, Nardoni NR, Chen AY, Horwich TB. Body composition changes during traditional versus intensive cardiac rehabilitation in coronary artery disease. *J Cardiopulm Rehabil Prev.* (2020) 40:388–93. doi: 10.1097/HCR.0000000000000497
138. Takagawa Y, Yagi S, Ise T, Ishii A, Nishikawa K, Fukuda D, et al. Improved exercise capacity after cardiac rehabilitation is associated with reduced visceral fat in patients with chronic heart failure. *Int Heart J.* (2017) 58:746–54. doi: 10.1536/ihj.16-454
139. Fang H, Liu C, Cavdar O. The relation between submaximal aerobic exercise improving vascular elasticity through loss of visceral fat and antihypertensive. *Clin Exp Hypertens.* (2021) 43:203–10. doi: 10.1080/10641963.2020.1847127
140. Sabag A, Way KL, Keating SE, Sultana RN, O'Connor HT, Baker MK, et al. Exercise and ectopic fat in type 2 diabetes: a systematic review and meta-analysis. *Diabetes Metab.* (2017) 43:195–210. doi: 10.1016/j.diabet.2016.12.006
141. Pituskin E, Haykowsky M, McNeely M, Mackey J, Chua N, Paterson I. Rationale and design of the multidisciplinary team IntervenTion in cArdio-oNcology study (TITAN). *BMC Cancer.* (2016) 16:733. doi: 10.1186/s12885-016-2761-8
142. Dieli-Conwright CM, Courneya KS, Demark-Wahnefried W, Sami N, Lee K, Buchanan TA, et al. Effects of aerobic and resistance exercise on metabolic syndrome, sarcopenic obesity, and circulating biomarkers in overweight or obese survivors of breast cancer: a randomized controlled trial. *J Clin Oncol.* (2018) 36:875–83. doi: 10.1200/JCO.2017.75.7526
143. Thompson RB, Pagano JJ, Chow K, Sekowski V, Paterson I, Ezekowitz J, et al. Sub-clinical pulmonary edema is associated with reduced exercise capacity in heart failure with reduced or preserved ejection fraction. *J Am Coll Cardiol.* (2017) 70:1827–8. doi: 10.1016/j.jacc.2017.07.787
144. Foulkes SJ, Howden EJ, Antill Y, Loi S, Salim A, Haykowsky MJ, et al. Exercise as a diagnostic and therapeutic tool for preventing cardiovascular morbidity in breast cancer patients–the BReast cancer EXercise InTervention (BREXIT) trial protocol. *BMC Cancer.* (2020) 20:655. doi: 10.1186/s12885-020-07123-6
145. Kirkham AA, Paterson DI, Prado CM, Mackey JR, Courneya KS, Pituskin E, et al. Rationale and design of the caloric restriction and exercise protection from anthracycline toxic effects (CREATE) study: a 3-arm parallel group phase II randomized controlled trial in early breast cancer. *BMC Cancer.* (2018) 18:864. doi: 10.1186/s12885-018-4778-7
146. Butler T, Kerley CP, Altieri N, Alvarez J, Green J, Hinchliffe J, et al. Optimum nutritional strategies for cardiovascular disease prevention and rehabilitation (BACPR). *Heart.* (2020) 106:724–31. doi: 10.1136/heartjnl-2019-315499
147. Ignarro LJ, Balestrieri ML, Napoli C. Nutrition, physical activity, and cardiovascular disease: an update. *Cardiovasc Res.* (2007) 73:326–40. doi: 10.1016/j.cardiores.2006.06.030
148. Brandhorst S, Longo VD. Dietary restrictions and nutrition in the prevention and treatment of cardiovascular disease. *Circ Res.* (2019) 124:952–65. doi: 10.1161/CIRCRESAHA.118.313352
149. Prado CM, Anker SD, Coats AJS, Laviano A, von Haehling S. Nutrition in the spotlight in cachexia, sarcopenia and muscle: avoiding the wildfire. *J Cachexia Sarcopenia Muscle.* (2021) 12:3–8. doi: 10.1002/jcsm.12673
150. Freimann S, Scheinowitz M, Yekutieli D, Feinberg MS, Eldar M, Kessler-Icekson G. Prior exercise training improves the outcome of acute myocardial infarction in the rat. Heart structure, function, and gene expression. *J Am Coll Cardiol.* (2005) 45:931–8. doi: 10.1016/j.jacc.2004.11.052
151. Aït Mou Y, Reboul C, Andre L, Lacampagne A, Cazorla O. Late exercise training improves non-uniformity of transmural myocardial function in rats with ischaemic heart failure. *Cardiovasc Res.* (2009) 81:555–64. doi: 10.1093/cvr/cvn229
152. Lee J, Cho HS, Park S, Kim WK. Regular exercise produced cardioprotective effects on rat's heart with hypertension induced by L-NAME administration. *Clin Exp Hypertens.* (2009) 31:364–75. doi: 10.1080/10641960902977924
153. Ghignatti PVC, Nogueira LJ, Lehnen AM, Leguisamo NM. Cardioprotective effects of exercise training on doxorubicin-induced cardiomyopathy: a systematic review with meta-analysis of preclinical studies. *Sci Rep.* (2021) 11:6330. doi: 10.1038/s41598-021-83877-8
154. Melo SFS, da Silva Júnior ND, Barauna VG, Oliveira EM. Cardiovascular adaptations induced by resistance training in animal models. *Int J Med Sci.* (2018) 15:403–10. doi: 10.7150/ijms.23150
155. Feng R, Wang L, Li Z, Yang R, Liang Y, Sun Y, et al. A systematic comparison of exercise training protocols on animal models of cardiovascular capacity. *Life Sci.* (2019) 217:128–40. doi: 10.1016/j.lfs.2018.12.001

Conflict of Interest: DIP reports consultant fees from Alnylam and Pfizer.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: frontiersin.org/about/contact

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership