OPTIMIZATION OF EXERCISE COUNTERMEASURES FOR HUMAN SPACE FLIGHT – LESSONS FROM TERRESTRIAL PHYSIOLOGY AND OPERATIONAL IMPLEMENTATION

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PUBLISHED IN: Frontiers in Physiology

frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88963-473-6
DOI 10.3389/978-2-88963-473-6

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OPTIMIZATION OF EXERCISE COUNTERMEASURES FOR HUMAN SPACE FLIGHT – LESSONS FROM TERRESTRIAL PHYSIOLOGY AND OPERATIONAL IMPLEMENTATION

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Human spaceflight has required space agencies to study and develop exercise countermeasure (CM) strategies to manage the profound, multi-system adaptation of the human body to prolonged microgravity (μG). Future space exploration will present new challenges in terms of adaptation management that will require the attention of both exercise physiologists and operational experts. In the short to medium-term, all exploration missions will be realised using relatively small vehicles/habitats, with some exploration scenarios including surface operations in low (<1G) gravity conditions.

The evolution of CM hardware has allowed modern-day astronauts to return to Earth with, on average, relatively moderate levels μG-induced adaptation of the musculoskeletal (MS) and cardiovascular (CV) systems. However, although the intense use of CM has attenuated many aspects of MS and CV adaptation, on an individual level, there remains wide variation in the magnitude of these changes. Innovations in CM programs have been largely engineering-driven, with new hardware providing capability for new modes of exercise and a wider range of exercise protocols, which, in turn, has facilitated the transfer of traditional, but effective, terrestrial concepts based around high frequency resistance (multiple-set, multiple repetition) and medium-intensity continuous aerobic training. As a result, International Space Station (ISS) CM specialists have focused their efforts in these domains, taking advantage of hardware innovations as and when they became available. However, terrestrial knowledge in human and exercise physiology has expanded rapidly during the lifetime of the ISS and, consequently, there is potential to optimize current approaches by re-examining terrestrial knowledge and identifying opportunities to implement this knowledge into operational practices.

Current terrestrial knowledge in exercise physiology is the product of a large number of intervention studies in which the variables that contribute to the effects of physical activity (mode, frequency, duration, intensity, recovery) have been controlled and systematically manipulated. However, due to limited opportunities to perform intervention studies in both spaceflight analogues – head-down bed rest (HDBR) being considered the 'gold standard' – and spaceflight itself, it will not be possible to systematically investigate the contribution of these factors to the efficacy of in-flight CM. As such, it will be necessary to draw on terrestrial evidence to identify solutions/strategies that may be best suited to the constraints of exploration and prioritise specific solutions/strategies for evaluation in HDBR and in flight.

Citation: Weber, T., Scott, J. P. R., Green, D. A., eds. (2020). Optimization of Exercise Countermeasures for Human Space Flight – Lessons from Terrestrial Physiology and Operational Implementation. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-88963-473-6

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frontiers in Physiology

EDITORIAL
published: 10 January 2020
doi: 10.3389/fphys.2019.01567

Editorial: Optimization of Exercise Countermeasures for Human Space Flight—Lessons From Terrestrial Physiology and Operational Implementation

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Keywords: microgravity, exercise countermeasures, human space exploration, cardiorespiratory, musculoskeletal

Editorial on the Research Topic

Optimization of Exercise Countermeasures for Human Space Flight – Lessons From Terrestrial Physiology and Operational Implementation

As we approach the 20th anniversary of the International Space Station (ISS), countermeasure (CM) exercise for human spaceflight has evolved from rudimentary physical activity into the complex, multi-modal programme that occupies ∼25% of each ISS working day. However, despite the long history of CM exercise, questions remain regarding both its efficacy and effectiveness, in particular with respect to the challenge of managing cardiorespiratory (CR) and musculoskeletal (MS) adaptation during future human exploration missions (Scott et al.). This Research Topic (RT) was a result of a Workshop convened in January 2018 at the European Space Agency's (ESA) European Astronaut Centre (EAC) in Cologne, Germany. In a series of invited reviews, 52 authors from 31 institutions have synthesized current terrestrial exercise physiology knowledge and considered how this might be employed to optimize future CM exercise.

Hurst et al. examined high-intensity interval training (HIT), which involves repeated bouts of intense exercise, interspersed with periods of rest or lower intensity active recovery. HIT can be performed with a range of exercise modalities, including those already available on ISS and the authors concluded that terrestrial data support its use as a time-efficient approach to improve aerobic fitness. Interestingly, recent data also suggests beneficial neuromuscular effects, such as increased muscle strength and power, and jump performance. As such, employment of HIT-type protocols may provide a time-efficient alternative to current exercise CM approaches without requiring new hardware.

Ralston et al. examined the effects of single-set and three-set resistance training on muscle strength changes for different body segments (upper and lower body) and joint types (single and multi-joint training). They concluded that, while three-sets are more effective, particularly in trained individuals, single-set programmes can also produce significant increases in muscular strength. As three-set training entails significantly greater training volume, single-set training may be a useful approach in the busy pre-flight period. For space exploration, where mission and life support system resources (e.g., food, water, oxygen) will be at a premium, this also suggests that single-set resistance exercise, whilst not optimal, might still be sufficient.

The performance of aerobic and resistance training is termed "concurrent" training, which may negatively impact training effectiveness. Jones et al. conclude that, if strength and aerobic exercise must be performed on the same day, strength training should be employed first, and ideally >4 h prior to aerobic training. While operational constraints will always exist and crew preferences must be considered to maximize adherence, this suggests that, wherever possible, CM resistance

OPEN ACCESS

Edited and reviewed by:
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Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: *23 October 2019*
Accepted: *12 December 2019*
Published: *10 January 2020*

Citation:
Scott JPR, Weber T and Green DA (2020) Editorial: Optimization of Exercise Countermeasures for Human Space Flight—Lessons From Terrestrial Physiology and Operational Implementation. Front. Physiol. 10:1567. doi: 10.3389/fphys.2019.01567

training should be performed first and ‘back-to-back’ (*i.e.* one immediately or shortly after the other) sessions (with aerobic training first) avoided.

One solution to the issue of concurrent training could be to use only one mode of exercise. Steele et al. examined the concept that adaptations to exercise are affected by the intensity of effort independent of modality. They concluded that, where effort and duration are matched, aerobic, and resistance training may produce broadly comparable physiological responses/adaptations, at least in terms of aerobic fitness and muscle strength/size. Thus, with appropriate protocols, one, uni-modal device might be sufficient for CM exercise, which has obvious advantages for exercise hardware provision and working volume requirements (Scott et al.). If one had to choose a mode, the authors conclude that resistance would provide the best outcomes. Candidate resistance training devices could be further simplified if the maximum training loads required were reduced. For instance, as reviewed by Behringer and Willberg, blood-flow restriction training requires only ∼30% of the one repetition maximum (1RM) to increase muscle mass and strength, although it presents challenges, particularly in terms of its safe implementation, which could potentially limit adoption in-flight.

Although the review of Steele et al. raises the possibility that a uni-modal CM program might be sufficient, their conclusions are based only on aerobic fitness and muscle strength/size data. However, CM exercise must also manage skeletal adaptation. Thus, Gruber et al. examined the effect of the stretch-shortening cycle (SSC), during which muscle activation generates high muscle forces via elastic energy storage and, critically, high skeletal strains, and strain rates. The authors show that plyometric-type exercises, such as jumping and hopping, and to a lesser extent whole-body vibration, activate the SSC and promote muscle and bone adaption. Furthermore, a summary of recent bed rest data provides evidence that CR and MS adaptation can be managed with only 3-min of jumping exercise per day using a horizontal sledge-jump device.

Although a plyometric-based CM exercise programme would require new hardware and engineering integration solutions (e.g., vibration isolation), it suggests that spaceflight adaption could potentially be managed with a single, uni-modal device *and* consuming significantly less time and life support resources compared with the current multi-modal ISS programme. Moreover, as discussed by Laurens et al., reducing the total energy expenditure associated with CM exercise may also serve to reduce the risk of a negative energy balance and its associated consequences. With an improved understanding of the time course of CR and MS adaptation to both microgravity (μG) and CM exercise, the efficiency of a CM exercise programme could be further optimized by the interspersion of fixed periods of abstinence. Winnard et al. provided an initial analysis of muscle outcome measures from bed rest Control groups, reporting that “moderate” effects are evident by 7–15 days, and “large” effects by 28–56 days of unloading.

In the absence of body weight in μG and thus the requirement for postural control, significant adaptation occurs in the spine and its surrounding structures including the lumbopelvic and spinal muscles. This is associated with lower-back pain and possibly an increased risk of intervertebral disc herniation. The current ISS CM exercise programme is not optimized to activate the core musculature and Hides et al. reviewed terrestrial strategies for restoring muscle size and function that could be implemented or adapted for use in μG.

All of the above assumes that CM exercise device(s) are constantly available. However, a comprehensive CM strategy must consider the possibility that devices are not available (due to failure), cannot be used (due to crew injury) or use limited (due to mission dynamics). As such, this RT also considered “complementary” CM strategies that could enhance the effects of, or reduce reliance on, exercise. In this context, Willis et al. examined the influence of hypoxia on responses to exercise training, while Maffiuletti et al. provided an overview of neuromuscular electrical stimulation (NMES) and some practical recommendations as an adjunct to exercise. In the case of the later, whilst NMES-based resistance training has potential, it may not be suitable for all muscles and the skeletal and cardiovascular effects are still largely unknown. Finally, evidence reviewed by Guillot and Debarnot suggests that motor imagery (MI) improves motor performance and learning in a similar manner to actual practice of the corresponding movement. As such, when muscle activation is not possible during a mission, such as following a MS injury, MI may provide a strategy to minimize motor performance decrements, although definition of optimal approaches is needed.

In summary, the constraints of future space missions present unique challenges that must be addressed if exercise is to remain at the heart of the CM programme. We hope that this RT will contribute to the identification of strategies which, together, will result in an effective, efficient, and comprehensive CM strategy suitable for implementation irrespective of specific mission scenarios. With so many factors to consider and limited opportunities to evaluate new approaches, this will require an international effort. This effort could, and should, be led by the recently formed International Crew Health & Performance Working Group (ICHP), with representatives from the National Aeronautics and Space Administration (NASA), the Roscosmos State Corporation for Space Activities (Roscosmos), and the European (ESA), Japanese (JAXA) and Canadian (CSA) Space Agencies, chartered to facilitate coordination of requirements, risks, and capability demonstration plans for the forthcoming ‘Gateway’ and beyond.

AUTHOR CONTRIBUTIONS

All authors contributed to the first draft of the manuscript, manuscript revision, and read and approved the submitted version.

Conflict of Interest: JS, TW, and DG are all employed by KBR GmbH, Cologne, Germany.

frontiers in Physiology

PERSPECTIVE
published: 07 March 2019
doi: 10.3389/fphys.2019.00173

Introduction to the Frontiers Research Topic: Optimization of Exercise Countermeasures for Human Space Flight – Lessons From Terrestrial Physiology and Operational Considerations

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OPEN ACCESS

Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Environmental, Aviation and Space Physiology, a section of the journal Frontiers in Physiology

Received: 30 August 2018
Accepted: 12 February 2019
Published: 07 March 2019

Citation:
Scott JPR, Weber T and Green DA (2019) Introduction to the Frontiers Research Topic: Optimization of Exercise Countermeasures for Human Space Flight – Lessons From Terrestrial Physiology and Operational Considerations. Front. Physiol. 10:173. doi: 10.3389/fphys.2019.00173

Exercise in space has evolved from rudimental testing into the multi-modal countermeasure (CM) program used on the International Space Station (ISS). However, with the constraints of future exploration missions, replicating this program will be a significant challenge. Recent ISS data suggest that crew now experience only relatively moderate levels of microgravity (μG)-induced adaptation, although significant variation remains, with some crew displaying marked changes despite significant time/effort investment. This suggests that the efficacy of exercise CMs is yet to be optimized for *all* individuals. With the current suite of exercise devices operational for almost a decade, and with exploration approaching, it is timely to re-visit the terrestrial literature to identify new knowledge relevant to the management of μG adaptation. As such, the aim of the Frontiers Research Topic *Optimization of Exercise Countermeasures for Human Space Flight – Lessons from Terrestrial Physiology and Operational Considerations,* is to synthesize current terrestrial exercise physiology knowledge and consider how this might be employed to optimize the use of exercise CM. The purpose of this Perspective, which serves as a preface to the Research Topic is threefold: to briefly review the use and apparent efficacy of exercise in space, to consider the impact of the transition from ISS to exploration mission vehicles and habitats, and to identify areas of terrestrial exercise physiology where current knowledge might contribute to the optimization of CM exercise for exploration. These areas include individual variation, high intensity interval training, strength development/maintenance, concurrent training, plyometric/impact exercise, and strategies to enhance exercise efficacy.

Keywords: microgravity, exercise countermeasures, human space exploration, cardiovascular, musculoskeletal

Abbreviations: ARED, Advanced Resistive Exercise Device; BMD, mean bone mineral density; CEVIS, cycle ergometer with vibration isolation and stabilization system; CM, countermeasure; CO_2, carbon dioxide; ESA, European Space Agency; HDBR, head-down bed rest; HIIT, high-intensity interval training; HR, heart rate; HR_{max}, maximum heart rate; iRED, interim resistive exercise device; ISS, international space station; LDM, long-duration mission; NASA, The National Aeronautics and Space Administration; TVIS, Treadmill Vibration Isolation System; US, United States; USOS, US Orbital Segment; VO_{2max}, maximal oxygen uptake; VO_{2peak}, peak oxygen uptake; μG, microgravity.

INTRODUCTION

Exposure to microgravity (μG) and the space environment results in a profound multi-system adaptation, characterized by both short- (Ortega and Harm, 2008) and long-term changes, including reductions in maximum oxygen uptake (VO_{2max}), muscle size and strength, and bone mineral density (BMD) (Demontis et al., 2017). As these changes appear to reflect those that occur with prolonged inactivity or the absence of gravitational loading, since the early days of human spaceflight, physical exercise has been identified as a potential method of managing the adaptation process (Berry et al., 1962; Moore et al., 2010). Today, exercise is the cornerstone of the International Space Station (ISS) μG countermeasure (CM) program for long duration missions (LDMs), with approximately 25% of each working day allocated to aerobic and resistance exercise including time to change clothing, set-up and stow hardware, and post-exercise hygiene (Loehr et al., 2015).

Space agencies are turning their attention to human missions beyond Low Earth Orbit. Such missions, and the vehicles and habitats used to execute them, will place even tighter constraints upon the use of exercise, including working volume (e.g., size and internal dimensions), environmental (e.g., removal of CO_2, heat and moisture), logistical (e.g., supply of food and water, and device maintenance/repair) and operational (e.g., time for exercise, interference with other crewmembers' work) challenges. Some of these constraints are self-evident (e.g., smaller vehicles/working volumes) (Gerstenmaier and Crusan, 2018; National Aeronautics and Space Administration [NASA], 2018c), whereas others will emerge only once key technological hardware limitations are understood and mission scenarios clearly defined. Irrespective, it is clear that a direct transfer of the ISS exercise CM program to exploration missions will be challenging.

Terrestrial exercise physiology knowledge is constantly evolving, driven by both the investigation of new ideas and the accumulation of evidence that either supports or questions existing principles. The current ISS CM exercise program and the suite of devices around which it is based has been operational for almost a decade, and, with the dawn of human space exploration approaching, it is timely to re-visit the terrestrial literature to identify where this knowledge might inform the future use of exercise to manage μG adaptation.

The aim of this Perspective, which serves as a preface to the Frontiers Research Topic *Optimization of Exercise Countermeasures for Human Space Flight – Lessons from Terrestrial Physiology and Operational Considerations*, is threefold: to briefly review the use and apparent efficacy of exercise in space, to consider the impact of the transition from ISS to exploration mission vehicles and habitats, and identify potential areas where terrestrial exercise physiology knowledge might contribute to the optimization of future spaceflight CM exercise. The Research Topic will focus primarily on the United States (US) space program due to the availability of information from NASA concerning its historical programs and current US Orbital Segment (USOS) crew, and because is currently leading the way in the development of exploration transport vehicles (National Aeronautics and Space Administration [NASA], 2018c) and habitats (Gerstenmaier and Crusan, 2018).

'Optimization' in the context of exercise CM may be defined in a number of ways depending on the specific goal(s) of the program. These goals might include maintenance of pre-flight physical status (i.e., prevent adaptation), preservation of sufficient capacity to safely execute mission tasks and/or function immediately on landing, a rapid return to pre-flight status in the post-flight period, or to minimize the risk of long-term health consequences. Alternatively, an optimal CM could simply be the approach that achieves the greatest physiological effect in the largest proportion of the target population. However, for the purposes of this Perspective and of future human space exploration, 'optimization' is defined by the goals of:

(1) maintaining sufficient physiological function in *all* crew to achieve mission-specific tasks, both nominal and off-nominal/emergency, including those immediately on landing, without approaching the limits of their physical capacity;
(2) using an exercise program than requires minimal additional utilization of mission and life support system resources.

THE USE OF EXERCISE IN SPACE: A BRIEF HISTORY

For a comprehensive history of the use of aerobic exercise in space, the reader is directed to the review of Moore et al. (2010) and for a concise summary of the exercise hardware available during each era, to Hackney et al. (2015). Initially use of physical activity in the US space program sought to explore the physiological effects of the μG environment, and only later was it considered as a potential CM for musculoskeletal and cardiovascular adaptation. The first medical observations on humans were made during Project Mercury. Crewmembers performed rudimentary exercise tests by pulling on a bungee cord (16lb [7.25 kg] at full extension) whilst evaluating cardiovascular reactivity. Despite the short mission durations, some post-flight postural hypotension was observed on return to Earth, resulting in NASA's Aerospace Medical Operations Office concluding in 1962 that a "*prescribed inflight exercise program may be necessary to preclude symptoms in case of the need for an emergency egress soon after landing*" (Berry et al., 1962).

The Gemini Program (1961–1966) provided the first series of studies detailing the physiological response to spaceflight during missions of up to 14-days. Exercise testing consisted of 30-s exercise sessions using a bungee pull cord device (Berry and Catterson, 1967). Post-flight testing of Gemini VII crew, suggested, albeit indirectly, that as little as 14-days in space significantly reduced aerobic exercise capacity (Dietlein and Rapp, 1966).

The Apollo Program (1961–1972) was the first to use in-flight exercise as a countermeasure. Whilst no formal exercise program was planned, all crewmembers used (with varying frequency and intensity) the 'Apollo Exerciser,' a modified commercial-off-the-shelf variable resistance rope friction device (**Figure 1**)

FIGURE 1 | Hardware used for exercise countermeasures. *Top Row* (from left to right): ESA Astronaut Alexander Gerst exercising using the advanced resistive exercise device (ARED) on the International Space Station (ISS); Copyright: ESA/NASA: Id 312342); ESA Astronaut Frank de Winne using the T2 treadmill on ISS (Copyright: NASA: ISS021-E-007807); ESA Astronaut Luca Parmitano using the Cycle Ergometer with Vibration Isolation and Stabilization System (CEVIS) on ISS (Copyright: ESA/NASA: Id 300078). *Middle Row* (from left to right): NASA Astronaut Dan Tani, Expedition 16 Flight Engineer, using the Interim Resistive Exercise Device (iRED) on ISS (Copyright: NASA: ID iss016e027909); Astronaut Joseph Tanner, STS-97 Mission Specialist, using the cycle ergometer aboard the Space Shuttle Endeavour (Copyright: NASA: ID sts097-317-017); Astronaut Sandra Magnus, Expedition 18 Flight Engineer, equipped with a bungee harness, using the Treadmill with Vibration Isolation and Stabilization System (TVIS) in the Zvezda Service Module on ISS (Copyright: NASA: NASA ID iss018e030096). *Bottom Row* (from left to right): The 'Apollo Exerciser' used by Apollo 11 astronauts during their July 1969 mission (Photo by Eric F. Long, Smithsonian National Air and Space Museum [NASM 2009-4775] Used with Permission [Permission Number: 19-BK-063]); The Teflon-covered treadmill-like device used during Skylab 4 (Photo Credit: NASA).

(Scheuring et al., 2007). The physiological benefits of such training are unclear (Orlee, 1973), although in-flight, crew reported that exercise helped with rest, relaxation, and stretching cramped and aching muscles (Scheuring et al., 2007).

Skylab (SL, 1973–1974) was utilized for three manned missions. SL-2 (28-days) crew were allocated 30 min/day for exercise and used the M171 cycle ergometer (286W maximum workload) (Michel et al., 1977), with protocols recommended, but not imposed (Sawin et al., 1975). On the recommendation of SL-2 crew, SL-3 (56-days) crew were allocated 60-min/day for exercise (Johnston, 1977). A modified commercial isokinetic device ("Mini-Gym" or MK-1) was also provided, as well as a pair of handles between which up to five extension springs could be attached ("MK-2") (Thornton and Rummel, 1977). Exercise allowance during SL-4 (84-days) was further increased to 90-min/day (Johnston, 1977) and a rudimentary treadmill-like system provided, consisting of a Teflon-covered surface with rubber bungee restraints (**Figure 1**) (Thornton and Rummel, 1977). Due to high loads on the calf muscles, exercise was limited to 10 min/day of walking, jumping, or jogging.

Leg extensor strength was reduced by ∼25% in SL-2 (0.9%/day) and SL-3 (0.4%/day), and by <10% (0.1%/day) during SL-4, with crew standing and walking without apparent difficulty on the day after landing/recovery (R+1) (Thornton and Rummel, 1977). Heart rate at 75% maximum work rate was unchanged during SL-2, SL-3 (Michel et al., 1975) and SL-4 (Michel et al., 1977). Despite ergometer workload limitations, it was concluded that SL-4 crew maintained, or even increased their aerobic capacity (Sawin et al., 1975), whilst post-flight recovery of numerous cardiovascular parameters appeared more rapid from SL-2 to SL-4 (Michel et al., 1977).

Space Shuttle (135 flights, 1981–2011) missions ranged from 2 to 17 days. A cycle ergometer (**Figure 1**) was the primary exercise device, although two treadmills and a rower were also evaluated (Hackney et al., 2015). Flight Rules stated that exercise should be performed no less than every other day for the Commander, Pilot and Flight Engineer, and every third day for Mission and Payload Specialists, but intensity and duration were not prescribed (Lee et al., 2015). Peak oxygen uptake (VO_{2peak}) was maintained during flights up to 14-days, but reduced 22% immediately post-flight (R+0), presumably due to reductions in blood volume, stroke volume and cardiac output (Levine et al., 1996).

The Extended Duration Orbiter Medical Project included comparisons of exercising and non-exercising Shuttle crew (Sawin et al., 1999). Individual exercise volume varied considerably, but whereas non-exercisers (and cycling only) showed a significant (12–13%) decrease in VO_{2max}, treadmill (−3%) and rower (-6%) users showed little change, although the former tended to be tested sooner after landing. Compared with crew who exercised < 3 sessions/week, crew who exercised ≥ 3 sessions/week had a lower HR response and maintained pulse pressure during a post-flight standing (orthostatic) test (Lee et al., 1999). Additionally, crew who exercised at ≥ 70% maximum HR (HR_{max}) demonstrated the smallest (−9 vs. −15 to −23%) reduction in VO_2 during exercise at 85% HR_{max} (Hayes et al., 2013).

THE CURRENT USE OF EXERCISE ON THE ISS AND ITS EFFECTIVENESS IN MANAGING SPACEFLIGHT ADAPTATION

For detailed overviews of the current USOS countermeasure program, the reader is directed to Hackney et al. (2015), Korth (2015), and Loehr et al. (2015). Briefly, the key characteristics are:

- Consists of both aerobic and resistance exercise;
- High-frequency program, consisting of two sessions/day (1x 30–45 min of aerobic and 1x 45-min of resistance), 6-days/week;
- Multi-modal, utilizing one resistance device [the Advanced Resistive Exercise Device, (ARED)] and two aerobic devices [a treadmill (T2), and the Cycle Ergometer with Vibration Isolation and Stabilization System, CEVIS] (**Figure 1**);
- Aerobic and resistance sessions are completed on the same day, sometimes with only a minimal break in-between;
- T2 allows running speeds up to 20.4 km/h (12.7 m/h) with vertical loads equivalent to 54.4–68.0 kg (120–150 lbs). In 2010, T2 replaced the Treadmill with Vibration Isolation and Stabilization System (TVIS) (**Figure 1**), which had a maximum speed of only 10 m/h (Korth, 2015) and produced foot forces that were substantially lower than during walking/running on Earth (Cavanagh et al., 2010; Genc et al., 2010);
- CEVIS provides workloads up to 350 W at 120 rpm (Danish Aerospace Company, 2018);
- Aerobic sessions consist of steady-state and interval-type protocols, with target intensities of 75–80 and 60–90% VO_{2max};
- ARED engages all major muscle groups, with loads up to 272 kg (600 lb). In 2009, ARED replaced the interim resistive exercise device (iRED) (**Figure 1**), which suffered from wide variations in load with position and rate of change of position, had its maximum load limited to 136 kg (Korth, 2015), and, like TVIS, resulted foot forces that were substantially less than on Earth (Cavanagh et al., 2010; Genc et al., 2010);
- Resistance protocols are multi-set, multi-repetition for the lower and upper body, with initial loads calculated from a 10-repetition maximum load (plus 75% of bodyweight to compensate for the absence of bodyweight) and adjusted thereafter based on actual performance.

A significant challenge in estimating exercise CM effectiveness is the absence of astronauts who have performed no CM exercise. On ISS, Flight Rules dictate that all LDM crewmembers perform exercise, which precludes abstinence and intervention studies with a 'no exercise' control group. As a result, the effectiveness of exercise CM can only be compared to previous missions (Sibonga et al., 2015), or to a time prior to a significant change in hardware, such as the replacement of iRED with ARED (English et al., 2015; Sibonga et al., 2015).

In ISS crew, BMD loss is approximately 3% at the lumbar spine, 6% at the hip and pelvis, and significantly less than that measured in MIR crew (117–438 days missions) except at the femoral neck (Sibonga et al., 2015). However, individual variation is marked, with some crew still losing 10–15% (1.7–2.5%/month based on a 6-month mission), as shown in a recent paper (see **Figure 2**, Sibonga et al., 2015). Replacement of iRED with ARED has reduced bone loss at all sites (−2.6 to −4.1 vs. −3.7 to −6.6). Isokinetic muscle strength in the trunk and lower limbs is reduced by 8–17% post-flight (lower 95% confidence intervals from −12 to over −20%), whilst ARED has, as yet, not significantly attenuated strength decrements vs. iRED (English et al., 2015). Compared with pre-flight, mean VO_{2peak} during cycling declines 17% early in-flight and recovers only slightly thereafter (Moore et al., 2014), whilst being reduced by 15% (vs. pre-flight) on R+1. Again, there is significant individual variation, with some retaining their pre-flight VO_{2peak} at Flight Day (FD)180, whilst others lose up to 25%. In addition, whilst fitter crew who achieve higher exercise intensities appear to sustain their pre-flight VO_{2peak}, they also appear more prone to the losses early in flight (Moore et al., 2014). On R+0 the proportion of ISS astronauts unable to complete an orthostatic tolerance test was 66% (4/6) compared with 20% (13/65) in Shuttle astronauts (Lee et al., 2015) and 83% (5/6) in Mir crew (Meck et al., 2001). Finally, in 10 tests of functional fitness including sit-and-reach, agility, calisthenics and strength, post-flight decrements at R+5-7 were seen only in sit-and-reach (−8%), agility (−11%), less press (−3%), and grip strength (−5%) (Laughlin et al., 2015).

THE FUTURE USE OF EXERCISE FOR HUMAN EXPLORATION MISSIONS

As described above, the evolution of ISS exercise CM hardware has enabled the comprehensive (i.e., not limited in terms of duration, frequency, or intensity/overload) adoption of terrestrial exercise training concepts, including continuous and interval-type aerobic exercise and high-intensity, multi-set/rep resistance training. Training programes based on these concepts appear to result in, *on average*, relatively moderate levels of μG-induced musculoskeletal and cardiorespiratory system adaptation, although significant individual variation remains. It is evident, therefore, that the efficacy of ISS exercise CMs are yet to be optimized for *all* individuals. Moreover, with the constraints of future exploration missions, direct transfer of the ISS CM exercise program will be a significant challenge. NASA's Orion vehicle has a habitable volume of less than 9 m^3 (compared to 388 m^3 on ISS) (National Aeronautics and Space Administration [NASA], 2018b,c), whilst the current concept of the Lunar Orbital Platform-Gateway, where crew may spend up to 30-days, envisions only two habitation modules, plus one utilization module (Gerstenmaier and Crusan, 2018). As a result, simply replicating the current efficacy of exercise CM during future exploration missions may be difficult. Furthermore, the size of these vehicles/habitats (limiting storage) and their remoteness from Earth (limiting re-supply) may, for the first time, require the burden of exercise on the supply of food (to maintain energy

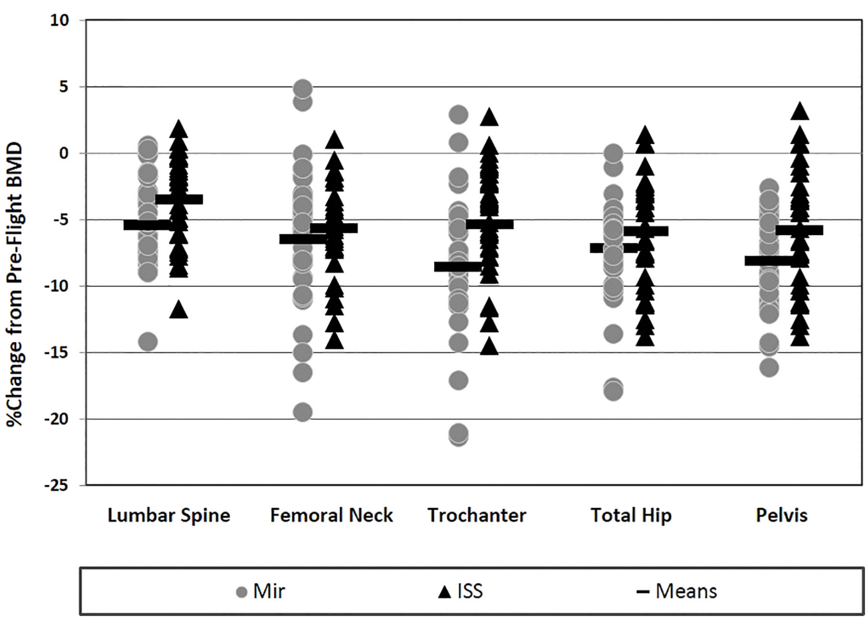

FIGURE 2 | Inter-individual variation in changes in bone mineral density (BMD) with long-duration spaceflight. Depicted are relative (%) changes from pre- to post-flight in ISS (n = 33, triangles) and Mir (n = 35, circles) crewmembers. BMD was measured using Dual-energy X-ray absorptiometry (DXA). (Figure reprinted with permission from: *Evaluating Bone Loss in ISS Astronauts,* Sibonga et al., 2015).

balance), and water (to maintain euhydration), as well as on the environmental management system's regulation of atmospheric CO_2, heat and moisture, to be considered (Matsuo et al., 2012; Scott et al., 2018). Taken together, it is clear that innovative approaches will be required.

A significant barrier in identifying new approaches is the limited opportunities to perform controlled intervention studies, both in space and in spaceflight analogs, of which long-duration head-down (typically −6°) bed rest (HDBR) is considered the 'gold standard' (Pavy-Le Traon et al., 2007; Hargens and Vico, 2016). Research in space is both costly and time-consuming, and NASA's 'SPRINT' study (National Aeronautics and Space Administration [NASA], 2018a), which is evaluating a high intensity, low volume exercise training that has shown encouraging results in both HDBR (Ploutz-Snyder et al., 2018) and μG (Goetchius et al., 2019), is a rare example of a controlled, in-flight exercise training intervention study. Even here, however, the control group will not refrain from exercise, but continue to perform normal ISS CM exercise. Despite running since 2011, the recent publication of SPRINT results highlights the time-consuming nature of this type of research. Albeit less so than space studies, HDBR campaigns are also expensive and challenging, but offer greater experimental control and allow questions to be answered more quickly. However, at present, HDBR campaigns are organized at a rate of only 1–2 per year, are not exclusively focused on exercise CM, and, in the near future at least, may be subject to other priorities (e.g., artificial gravity) (Clément, 2017).

A NEW FRONTIERS RESEARCH TOPIC

Almost a decade has past since the current suite of ISS exercise devices became operational, and with exploration missions approaching yet limited opportunities to evaluate new strategies, it is an opportune moment to re-visit the terrestrial exercise physiology literature to inform current and future exercise CM strategies. This literature includes a large number of controlled intervention studies in which exercise variables (i.e., mode, frequency, duration, workload, time-under-tension, recovery) have been controlled and systematically manipulated. This body of knowledge has expanded rapidly during the lifetime of the ISS and traditional exercise concepts have been re-visited and established beliefs challenged. As such, the literature may contain novel information to help identify strategies that may be both effective and compatible with exploration constraints. Topics identified as potentially conducive to the optimization of in-flight CM exercise include, but are not limited to:

- Individual variation: real variation vs. within-subject random variation (Atkinson and Batterham, 2015);
- High intensity interval training: efficacy and safety (Weston et al., 2014; Milanović et al., 2015);
- Strength development and maintenance: the contribution of different training variables to the effectiveness of resistance training (Ralston et al., 2017);
- Concurrent training: the scheduling of aerobic and resistance exercise for maximizing training gains (Wilson et al., 2012);
- 'Combined training': resistance exercise benefits across multiple physiological systems (Taylor et al., 2015; Paoli et al., 2017);
- Plyometric/impact exercise: effects on both the musculoskeletal *and* cardiovascular systems (Kramer et al., 2017);
- 'Efficient' training: is the efficacy of exercise training maintained when volume (e.g., duration, frequency) is reduced? (Metcalfe et al., 2012; Baker et al., 2013);
- The role of nutrition in promoting adaptations to exercise training (Hawley et al., 2011; Papageorgiou et al., 2018);
- Complementary strategies: CM that could enhance the effects of, or reduce reliance on, exercise (Carraro et al., 2015; Hackney et al., 2016).

These topics are to be evaluated initially in terms of the strength of the terrestrial evidence-base, then by potential operational advantages over current exercise CM approaches, and finally by the opportunities/challenges associated with integrating them into human spaceflight operations.

Therefore, the aim of the Frontiers Research Topic *Optimization of Exercise Countermeasures for Human Space Flight – Lessons from Terrestrial Physiology and Operational Considerations* is to synthesize current exercise physiology knowledge and consider how it might be employed to optimize the use of exercise to manage μG-induced adaptation.

AUTHOR CONTRIBUTIONS

JS, TW, and DG wrote and edited the article.

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Conflict of Interest Statement: All authors are employed by KBRWyle GbmH, Cologne, Germany.

frontiers in Physiology

MINI REVIEW
published: 25 January 2019
doi: 10.3389/fphys.2019.00033

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Application of Blood Flow Restriction to Optimize Exercise Countermeasures for Human Space Flight

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In recent years there has been a strong increase in publications on blood flow restriction (BFR) training. In particular, the fact that this type of training requires only low resistance to induce muscle strength and mass gains, makes BFR training interesting for athletes and scientists alike. For the same reason this type of training is particularly interesting for astronauts working out in space. Lower resistance during training would have the advantage of reducing the risk of strain-induced injuries. Furthermore, strength training with lower resistances would have implications for the equipment required for training under microgravity conditions, as significantly lower resistances have to be provided by the training machines. Even though we are only about to understand the effects of blood flow restriction on exercise types other than low-intensity strength training, the available data indicate that BFR of leg muscles is also able to improve the training effects of walking or running at slow speeds. The underlying mechanisms of BFR-induced functional and structural adaptations are still unclear. An essential aspect seems to be the premature fatigue of Type-I muscle fibers, which requires premature recruitment of Type-II muscle fibers to maintain a given force output. Other theories assume that cell swelling, anabolic hormones, myokines and reactive oxygen species are involved in the mediation of BFR training-related effects. This review article is intended to summarize the main advantages and disadvantages, but also the potential risks of such training for astronauts.

Keywords: human space flight, exercise countermeasure, adaptations to microgravity, BFR training, space adaptations

OPEN ACCESS

Edited by:
Jonathan Paul Richard Scott, KBRwyle GmbH, Germany

Reviewed by:
Y. Gul Ozkaya, Akdeniz University, Turkey
Ginés Viscor, University of Barcelona, Spain

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Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: *31 October 2018*
Accepted: *11 January 2019*
Published: *25 January 2019*

Citation:
Behringer M and Willberg C (2019) Application of Blood Flow Restriction to Optimize Exercise Countermeasures for Human Space Flight. Front. Physiol. 10:33. doi: 10.3389/fphys.2019.00033

INTRODUCTION

Human Spaceflight is still a technical and life science challenge. It is well known, that there are several hazards for the human body in space due to microgravity exposure, radiation, sensory deprivation, the disruption of circadian rhythms as well as the artificial environment (Dayanandan, 2011). In short- and long-term space flights, microgravity has physiological effects on the cardiovascular and musculoskeletal system, solving in compromised aerobic capacity, a decrease of bone density and mineral content as well as muscular atrophy and loss of muscular strength (Widrick et al., 1999; Fitts et al., 2001; Sibonga et al., 2007; Trappe et al., 2009). In order to counteract these changes, special training equipment for use in microgravity was developed and used quite early in the history of manned spaceflight. During the 28- to 84-day Skylab missions in the 1970s, a cycle ergometer was shipped to the international space station (ISS). However, even with a daily training program on the ergometer, the astronauts' maximum oxygen uptake, muscle mass and bone density was decreased on their return from the Skylab missions (Sawin et al., 1976; Vernikos and Schneider, 2010). More recent data indicate that tendon fibers are also adversely affected by prolonged exposure to microgravity (Galloway et al., 2013; McCrum et al., 2018).

Much time has passed since these early Skylab missions and the training equipment for use in microgravity has been continuously refined since then (for review see Loerch, 2015). In the belief that high mechanical forces are required as training stimuli to prevent the musculoskeletal system from being de-adapted, a special focus has been placed on the development of exercise devices that can realize these high mechanical forces (Loerch, 2015). As a result of these efforts, astronauts currently have a multifunctional strength training device the Advanced Resistive Exercise Device (ARED) available, which can realize high resistances of up to up to 110 kg for cable and 270 kg for bar exercises (Trappe et al., 2009). Since it is well documented that resistance training with moderate to high loads is effective in inducing muscle mass and strength gains both on earth (Garber et al., 2011) and under microgravity conditions (Loehr et al., 2011), the availability of the ARED on the ISS is a major step forward for the maintenance of astronauts' health.

Although, it seems obvious that unloading is best compensated by the application of training stimuli that primarily place mechanical stress on the musculoskeletal system, there is a growing body of evidence, indicating that low-load resistance training also provides a potent training stimulus, when combined with blood flow restriction (BFR) (Kubota et al., 2008; Hackney et al., 2012; Schoenfeld, 2013; Lixandrão et al., 2018). The resistances used in BFR-training averages 30% of the one repetition maximum (1RM) which is well below the lower limits recommended for strength training (Schoenfeld, 2013). Nevertheless, muscle mass and strength gains induced by BFR-training, are comparable to that of high-intensity training regimen (Loenneke et al., 2012b). For use in microgravity, lower resistances during training would have the advantage of reducing the risk of strain-induced injuries for astronauts (Scheuring et al., 2009; Gabbett, 2016). Furthermore, it would have implications for the equipment required for training under microgravity conditions, as significantly lower resistances have to be provided by the training machines. This would comply with challenges of future space missions as vehicle resources, intra- and extravehicular physical constraints or access to earth-based monitoring (Loerch, 2015). Moreover, BFR has been shown to place a potent, gravitation-like stimulus on the cardiovascular system which may reduce the orthostatic intolerance upon the return to Earth (Iida et al., 2007; Nakajima et al., 2008).

This review article summarizes the possible advantages and disadvantages of BFR training in microgravity to counteract muscle atrophy, discusses the underlying mechanisms, and addresses the question of whether bones and tendons could also benefit from BFR training.

EFFECTS OF MICROGRAVITY ON THE MUSCULOSKELETAL SYSTEM

Prolonged mechanical unloading is well known to result in a significant de-adaptation of the musculoskeletal system (Lloyd et al., 2014). Muscle atrophy is thought to primarily result from a decreased protein synthesis based on a reduced activation of the IGF1-Akt-mTOR and the FAK-Akt-mTOR pathways (Gao et al., 2018). While the former seems to result from an unloading associated insulin resistance and an impaired insulin-like growth factor (IGF-1) signaling, the latter signaling pathway is directly affected by the elimination of mechanical stress, as the mechanosensitive focal adhesion kinase (FAK) is no longer activated (Graham et al., 2015). Bone loss is mainly driven by an altered differentiation of mesenchymal stem cells by an impaired integrin/mitogen protein kinase pathway due to mitogen-activated protein kinase (MAPK) (Yang et al., 2005). Beside integrins, osteocytes perceive mechanical stress via interstitial fluid, causing a biological cascade which results in WNt/β-catenin signaling that triggers bone remodeling (Rochefort and Benhamou, 2013). This and the dysfunction of osteoblasts, expressed due to reduced osteoblast proliferation and activity as well as a reduced cell differentiation lead to an impaired bone formation (Arfat et al., 2014). In comparison to muscle and bone, tendons have so far received little attention regarding adaptation to space flight. However, it is known that tendons adapt to the load that they have to withstand (Vanderby et al., 1990). With the lack of mechanical stress, as it appears in microgravity, proteoglycan and collagen synthesis get inhibited, leading to changes in structure (loss of diameter and density) and in chemical compositions (Johnson et al., 2005).

IN-FLIGHT EXERCISE PROTOCOLS

In-flight exercise protocols are generally designed to minimize the loss in aerobic capacity, bone, muscle strength and endurance and to counteract neuromuscular dysfunction. The main goal thereby is to maintain in-flight and post-flight performance capabilities of the astronauts (Loehr et al., 2015). Crewmembers are commanded to adhere to their personal exercise protocols, including resistance (ARED) and cardiovascular exercise on a Treadmill or Veloergometer with Vibration Isolation and Stabilization System (TVIS, CEVIS). The training devices save personal data as well as physiological and training parameter, which allows the Mission Control Center (based on Earth) to adjust individual exercise schedules. Since the installation of the ARED in the International Space Station Expedition 18, high resistances can be applied during strength training on the ISS and the device allows about 29 different exercises. However, the ARED is very space-consuming and carries the potential risk of being temporarily unavailable due to technical faults (Hanson et al., 2014; Loehr et al., 2015), which motivates the search for and the exploration of smaller and technically simpler devices (Behringer et al., 2016). In addition, high training intensities are associated with an increased risk of injury to the musculoskeletal system (Gabbett, 2016), a fact to be taken seriously, as training-related injuries are the most common source of injury to astronauts on board the ISS (Scheuring et al., 2009). Therefore, the question arises whether BFR training can be a reasonable alternative or supplement for in-flight training sessions. In the following sections, the effects of primarily mechanical stimuli on the musculature are briefly presented and compared with those of more metabolically accentuated stimuli through BFR training.

HIGH MECHANICAL TENSION AS TRAINING STIMULUS FOR MUSCLES, BONES, AND TENDONS

High mechanical tension is well known as a potent stimulus to trigger muscle growth (Spurway and Wackerhage, 2006; Schoenfeld, 2010), bone mineral accrual (Bolam et al., 2013), and tendon stiffness (Brumitt and Cuddeford, 2015). In case of skeletal muscles, the mechanical forces are converted into intracellular anabolic signals by mechanosensors that are sensitive to the magnitude and the duration of the applied external force (Greenberg et al., 2016). Downstream processes are thought to be regulated by Akt/mTOR pathway (Latres et al., 2005), whereby mechanical tension stimulates mammalian target of rapamycin (mTOR) directly (Hornberger et al., 2006) or $p70^{S6K}$ is phosphorylated (independent of mTOR) by phosphatidic acid (Lehman et al., 2007). Both pathways increase the protein synthesis of skeletal muscle cells. Furthermore, evidence suggests that mechanical tension activates the mechanosensitive FAK, which upregulates mTOR and thereby the protein synthesis (Chen et al., 1996; Bloch and Gonzalez-Serratos, 2003). However, the fact that high-intensity strength training is often accompanied by neuronal adjustments but only slight increases in muscle growth. Behm (1995) suggests that muscular tension alone cannot be responsible for muscle growth. Beside mechanical tension, stretch, cell swelling, systemic hormonal release, hypoxia, muscle damage, and ROS production are discussed as further reasons, activating anabolic signaling in skeletal muscle cells (Spurway and Wackerhage, 2006; Ozaki et al., 2015; de Freitas et al., 2017).

High mechanical forces placed on the musculoskeletal system result in bone matrix deformations inducing shear stress by bone fluid perturbations and cell membrane deformations through tethering elements of the glycocalyx (Bonewald and Johnson, 2008). Fluid flow, as well as intramedullary pressure are supposed to be influenced by mechanical loading, as well as vascular blood pressure, resulting in changing anabolic stimuli (Qin et al., 2003; Stevens et al., 2006). This mechanical stress is sensed by osteocytes (sensor cells) that transmit the signal to osteoblasts and osteoclasts (effector cells), ultimately stimulating bone formation on both, trabecular and cortical bone (Fujimura et al., 1997; Mi et al., 2005; Fritton and Weinbaum, 2009). Evidence is given, that biomarkers of bone formation like osteocalcin or bone-specific alkaline phosphatase (B-ALP) are increased after resistance training. Especially high training loads correlate with this response (Fujimura et al., 1997; Hu et al., 2011). However, since bone cells rapidly desensitize from mechanical stimuli intermittent loading regimens are necessary to allow for a resensitization of mechanoreceptors (Robling et al., 2002a,b; Saxon et al., 2005). Recent investigations expect the wingless-type (Wnt)/β-catenin canonical signaling pathway to be an important regulator in this process (Rochefort and Benhamou, 2013). While in osteoblasts, this pathway is crucial for synthesis, proliferation, and differentiation of the bone matrix, it enables osteocytes to transmit the sensed mechanical signals to cells on the bone surface.

Similar to the mechanisms in muscles and bones, mechanical tension in the tendon leads to the activation of mechanotransduction pathways, causing anabolic tissue responses (Arampatzis et al., 2009). Depending on the duration, frequency and intensity of the mechanical stimulus, the matrix protein synthesis, the expression and arrangement of collagen fibers as well as the expression of proteoglycans are adapted (Arampatzis et al., 2007). According to Arampatzis et al. (2007), the applied mechanical tension needs to exceed a certain threshold to induce adaptations of mechanical and morphological properties. This is supported by Kubo et al. (2006), who found that high- but not low-load isokinetic training of the knee extensors increased the stiffness of the vastus lateralis tendon–aponeurosis.

METABOLIC STRESS AS AN ANABOLIC SIGNAL FOR THE MUSCULATURE

The mechanisms underlying the BFR-mediated muscle mass and strength gains still remain unclear. Since the mechanical load during this type of resistance training is low, it is assumed that the metabolic stress is primarily responsible for the induced adaptations. This is supported by the observation of Takada et al. (2012) who reported that hypertrophy and strength gains were correlated with the decrease of the intramuscular pH (hypertrophy: $r = 0.80$; strength gains: $r = 0.65$) and the accumulation of inorganic phosphate (hypertrophy: $r = 0.88$; strength gains: $r = 0.60$) during low-intensity (20% 1RM) BFR-training.

BFR-associated metabolic stress is a consequence of decreased oxygen supply caused by reduced blood flow (Kon et al., 2012), resulting in an impairment of the aerobic metabolism and premature fatigue of the aerobic slow-twitch fibers (Scott et al., 2014). Despite low external loads, the skeletal muscle is forced under these conditions to recruit fast-twitching muscle fibers to maintain force output, which further aggravates the accumulation of metabolites (Loenneke et al., 2011a). The accumulated metabolites are thought to provoke a reflex inhibition of alpha-motoneurons via type III and IV afferents resulting in a further increase of type II motor unit recruitment

(Scott et al., 2014). Some authors see the recruitment of fast-twitch fibers as one of the central mechanisms by which BFR can trigger hypertrophy (Pope et al., 2013; Pearson and Hussain, 2015). Others believe that the acute release of anabolic hormones such as the human growth hormone (Abe et al., 2012; Pope et al., 2013; Park et al., 2015) or IGF-1 (Loenneke et al., 2011a; Scott et al., 2014; Park et al., 2015; Pearson and Hussain, 2015) contributes significantly to the BFR-mediated effects on muscle growth. The release of growth hormone appears to be associated with metabolic stress via the metaboreflex. This reflex is caused by locally accumulated metabolites activating metaboreceptors, which in turn activate the hypothalamic-pituitary axis via type III and IV afferents (Inagaki et al., 2011). Acute releases of catecholamines (e.g., norephrine response) have also been discussed as a factor for the exercise induced protein synthesis (Pope et al., 2013). However, several researchers have questioned the role of such acute exercise-induced hormone releases for muscle hypertrophy (Loenneke et al., 2012c; Pope et al., 2013).

The accumulation of osmotically active metabolites as lactate further leads to swelling of the muscle fibers as fluid shifts from the extra- to the intracellular space to equilibrate the osmotic gradient (Schoenfeld and Contreras, 2014). The resulting intracellular pressure is sensed by integrin-associated, cell-intrinsic volume sensors that activate mTOR and MAPK pathways, by which cell swelling is thought to trigger the muscular protein synthesis (Low et al., 1997; Abe et al., 2012; Pearson and Hussain, 2015). Kim et al. (2017) hypothesize that this muscle cell swelling induced pathway is one of the key mechanisms by which low-intensity BFR-training is able to induce anabolic effects (Loenneke et al., 2012a).

Another mechanism that could support BFR training induced muscle growth is the effect of reactive hyperemia on the vascular system. Two-fold increases in blood flow after BFR training over a period of more than 1 h have been reported (Gundermann et al., 2012). It is assumed that this long-lasting shear stimulus is responsible for the improved dilatory capacity of resistance vessels following BFR-Training (Hunt, 2014). In addition, BFR training increases microvascular filtration capacity as a sign of increased capillarization (Evans et al., 2010). Since adequate perfusion of the muscle fibers is crucial for muscle growth (Snijders et al., 2017), BFR-associated hyperemia with its effects on the vascular system could be an important factor supporting training-induced hypertrophy.

Furthermore, the ischemic conditions due to BFR lead to an upregulation of endothelial NOS, mRNA, and hypoxia inducible factor1α (HIF-1α), which influence autocrine factors (IGF-1) and satellite cell activation and thus, lead to increased protein synthesis (Pope et al., 2013; Pearson and Hussain, 2015). There are also some investigations that consider reactive oxygen species, increased glycogen storage or reduced myostatin to be influencing factors for muscle protein synthesis (Pope et al., 2013; Pearson and Hussain, 2015). However, there is no clear evidence for those factors. For example, it is well known that ROS production increases when blood supply returns (reperfusion) after sustained ischemia (Korthuis et al., 1985; Tsutsumi et al., 2007). Based on these observations, it could be assumed that the BFR-associated ischemia-reperfusion sequence exacerbates the hypoxic signaling cascade (dependent on HIF-1α). However, the data available so far often show no increase in ROS as a result of BFR training (Goldfarb et al., 2008; Rozales Ramis et al., 2017), so that the question of usefulness of antioxidant administration cannot yet be conclusively clarified.

EFFECTS OF LOW-INTENSITY BFR-TRAINING ON BONE HEALTH

The majority of available literature on BFR training has dealt with its effects on skeletal muscle fibers, while only a few studies have investigated the effects on other tissues of the musculoskeletal system. However, some evidence is available that low-intensity BFR-training positively affects bone metabolism, formation and resorption (Bittar et al., 2018). Increased intramedullary pressure and interstitial fluid flow within the bone, caused by vascular occlusion, are hypothesized to be the main mechanisms affecting bone remodeling (Loenneke et al., 2012d). The effectiveness of BFR as a countermeasure for the bone loss was investigated by an increase of B-ALP, which is considered to display the activity of osteoblasts (Beekley et al., 2005). Further, bone resorption markers as C-terminal cross-linking telopeptide of type I collagen (CTX/NTX) has been reported to be decreased after BFR exercise (Bemben et al., 2007). Karabulut et al. (2011), who compared serum concentrations of bone markers in older man following high-intensity resistance training and low-intensity BFR-training, found B-ALP and B-ALP to CTX ratio improved after both training protocols. Although these results indicate that high mechanical loads are not necessary to prevent bone loss in microgravity, further research is needed to develop a better understanding of the BFR-training mediated effects.

EFFECTS OF LOW-INTENSITY BFR-TRAINING ON TENDONS

There is some evidence that hypoxic conditions improve the proliferation of human tendon stem cells, when compared to normoxic conditions (Lee et al., 2012; Millar et al., 2012; Huang et al., 2013; Zhang and Wang, 2013; Jiang et al., 2014). Furthermore, hypoxia has been reported to be essential for the healing of the bone-tendon junction in which HIF-1α plays a key role (Zhao et al., 2011). Although, there are studies that have used BFR training in the rehabilitation of tendon injuries, the researchers' main aim in those studies was to use BFR training to reduce the required training intensity to improve muscle strength (Yow et al., 2018). To the best of the authors' knowledge, only few data are available regarding the effects of BFR training on the structure and function of tendons. In one study, Mohmara et al. (2014) investigated the effect of low-intensity (30% 1RM) leg-calf-raises either with or without BFR on the Achilles tendon thickness. The authors found no difference in tendon thickness between both conditions immediately and

24 h after the exercise protocol. However, this acute reaction does not provide any information about chronic tendon adaptations to BFR training programs. Kubo et al. (2006) reported that a 12-week resistance training (3 days/week) improved the stiffness of tendon-aponeurosis complex in the vastus lateralis only in the high-intensity (80% 1RM) but not in the low-intensity (20% 1RM) BFR group. Thus, according to the available literature it seems that high-mechanical forces cannot be dispensed with, if adaptations of the tendons are wanted. However, the data available on this topic are still very weak, so that further studies are required in order to be able to make reliable statements on this issue.

POTENTIAL RISK FACTORS OF BFR IN SPACE

The risk of negative side effects of BFR-training has already been reviewed by others, whereby bruising under the cuffs (13.1%) due to the applied cuff pressure was most common (see, Loenneke et al., 2011b). In this regard, there is some disunity about the required cuff pressure and width for an optimal training response with as little vascular stress as possible. However, due to the potential side effects, there is broad agreement that individual cuff pressures should be preferred over fixed cuff pressures (Cook et al., 2007; Clark et al., 2011). Furthermore, there is some evidence that low cuff pressures (∼50% of the individual occlusion pressure) are sufficient to provoke the desired BFR-mediated effects on the musculoskeletal system and reduces the risk for negative side effects associated with higher pressures near arterial occlusion decrease (Loenneke et al., 2014a). Based on these arguments, it becomes clear that the measurement of the individual occlusion pressure of the astronauts is necessary to standardize the pressure of the cuff. Given the fact that blood pressure behaves differently under microgravity conditions (Norsk, 2014), pre-flight measurements are unsuitable for determining the individual occlusion pressure for training in space. Fortunately, BFR equipment is now available that automatically measures the individual closing pressure and adjusts the cuff pressure for the training accordingly. It is also conceivable that BFR training damages the muscles distal to the cuff. However, the small increase in muscle damage markers after BFR training speaks against this assumption (Loenneke et al., 2014b). One reason for the low level of damage is certainly the use of low resistance in this training method. Apparently, however, the induced ischemia is also not strong enough to have a direct or indirect (via. reperfusion injury) damaging effect on the muscle tissue (Thiebaud et al., 2013; Loenneke et al., 2014b). Reperfusion injury is caused by completely occluded blood flow to a limb, whereas the intensity and duration are pivotal role. In muscle tissue, irreversible damage can be seen after 4–6 h of occlusion (Blaisdell, 2002) and therefore the injury risk during BFR training is considered to be low. Nevertheless, there are also a few contradictory findings. Some authors reported that BFR increased the perceived muscle soreness as well as the sarcolemma permeability (Wernbom et al., 2012) and reduced the endothelial function (Renzi et al., 2010). In summary, however, the majority of the data indicate that the risk of muscle damage from BFR training is low.

Another common concern is the coagulation of blood and formation of thrombi by the BFR-induced disturbance of the laminar blood flow. Surprisingly, however, fibrinolytic activity has been reported to be increased after BFR training and the incidence of thrombosis to be lower compared to the general population (Nakajima et al., 2006). Other cardiovascular risk factors of BFR training are related to the decreased venous blood return to the heart. As a consequence, the heart rate and blood pressure increase to maintain cardiac output (Takano et al., 2005). This might be an important risk factor for people with an increased predisposition to cardiovascular disease. However, since astronauts are under strict medical supervision and are only allowed to fly into space if pre-flight medical examinations have been passed, this risk appears to be low for astronauts.

CONCLUSION

Microgravity exposure has degenerative effects on the musculoskeletal system. Regarding further long duration flights like future Mars Expeditions, there is a need to tweak existing exercise protocols, to gain maximum training effects by using minimal equipment. Low load BFR-training allows for muscle mass and strength gains without the risk of injury associated with high resistances. Additionally, some evidence is available that bone mass and density can be increased by BFR exercise.

Despite the numerous positive findings on low-intensity strength training with BFR, it should be noted that these data were collected under normobaric and normoxic conditions. Therefore, future studies should clarify whether a hypobaric hypoxia (as may occur on board of future Mars Expeditions) or blood redistribution caused by weightlessness has an influence on BFR training results. It seems plausible that under these conditions lower cuff pressures are sufficient to trigger the effects of BFR training.

The low resistances required to achieve these goals also have an advantage regarding the equipment. Exercise devices would have to provide lower resistances, which facilitates their construction and preserves the vehicle capacity. Unfortunately, to date very little data are available whether low-intensity BFR-training is able to avoid the unloading associated deterioration of tendons. Nevertheless, the results of the review clearly show that BFR training is a useful supplement to training in microgravity.

Future studies are needed to investigate whether the blood redistribution caused by weightlessness has an influence on BFR training results. Therefore, long-term, 6° head down tilt bed rest studies investigating BFR-training should be sought to evaluate physiological adaptations of the musculoskeletal system.

AUTHOR CONTRIBUTIONS

MB and CW did the research for this topic, the framework and structure of this article, and discussed the possible effects.

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Conflict of Interest Statement: 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 Physiology

CORRECTION
published: 26 March 2019
doi: 10.3389/fphys.2019.00276

Check for updates

Corrigendum: Application of Blood Flow Restriction to Optimize Exercise Countermeasures for Human Space Flight

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Keywords: human space flight, exercise countermeasure, adaptations to microgravity, BFR training, space adaptations

A Corrigendum on

Application of Blood Flow Restriction to Optimize Exercise Countermeasures for Human Space Flight
Behringer, M., and Willberg, C. (2019). Front. Physiol. 10:33. doi: 10.3389/fphys.2019.00033

In the original article, there was an error. The International Space Station Expedition was incorrectly referred to as "the Skylab Expedition 18."

A correction has been made to the **In-Flight Protocols** section:

"In-flight exercise protocols are generally designed to minimize the loss in aerobic capacity, bone, muscle strength and endurance and to counteract neuromuscular dysfunction. The main goal thereby is to maintain in-flight and post-flight performance capabilities of the astronauts (Loehr et al., 2015). Crewmembers are commanded to adhere to their personal exercise protocols, including resistance (ARED) and cardiovascular exercise on a Treadmill or Veloergometer with Vibration Isolation and Stabilization System (TVIS, CEVIS). The training devices save personal data as well as physiological and training parameter, which allows the Mission Control Center (based on Earth) to adjust individual exercise schedules. Since the installation of the ARED in the International Space Station Expedition 18, high resistances can be applied during strength training on the ISS and the device allows about 29 different exercises. However, the ARED is very space-consuming and carries the potential risk of being temporarily unavailable due to technical faults (Hanson et al., 2014; Loehr et al., 2015), which motivates the search for and the exploration of smaller and technically simpler devices (Behringer et al., 2016). In addition, high training intensities are associated with an increased risk of injury to the musculoskeletal system (Gabbett, 2016), a fact to be taken seriously, as training-related injuries are the most common source of injury to astronauts on board the ISS (Scheuring et al., 2009). Therefore, the question arises whether BFR training can be a reasonable alternative or supplement for in-flight training sessions. In the following sections, the effects of primarily mechanical stimuli on the musculature are briefly presented and compared with those of more metabolically accentuated stimuli through BFR training."

The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

OPEN ACCESS

Approved by:
Frontiers in Physiology, Frontiers Media SA, Switzerland

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Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: *26 February 2019*
Accepted: *01 March 2019*
Published: *26 March 2019*

Citation:
Behringer M and Willberg C (2019) Corrigendum: Application of Blood Flow Restriction to Optimize Exercise Countermeasures for Human Space Flight. Front. Physiol. 10:276. doi: 10.3389/fphys.2019.00276

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Scheuring, R. A., Mathers, C. H., Jones, J. A., and Wear, M. L. (2009). Musculoskeletal injuries and minor trauma in space: incidence and injury mechanisms in U.S. Astronauts. *Aviat. Space Environ. Med.* 80, 117–124. doi: 10.3357/ASEM.2270.2009

frontiers in Physiology

REVIEW
published: 22 March 2019
doi: 10.3389/fphys.2019.00311

Check for updates

The Importance of Impact Loading and the Stretch Shortening Cycle for Spaceflight Countermeasures

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Pronounced muscle and bone losses indicate that the musculoskeletal system suffers substantially from prolonged microgravity. A likely reason for these detrimental adaptations in the lower extremity is the lack of impact loading and the difficulty to apply large loading forces on the human body in microgravity. The human body is well adapted to ambulating in Earth's gravitational field. A key principle herein is the periodic conversion of kinetic to elastic energy and *vice versa*. Predominantly tendons and to a lesser extent muscles, bones and other tissues contribute to this storage and release of energy, which is most efficient when organized in the stretch-shortening cycle (SSC). During SSC, muscles, especially those encompassing the ankle, knee, and hip joints, are activated in a specific manner, thereby enabling the production of high muscle forces and elastic energy storage. In consequence, the high forces acting throughout the body deform the viscoelastic biological structures sensed by mechanoreceptors and feedback in order to regulate the resilience of these structures and keep strains and strain rates in an uncritical range. Recent results from our lab indicate, notably, that SSC can engender a magnitude of tissue strains that cannot be achieved by other types of exercise. The present review provides an overview of the physiology and mechanics of the natural SSC as well as the possibility to mimic it by the application of whole-body vibration. We then report the evidence from bed rest studies on effectiveness and efficiency of plyometric and resistive vibration exercise as a countermeasure. Finally, implications and applications of both training modalities for human spaceflight operations and terrestrial spin-offs are discussed.

Keywords: plyometric exercise, whole-body vibration, muscle, bone, mechanoadaptation

OPEN ACCESS

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Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: *13 December 2018*
Accepted: *07 March 2019*
Published: *22 March 2019*

Citation:
Gruber M, Kramer A, Mulder E and Rittweger J (2019) The Importance of Impact Loading and the Stretch Shortening Cycle for Spaceflight Countermeasures. Front. Physiol. 10:311. doi: 10.3389/fphys.2019.00311

INTRODUCTION

Despite considerable amounts of crew time spent with countermeasure exercises on the International Space Station (ISS), astronauts still return to Earth with substantial musculoskeletal deficits (Rittweger et al., 2018), and these deficits are resilient to rehabilitation. One obvious explanation for the limited effectiveness of existing countermeasures is that subject loading forces on ISS are well below those on Earth. For example, foot and ground reaction forces are halved on the treadmill with vibration isolation and stabilization system (TVIS) that has been used on ISS since 2009 (Genc et al., 2010) and on the currently used T2 treadmill (De Witt and

Ploutz-Snyder, 2014) when compared to running on Earth. This must lead to great reduction of musculoskeletal forces, and diminishment of tissue strains. However, sufficiently high strains and strain rates are a prerequisite for tissue maintenance in bone (Frost, 1987b) and tendon (Arampatzis et al., 2007). Likewise for muscle, costameric proteins are strain-sensitive, and their phosphorylation is impinging on anabolic and catabolic pathways (Fluck, 2006). Importantly, one has to understand that tissue adaptation is driven by the magnitude of tissue strains (see **Figure 1A**), and likely also strain rates (Mosley and Lanyon, 1998), and that, thereby, achieving loading forces of similar magnitude as on Earth, seem a prerequisite for full countermeasure effectiveness. One should consider also in this context that muscle contractions are crucially involved in the loading of the other skeletal structures (Schiessl et al., 1998; Rittweger, 2007; Yang et al., 2015).

The difficulty in achieving full loading forces in space is likely related to limitations in the external force that pulls the human body down toward the ground. While this pull-down force originates from gravitational attraction of the human body's mass on Earth, it has to be generated artificially by, e.g., bungees or pneumatic cylinders. Very importantly, the artificially generated pull-down force has to be applied through interfaces such as shoulder pads, belts, etc. in microgravity (see **Figure 1B**). These interfaces can inflict pain and apprehension at higher loading forces, and it is therefore very difficult to train with a constant pull-down force in space that is equivalent to the body's full weight.

With the pull-down force, the body can generate movements that involve specific time courses of loading, e.g., during jumping. Thus, the human body can generate ground reaction forces in excess of the magnitude of the primarily constant pull force. An example is illustrated in **Figure 1C**: despite a pull-down force of less than 250 N, peak ground reaction forces of more than 1,500 N are generated during hopping. Body movement is caused by muscle contractions within the human body, and modulation of ground reaction forces therefore is associated with modulation of muscle force and muscle length. Very importantly, muscles can generate greater forces when lengthening than when shortening (see **Figure 1D**). Optimal countermeasures for bone, tendon, and muscle therefore should involve active muscle stretching, which goes under the term "eccentric" contraction, simply because greater muscular forces can be generated than during isometric or concentric contraction. Since most of the human habitual activities, such as walking, running and jumping involve, alternating stretching and shortening of the muscle-tendon units, to the so-called "stretch-shortening cycles" (SSC), which enable storage and release of elastic energy, the anatomical and physiological features of the human organism are geared to optimize this important musculoskeletal function. In line with this understanding, recent data demonstrate that bone tissue strains are largest during hopping, followed by running and walking, and actually quite low during static exercises (Milgrom et al., 2000b). Hence, so-called plyometric training, which emphasizes stretch-shortening stimuli, constitutes an elegant strategy to enhance tissue strains when pull-down forces are limited. The current publication therefore ponders the countermeasure potential of reactive jumps as a physiological and of resistive vibration exercise as a technology-assisted way to elicit SSC.

PHYSIOLOGY AND APPLICATION OF REACTIVE JUMP TRAINING

Already Cavagna et al. (1964) showed that while running, a substantial amount of energy is delivered at low cost. The mechanism underlying such a high movement efficiency has been described first by Goslow et al. (1973) in the cat hindlimb, and later on, Grillner (1975) proposed the SSC as a fundamental mechanism to increase power during natural movement tasks without extra energy expenditure. The SSC is not restricted to locomotion but constitutes a basic motor control scheme that is underlying many human movements, like throwing, kicking, and hitting. The fundamental principle is to store elastic energy in tendons, muscles, and other tissues. Running and hopping are ideal examples to illustrate how energy transformation helps to save metabolic energy and increase the economy of a movement. Thus, from an anatomical point of view, the Gastrocnemius-Achilles tendon complex, with its short and strong muscle and its long and compliant tendon seems an optimized structure for SSC function (e.g., exemplified in the anatomy and locomotion of the kangaroo).

To ensure proper elastic energy storage, the respective muscle has to be considerably stiffer than its tendon so that pronounced lengthening of the tendon can occur with only minimal muscle lengthening (Lichtwark et al., 2007). This is beneficial for the storage of elastic energy as the tendon undergoes considerable stretching without energy losses, whereas muscle lengthening would imply futile cross bride cycles within the contractile elements (Flitney and Hirst, 1978; Lichtwark and Wilson, 2005). In contrast to the stiffness of the tendon, the stiffness of the muscle can be modulated within a fraction of seconds over a wide range by increasing or decreasing the number of cross-bridges. Whereas size and length represent anatomical features for optimized tendon and muscle function, this modulation of muscle stiffness mainly depends on muscle activation, underpinning the crucial role of neural control during SSC tasks (Taube et al., 2012).

The motor command that activates the muscle in a specific manner determines whether it dissipates energy, e.g., during landing, or stores energy, e.g., during hopping. In this respect, tendon and muscle can be seen as a cooperative couple able to attenuate or amplify power during specific motor tasks (Roberts, 2016). Note that during SSC, the overall performance is determined by the work done during the phase while the muscle-tendon units shorten. Without the tendon, the force-velocity properties of the muscle would limit force and consequently work with an increase in shortening speed during fast movements like jumps. With a tendon that stretches during the eccentric phase and recoils at high speed during this phase, the muscle itself can shorten more slowly, enabling a higher force production, and when we assume a similar strain, an increased muscle work.

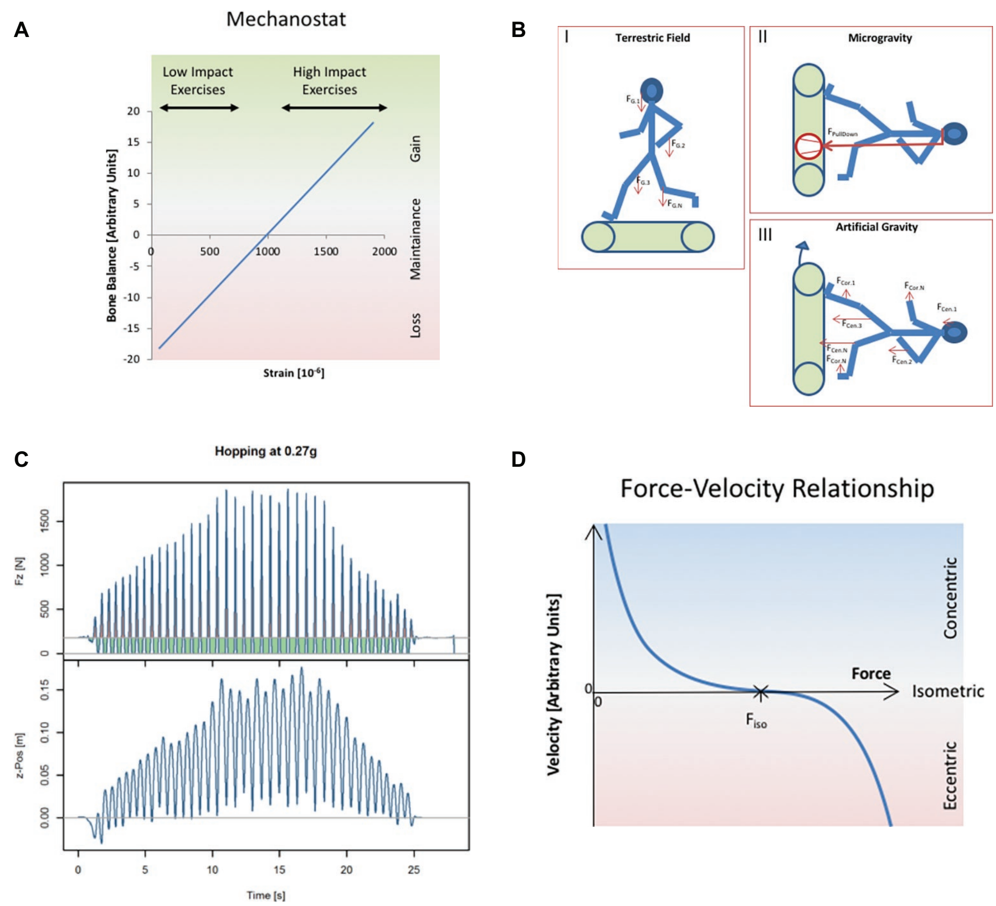

FIGURE 1 | (A) Conceptualizationthe effect that tissue strains have on adaptive processes. This concept is well known in the bone field as "mechanostat" (Frost, 1987a), and it seems in principle to apply also to tendon, muscle, and likely other tissues. The mechanostat concept considers tissue's mechanoadaption as a negative feed-back system, analogous to a thermostat. While thermostats enable constancy of temperature, the mechanostat keeps the tissue strains constant by adding or removing material in response to altering forces. Material evidence for the mechanostat concept had been provided by Rubin and Lanyon (1987), whose data are exemplified in the present diagram. Exercise-induced tibial compression strains are taken from Milgrom et al. (2000a,b) (low impact exercises, walking and bicycling; high impact exercises, running and drop jumps from different heights). **(B)** Different strategies to replace gravity by artificial pull-down forces. (I) Pull-down in the Earth's gravitational field is a result of the body's weight, which can be conceptualized as a homogeneous vector field within the entire body. (II) In microgravity, pull-down forces are generated by, e.g., pneumatic systems or bungees, and they are applied to the body *via* interfaces at the shoulders or hips. This "force concentration" is illustrated by size and thickness of the vector. (III) Artificial gravity replaces gravitational acceleration by centrifugal centrifugation. This avoids the problem of force application. However, it leads to in-homogeneity of the gravitational field (indicated here by different sizes of vectors) and generation of Coriolis forces, both of which become more pronounced with shorter radius of centrifugation. **(C)** Illustration of the time course of ground reaction forces during hopping, exemplified here for hopping during hypogravity simulation at $g = 0.27$ (first published in Weber et al., 2019). The vertical elevation of the body's center of mass (z-position, lower panel) demonstrates that hops of increasing height are associated with increasing vertical ground reaction forces (Fz, upper panel). Green areas denote periods where Fz < weight (i.e., downward acceleration), and the red areas denote periods where Fz > weight (upward acceleration). Since no vertical net movement had occurred at the end of the hopping trial, the green and red areas are of equal size. Effectively, by fractioning the static load into "duty cycles," one can produce ground contact forces that exceed the static loading force. The diagram therefore illustrates how jumping exercises can generate peak Fz that are substantially greater than static bodyweight. **(D)** The muscle's working diagram, which also is known as "Hill's" curve, is describing the force-velocity relationship of maximally activated muscle. In concentric mode, the muscle is shortening (v is positive) because the resistive force is smaller than the muscle's contractile force. In isometric mode, resistive force and contractile force are equal, and $v = 0$. In eccentric mode, the resistive force exceeds the contractile force, and the muscle is lengthening (negative v). The force-velocity relationship is empirically described by a hyperbolic function (Hill, 1938).

Hopping is an ideal example to illustrate the fundamental neuromechanics of the SSC. The muscle activity pattern that constitutes the SSC can be divided into four distinctive parts: the preactivity (PRE), the short latency response (SLR), the medium latency response (MLR), and the long latency responses (LLR1 and LLR2) (Taube et al., 2008). The leg extensor muscles (triceps surae and quadriceps femoris) must be activated before touchdown when impact loading starts (PRE). The timing and activation level during PRE are crucial to adjust the stiffness of the muscle and control the impact loading during the ground contact. After ground contact during the breaking phase, the muscle-tendon unit lengthens, mainly because the tendon lengthens and stores elastic energy. It has been shown that stretch reflexes act in concert with descending motor commands to ensure a high activation of the extensor muscles throughout ground contact (Taube et al., 2008; Zuur et al., 2010).

When increasing jump height, besides stiffness, force control of the muscle becomes more and more important. For maximal jumps, this often results in maximal forces in the leg extensor muscles with the unique feature that maximal muscle force can be reached in a much shorter time period during the SSC when compared to a maximal isometric contraction, resulting in a much higher strain rate.

In conclusion, the prerequisite of an efficient SSC is a stiff muscle and a tendon that can lengthen (absorb energy) and shorten (recoil energy) during movement. In addition, it has been proposed that the transition time between muscle-tendon unit stretching and shortening need to be minimal to avoid dissipation of stored elastic energy as well as a decrease in muscle force prior to the concentric phase (Komi and Gollhofer, 1997). As a consequence, the SSC is most economical with short SSC durations of often less than 200 ms. In this regard, the mechanical and neural properties of the muscle-tendon unit and the sensorimotor control loops seems to be perfectly tuned for an efficient SSC.

An exercise mode that is particularly suitable to train the SSC is plyometric training. Plyometrics are usually employed to increase jump height and leg power in athletes. As jumps are the exercise mode with the highest power output (Davies, 1971), it is not surprising that plyometrics consistently improve maximal jump height and peak power, with medium to large effect sizes, depending on the type of jumping exercise and training duration (Markovic, 2007; Moran et al., 2018). Using more than 50 jumps per session as well as a combination of different types of jumps seems to be beneficial (de Villarreal et al., 2009). In addition to jumps, other types of fast movements such as short sprints and change-of-direction maneuvers seem to benefit from plyometrics (Slimani et al., 2016). Fewer studies assessed the effect of jump training on maximal leg strength, but a recent meta-analysis reported high effect sizes for maximal leg strength after plyometrics (0.97), although they were lower than when plyometrics were combined with strength training (de Villarreal et al., 2009).

Plyometrics also lead to extremely high bone strains, especially in the tibia (Milgrom et al., 2000a,b; Ebben et al., 2010), and thus constitute a strong stimulus for bone. Indeed, habitual athletes in high-impact sports such as triple jumping (Niinimäki et al., 2017), volleyball (Rantalainen et al., 2010), sprint running (Wilks et al., 2009), or fencing (Chang et al., 2009) tend to exhibit higher bone mass and strength than matched controls.

In participants subjected to 2 months of bed rest, plyometrics have been successfully used as an integrated countermeasure (Kramer et al., 2017b), preserving muscle mass of leg extensors, maximal leg strength, and peak power as well as tibial mineral density and content, whereas the inactive control group showed profound losses in these parameters (Kramer et al., 2017a, 2018). Moreover, the jump training was able to prevent most of the deteriorations in functional parameters such as balance control, gait and mobility (Ritzmann et al., 2018). Excluding breaks, the training group exercised for about 3 min per day on 6 days per week. On average, each session consisted of 4 × 12 countermovement jumps and 2 × 15 repetitive hops, with each jump performed with maximal effort, and with 30–60 s of rest in between sets. For a detailed description of the training program, see (Kramer et al., 2017b). The high-intensity nature of the training may have been responsible for the cardiovascular adaptations (Maggioni et al., 2018). Indeed, other studies using jumps and other bodyweight exercises as a low-volume, high-intensity type of training demonstrated the effectiveness of this exercise mode for improving maximal oxygen uptake, which is considered to be the net criterion for cardiovascular function (McRae et al., 2012). A recent study examined the effect of different rest intervals on the acute physiological responses to jump exercise (Kramer et al., 2019). The authors report that jumping can elicit up to 98% of maximal oxygen uptake capacity ($V'O_{2max}$) and maximal heart rate, with up to 40% of the exercise session spent above 90% of $V'O_{2max}$ and a lactate accumulation of up to 9 mmol/L, provided the rest intervals are less than a second in between jumps and less than 30 s in between sets. Thus, with adequate work interval durations and work to rest ratios, jumps seem to be suitable as a form of high-intensity interval training (HIIT). As it is the case with other types of HIIT, there are several ways to effectively program a jump HIIT session, but one of the most important parameter seems to be the total time spent above 90% of $V'O_{2max}$. For a review, see Buchheit and Laursen (2013).

This strongly suggests potential for plyometrics as a countermeasure against inactivity-induced neuromuscular and musculoskeletal deteriorations. In addition, with sufficiently short rest intervals, jumps can be used as a form of high-intensity interval training, thus not only putting high demands on the musculoskeletal but also the cardiovascular system.

PHYSIOLOGY AND APPLICATION OF RESISTIVE VIBRATION EXERCISE

In contrast to plyometrics where a force accelerates the human body against the ground, the principle idea behind vibration exercise is the utilization of a machine-generated force at the feet to elicit the training stimulus. By using sinusoidal oscillations, the external force becomes predictable to the user, and the harmonic waveform avoids higher frequency components that would be destructive to material of human and machine interfaces.

Vibration exercise, for the purpose of strength and neuromuscular training, is typically done with vibration frequencies between 20 and 40 Hz, and with peak-to-peak amplitudes (A_{p2p}) up to 12 mm. Mathematically, the peak acceleration (a_{pik}) in the sinusoidal cycle is given by the following:

$$a_{\mathrm{pik}} = 2 \cdot A_{\mathrm{p2p}} \cdot (\pi \cdot f)^2$$

where f is the vibration frequency. Thus, for a typical constellation with vibration with frequency f = 25 Hz and amplitude A_{p2p} = 10 mm, a_{pik} amounts to 123.4 m/s^2, or 12.6 g. It is important to note that such large accelerations can usually not be achieved with other types of exercise. Equally important, periods of great loading alternate with periods of low loading magnitude. Thereby, the rate at which phases of high and low ground reaction forces alternate is greater than during walking or hopping (see **Figure 1C**). Thus, from a pure perspective of force magnitude, SSC must be expected to occur also during vibration exercise. The question still arises whether SSCs are also possible with period cycles of milliseconds only. That question had been addressed by Cochrane et al. (2009) who measured muscle contractile tissue displacement by B-mode ultrasound along with modulation of EMG activity during acute whole-body vibration. The authors report modulation of tendon length and muscle contractile length, both of them phase locked to the movement of the vibration platform. That study therefore clearly demonstrates the presence of SSC at 6 Hz vibration frequency, and a current study in our lab ought to establish whether even higher vibration frequencies allow SSC in the exercising muscle.

Solid evidence is also available to demonstrate that vibration-induced SSC is associated with phase-locked modulation of electromyographic activity in the stretched muscles (Cochrane et al., 2009; Ritzmann et al., 2010), thus strongly suggesting the occurrence of stretch reflexes (Burke et al., 1976; Rittweger, 2010; Ritzmann et al., 2010), although this notion has been questioned (Cakar et al., 2015) and an alternative reflex pathway has been proposed (Karacan et al., 2017). Thus, future research should establish the exact nature of the reflex responses to vibration, and also the magnitude of the musculoskeletal force modulation during vibration-induced SSC. Most probably, these forces are much lower than the ones elicited by plyometrics, but what vibration lacks in force magnitude might be compensated by the very high number of repetitions. Keep in mind that even only 1 min of vibration training at 30 Hz translates to 1,800 cycles. When used in a bed rest study, whole-body vibration, applied twice daily at 20 Hz, with $A_{p2p} \leq 4$ mm, with additional loads of 15% of body weight and no additional exercises was found ineffective to maintain both the musculature (Zange et al., 2008) and bone (Baecker et al., 2012). By contrast, in the 56-day Berlin Bed Rest (BBR) study, vibration was combined with resistive exercise (Rittweger et al., 2006). With a progressive overload protocol, subjects performed squatting exercise, heel raises, toe raises, and kicking exercise with a loading equivalent to twice the body weight in bouts of 60–100 s. This was performed 11 times per week, with inter-subject' competition days on Wednesdays and resting days on Sundays. This training regimen could preserve muscle strength and power (Mulder et al., 2006; Buehring et al., 2011), prevent bone loss (Armbrecht et al., 2010; Rittweger et al., 2010), and mitigate spinal deconditioning (Belavy et al., 2008) and shrinkage of the femoral artery (Bleeker et al., 2005). In a follow-up study (Belavy et al., 2010), it was demonstrated that vibration *per se* can contribute to bone maintenance (Belavy et al., 2011), but no such effect could be demonstrated for muscle (Mulder et al., 2009). In conclusion, in the bed rest setting, resistive vibration exercise has demonstrated excellent effectiveness against musculoskeletal de-conditioning, and also some cardiovascular effectiveness. It is also noteworthy in this context that vibration exercise is increasingly used not only in rehabilitation medicine, foremost in the field of pediatrics, but also in geriatrics (Semler et al., 2008; Stark et al., 2010).

DEFINING AN OPTIMIZED PRESCRIPTION IMPACT LOADING FOR SPACE

In the aforementioned RSL bed rest study, the participants used a sledge jump system (SJS) to perform the jump training in a horizontal position. This system was designed for the use in microgravity, as it does not require gravitational forces (**Figure 2A**). Instead, the counterforce for the jumps is generated by low-pressure cylinders, allowing for forces above and below bodyweight to be used to adjust the training load (Kramer et al., 2012b). Before transferring this terrestrial concept to microgravity, the subject fixation in the SJS would have to be slightly altered, as the gravitational pull that stabilizes the subject during the jumps is lacking in microgravity. In addition, the feasibility of attaching the SJS to the spacecraft's structure without transferring excessive forces has to be verified. Both of these modifications could be tested during a parabolic flight campaign.

The advantage of plyometric training is that it would be highly compliant with current ISS operations, as the training time would be much shorter than the currently scheduled two to two and a half hours per day. This would also be an advantage in future human exploration missions with restrictions on exercise time and minimal ground communication. However, the challenge would be to fit the SJS into a smaller spacecraft, as the minimum length even of a modified system would be the height of the astronaut plus his or her maximal jump height, i.e., for taller astronauts about 2.5 m.

If plyometrics were successfully used by astronauts as a short exercise countermeasure for the deconditioning of muscle, bone and also the cardiovascular system, this could have a major impact on the use of such a training program in sedentary populations, due to the astronauts' function as role models. If a major part of the sedentary population would adopt such a short plyometric training, this might result in a pronounced decrease in sarcopenia, dynapenia, osteoporosis, and cardiovascular diseases.

Plyometric training could be complemented by resistive vibration exercise. This is particularly true where plyometric training is not possible due to operational constraints (e.g., mass upload, available room) or limited exercise capacity or willingness on the side of exercisers. In the first Berlin bed rest study, a platform with two excenter rotations in anti-phase was used that was specifically designed for that study (Rittweger et al., 2006). In the second Berlin bed rest study, a commercially available platform with directly driven oscillation was used (Belavy et al., 2010). In addition, whole-body vibration was already successfully tested during several parabolic flight campaigns (Kramer et al., 2013), see **Figure 2B**. It would be straightforward to implement flight models built on one of these already tested vibration systems.

With regard to exercise prescription, it must be expected that astronauts have to exercise at least once a day. This is

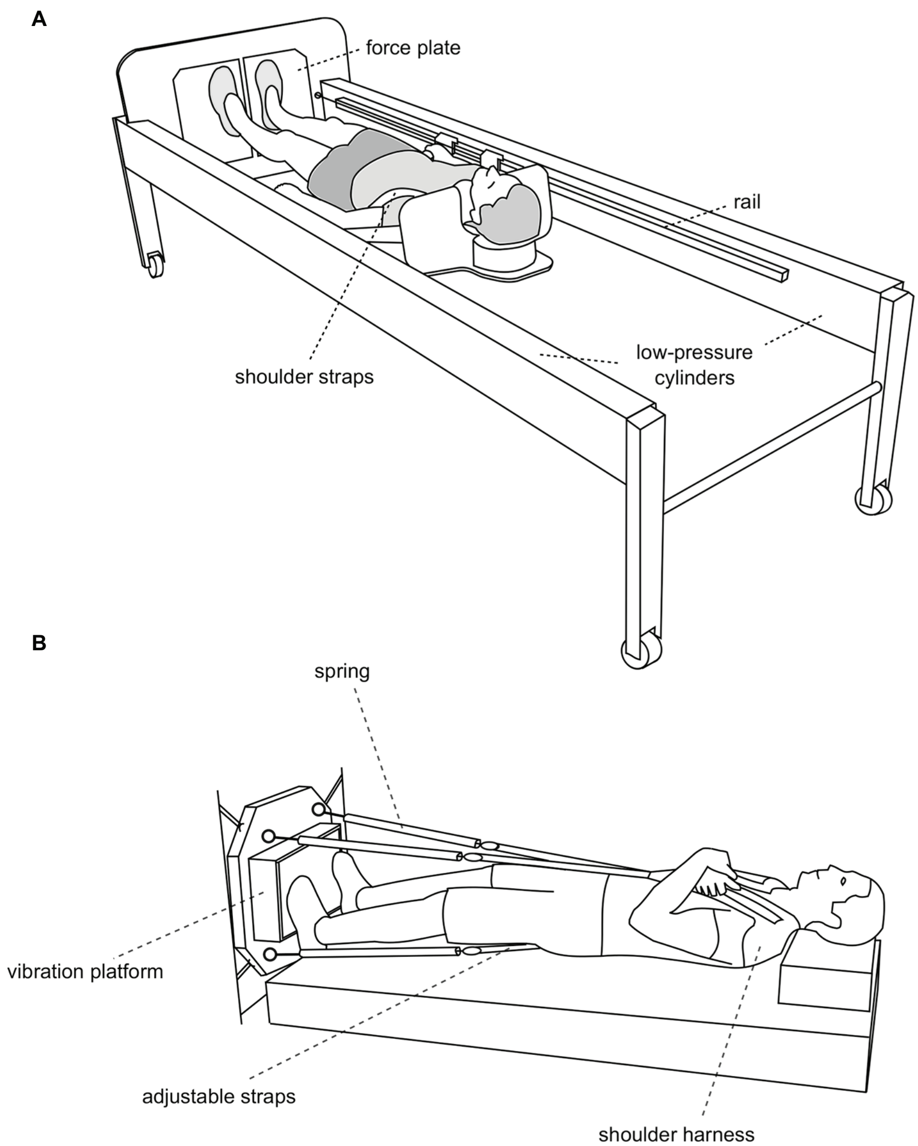

FIGURE 2 | (A) The jump training device (sledge jump system, SJS, adapted from Kramer et al., 2017b). The participant is fixed to the sledge with shoulder straps, and his thighs rest on additional straps. The straps are attached to the rails and can slide alongside the rails with minimal friction. The forces generated by the two low-pressure cylinders substitute the gravitational force. Any force between 0 and 1,800 N can be set by altering the pressure of the cylinders. Details about the system can be found elsewhere (Kramer et al., 2010, 2012a,b). **(B)** Whole-body vibration (WBV) in microgravity (adapted from Kramer et al., 2013). The subject is pulled toward the vibration platform by four springs *via* four adjustable straps. The straps are adjusted in a way that the springs exert a force that matches the subject's body weight.

based on the existing evidence that a total of 11 exercise sessions on 6 days of the week, as prescribed in the first Berlin bed rest study fully prevented bone loss and muscle weakening (Rittweger et al., 2010), but the performance of virtually the same training on 3 days only of the week was not enough to fully prevent bone loss (Belavy et al., 2011) and muscle weakening (Mulder et al., 2009). Ideally, exercises would be performed in bouts of 30–60 s, which leads to provenly high serum lactate levels, mimicking some of the physiological demands of many of the well-established "high intensity interval training" prescriptions.

AUTHOR CONTRIBUTIONS

MG and JR contributed structure of the work. MG, AK, and JR drafted the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

FUNDING

We received a fund from the University of Konstanz for the open access publication fee.

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Conflict of Interest Statement: 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 Physiology

REVIEW
published: 29 March 2019
doi: 10.3389/fphys.2019.00321

Revisiting the Role of Exercise Countermeasure on the Regulation of Energy Balance During Space Flight

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OPEN ACCESS

Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: *31 October 2018*
Accepted: *11 March 2019*
Published: *29 March 2019*

Citation:
Laurens C, Simon C, Vernikos J, Gauquelin-Koch G, Blanc S and Bergouignan A (2019) Revisiting the Role of Exercise Countermeasure on the Regulation of Energy Balance During Space Flight. Front. Physiol. 10:321. doi: 10.3389/fphys.2019.00321

A body mass loss has been consistently observed in astronauts. This loss is of medical concern since energy deficit can exacerbate some of the deleterious physiological changes observed during space flight including cardiovascular deconditioning, bone density, muscle mass and strength losses, impaired exercise capacity, and immune deficiency among others. These may jeopardize crew health and performance, a healthy return to Earth and mission's overall success. In the context of planning for planetary exploration, achieving energy balance during long-term space flights becomes a research and operational priority. The regulation of energy balance and its components in current longer duration missions in space must be re-examined and fully understood. The purpose of this review is to summarize current understanding of how energy intake, energy expenditure, and hence energy balance are regulated in space compared to Earth. Data obtained in both actual and simulated microgravity thus far suggest that the obligatory exercise countermeasures program, rather than the microgravity *per se*, may be partly responsible for the chronic weight loss in space. Little is known of the energy intake, expenditure, and balance during the intense extravehicular activities which will become increasingly more frequent and difficult. The study of the impact of exercise on energy balance in space also provides further insights on lifestyle modalities such as intensity and frequency of exercise, metabolism, and the regulation of body weight on Earth, which is currently a topic of animated debate in the field of energy and obesity research. While not dismissing the significance of exercise as a countermeasure during space flight, data now challenge the current exercise countermeasure program promoted and adopted for many years by all the International Space Agencies. An alternative exercise approach that has a minimum impact on total energy expenditure in space, while preventing muscle mass loss and other physiological changes, is needed in order to better understand the in-flight regulation of energy balance and estimate daily energy requirements. A large body of data generated on Earth suggests that alternate approaches, such as high intensity interval training (HIIT), in combination or not with sessions of resistive exercise, might fulfill such needs.

Keywords: energy intake, energy expenditure, appetite, resistive exercise, aerobic exercise, HIIT, microgravity, astronauts

INTRODUCTION

Humans have been present in space for more than 50 years. Data generated during human spaceflights have demonstrated that the space environment, characterized by microgravity, 90-min light/dark cycles and confinement, impacts almost all physiological systems inducing a myriad of adaptive responses. These alterations of the body's physiology can jeopardize crew health and performance and thereby impact the overall success of the mission with a healthy return to Earth. Responses to microgravity include fluid redistribution, reduced plasma volume, rapid loss of muscle mass and strength, a switch from oxidative type I toward glycolytic type II muscle fibers, cardiovascular deconditioning, impaired aerobic exercise capacity, bone loss, immune and metabolic alterations, as well as central nervous system effects (Aubert et al., 2016; Bergouignan et al., 2016; White et al., 2016; Lang et al., 2017).

Another common observation in most spaceflights was a systematic body mass loss independent of the space mission duration (**Figure 1**) (Wade et al., 2002; Matsumoto et al., 2011). On Mir (Smith et al., 1999, 2001), Shuttle (Stein et al., 1999a; Wade et al., 2002) and early ISS missions (Smith et al., 2005; Matsumoto et al., 2011), astronauts usually lost more than 5% of their pre-flight body mass. This was observed despite adequate food onboard (Lane and Schoeller, 1999). In many cases, this loss even exceeded 10%, which is clinically significant. However, body mass was successfully maintained stable in some missions like SLS1 and SLS2 in the 1970s (Thornton and Ord, 1975) or, more recently, on the ISS (Stein et al., 1996; Smith et al., 2005, 2012). Most recent reports on the ISS, however, show that astronauts still lose from 2 to 5% of their initial body mass during their time in space (Zwart et al., 2014). To prevent the loss of body mass was never a priority during the early missions, they were short and a moderate energy deficit is tolerable due to the availability of body fat stores. Concerns have been raised when missions targeting long stays in space in the context of planetary exploration were discussed. Beyond the simple loss of body weight, the energy deficit may have adverse health consequences over the long run.

Loss of body mass during spaceflight is associated with decreased muscle mass and functionality, incidence of cardiovascular issues, and oxidative stress (Stein, 2002; Smith and Zwart, 2008). Other human clinical studies and bed-rest studies conducted on Earth have demonstrated that a chronic energy deficit induces several deleterious consequences that are generally observed during space flight such as orthostatic intolerance, or may aggravate microgravity-induced adverse changes such as muscle loss, aerobic deconditioning, or disrupted immunity responses. This suggests that energy deficit may exacerbate the physiological adaptive responses to microgravity. Roadmaps establishing research priorities for planetary exploration raised the significance of energy balance regulation to a critical level, given it may represent an issue jeopardizing health and performance for long-duration missions (Stein, 2000; Bergouignan et al., 2016).

Although body water loss occurs during spaceflights (Zwart et al., 2014), it can only account for a portion of body mass loss. Muscle atrophy due to muscle disuse during space flights clearly contributes to body mass loss; however, it does not explain all of it. Body fat loss was indeed reported during in-flight experiments. For example, a decrease of about 2 kg in fat mass was observed following 2 weeks in space (Stein et al., 1999a). After the stabilization of fluid balance in the first few days in space, the body mass loss observed is therefore necessarily paralleled by a chronic alteration of energy balance: energy intake is not sufficient to match energy expenditure. Among the four studies published so far that investigated energy balance, three demonstrated a severe energy deficit during space flight (Rambaut and Leach, 1977; Stein et al., 1996, 1999a; Lane et al., 1997). During the 16-day LMS mission, by objectively measuring inflight double-labeled water-derived total energy expenditure, Stein demonstrated that energy expenditure was not matched by caloric intake. This mismatch led to an energy deficit as large as 5.7 $\pm$ 0.3 MJ/day in four astronauts (Stein et al., 1999a). If sustained, this may cause a weight loss of $>$5 kg/month. Recent developments of body mass measurement in space suggest that such a decrease in body mass may likely happen during the first month but then body mass would remain stable over the course of the mission (Zwart et al., 2014). However, when compiling all the available data on weight change during space missions (n = 619 missions), the extrapolation of weight loss via a linear model predicted that cumulative mean weight loss would be of 2.4% per 100 days (Matsumoto et al., 2011). A mission to Mars could therefore induce 15% loss of initial body mass or more, which could have serious health implications. Nevertheless, it is important to point out that all these studies were conducted with a very low sample size and a large inter-individual variability exists. This prevents drawing clear-cut conclusions but also emphasizes that energy balance regulation is a complex process.

Understanding how energy balance is regulated during space flight is key to prescribing the right amount of food to be consumed by the astronauts. A negative energy balance can be due to either insufficient energy intake, too high energy expenditure, or both. During space missions, an exercise countermeasure is commonly applied to astronauts to mitigate the microgravity-induced physiological adaptations, primarily muscle and bone alterations, and cardiovascular deconditioning.

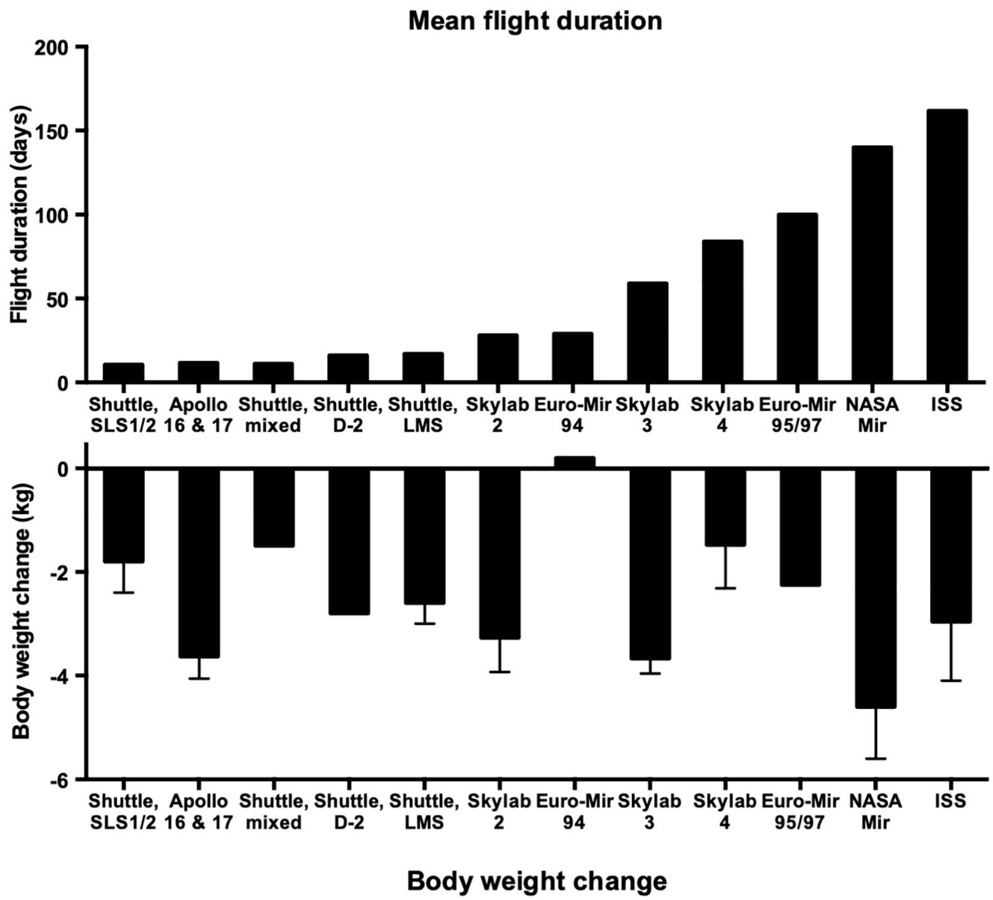

FIGURE 1 | Body weight loss in space during past missions of different duration. Adapted from Wade et al. (2002) and Matsumoto et al. (2011).

As currently prescribed, the exercise countermeasure program along with extravehicular activities impose a high volume of physical activity. This can be energetically costly and have a major influence on total energy expenditure. If food intake is not adjusted to match requirements, the high energy expenditure may lead to negative energy balance.

The purpose of this review is to summarize current understanding of the regulation of energy balance (i.e., energy intake and expenditure) in space and how the exercise countermeasure, as currently prescribed, affects this regulation. Based on the most recent evidence, we explain how the current exercise countermeasure program may be challenged, and what alternative approaches may be proposed for future space missions. Finally, we compare the impact of exercise on the regulation of energy balance in space and on Earth.

ENERGY INTAKE AND ANOREXIA DURING SPACEFLIGHTS

A common observation in all manned spaceflight is that astronauts eat less than on Earth. They consume about 20–25% less calories than theoretically necessary to maintain a stable energy balance and therefore a stable body mass (Stein et al., 1999a, Heer et al., 2000; Stein, 2000; Smith et al., 2005; Zwart et al., 2014). However, this apparent reduction in food intake was derived as compared with the World Health Organization estimate of energy needs on Earth. Earth energy requirements may likely be different from energy needs in space. In addition, while calorie intake of astronauts on board the ISS has been slowly increasing during the last years, a large interindividual variability still exists (Zwart et al., 2014). Different factors may contribute to this uncoupling between energy intake and energy expenditure.

A first potential reason for reduced food intake is the poor attractiveness of the food available in space (Drummer et al., 2000; Cena et al., 2003). Even if food quality has been improved since the beginning of the space program thanks to partnerships with the food industry, the palatability of food provided to astronauts is still not comparable to what is available on Earth, and its diversity is limited. In addition, before the ISS, food habits, especially those related to cultural background, were not considered, which may have played a role in the lower food intake. International coordination imposed by the ISS has, however, slowly changed this aspect. The improvement in both variety and quality of food as well as awareness of cultural dietary preferences in space may have helped improve energy intake during recent missions. These changes may explain, at least partially, the reduction in body weight loss during the more recent ISS missions.

In addition to food intake, the type of food consumed and the amount of nutrients going through enterocytes and entering blood to be used by cells (i.e., metabolizable energy) can influence caloric intake. Astronauts are often susceptible in the first few days of the missions to space motion sickness, through neuro-vestibular mechanisms, which obviously acutely decreases food intake. This has subsequent modifications of gastric acid secretion, rhythmic contractions of stomach and intestine, and finally alteration of gastric emptying (Da Silva et al., 2002). The lower gastro-intestinal passage may also be driven by the microgravity-induced cardiovascular alterations that modify splanchnic blood flow, a physiological determinant of gastric emptying (Amidon et al., 1991). However, no direct measurements have been made during space missions. During a 20-day bed rest, we used a dietary tracer to assess changes in the kinetics of nutrient appearance in the blood as well as in nutrient extraction but did not notice any modification (Rudwill et al., 2018). This suggests that microgravity, at least under simulated conditions, does not modify the quantity of metabolizable energy. The macronutrient composition of the diet can also influence caloric intake. Astronauts have frequently reported a shift in dietary preference toward carbohydrates, which could play an independent role on energy intake (Bourland, 2000; Da Silva et al., 2002) Because carbohydrates are less energy dense than fats (4 versus 9 kcal/g), a diet relying upon a greater proportion of carbohydrate will provide less energy to the body. Another potential factor is the reduced thirst that is one of the early symptoms of space flight due to inoperant mechanisms underlying fluid and electrolyte balance (Vernikos, 1996).

The decrease in energy intake can also result from the loss of appetite that has been repeatedly reported during spaceflight. It may be due to both biological changes induced by microgravity and the influence of the space environment. The sensory responses to taste, smell, and texture of food (Drummer et al., 2000; Cena et al., 2003) are reduced, therefore leading to an alteration of food attractiveness/appeal. A number of additional satietogenic and orexigenic neurohormonal factors seem to be at play, directly or indirectly, during spaceflight. Anorexia during spaceflight and the potential underlying mechanisms have been fully reviewed by Da Silva et al. (2002). By compiling data from actual and simulated microgravity and human clinical studies and data from rodent models of simulated microgravity, they suggested that food intake and weight loss in the presence of microgravity are regulated by a complex repertoire of neuroendocrine and physiologic changes. In brief, concentration of leptin, a hormone secreted by adipose tissue that is known to increase satiety and reduce food intake, is increased during spaceflight (Stein et al., 1999b). A similar increase in plasma leptin concentration was observed under simulated microgravity conditions when adjusting for changes in fat mass (Bergouignan et al., 2010). In this same study, a rise in glucagon-like peptide-1 (GLP-1) plasma concentration, a satiety hormone produced by the intestine, was also observed, while ghrelin, the only orexigenic hormone known to date, was not modified (Bergouignan et al., 2010). Altogether these changes in appetite-related hormones may contribute to the reduced appetite observed during space flights. Other biological factors can influence appetite such as the preference of astronauts toward carbohydrates rather than fat. Greater carbohydrate intake has been associated with an increase in brain free-plasma tryptophan concentration, a precursor of the satietogenic serotonin neurotransmitter (Da Silva et al., 2002; Lam et al., 2010). The increase in astronaut body core temperature during spaceflight (Stahn et al., 2017) can be another one. Based on the "thermostatic theory of food intake" (Brobeck, 1948), high temperature has been associated with increased plasma concentration of the anorexigenic hormone polypeptide YY (PYY) and decreased relative energy intake in response to exercise (Shorten et al., 2009), while cold temperatures have been associated with greater food intake (Stroebele and De Castro, 2004). However, an inverse relationship has been reported between circadian core temperature variations and leptin concentrations (Simon et al., 1998), which rather suggests an association between lower physiological core temperature and satiety signals. Finally, stress experienced by the astronauts during spaceflights can alter both appetite and energy intake (Marti et al., 1994; Ans et al., 2018). Direct study of food intake, perceived appetite, changes in appetite-regulating hormones, and other physiological functions such as thermoregulation or digestion are clearly needed to provide insights on the biological mechanisms underlying the decrease in energy intake during space missions.

Space environment can also impact caloric intake. In a murine model of microgravity (i.e., hindlimb suspension), an increase in ambient CO_2 concentration was shown to reduce food consumption (Wang and Wade, 2000). This suggests that the high concentration in CO_2 present in the spacecrafts and the ISS may alter energy intake (Frey et al., 1998). It has also been suggested that light exposure continuously below threshold inside the spacecraft and intermittent 90-min day/night cycles in Earth orbit would be expected to affect eating behavior (Varma et al., 2000; Cena et al., 2003). Indeed, an alteration in the dark-and-light cycle disrupts circadian rhythm (Navara and Nelson, 2007; Wright et al., 2013) with consequences on hormone secretion and homeostasis (Kim et al., 2015). For example, alteration in light-dark cycle has been shown to alter the rhythmic secretion of leptin in rodents, and to impact food intake and body weight (Challet, 2017). On Earth, disruptions in circadian rhythms as well as sleep have been reported to alter the normal leptin 24-h pattern in humans (Simon et al., 1998). The continuous light astronauts are exposed to may therefore, at least partly, explain the greater leptin concentration observed in astronauts (Stein et al., 1999b), which may be involved in their development of loss of appetite during spaceflight (Varma et al., 2000). The influence of the space environment on appetite and energy intake warrants more research. However, it is important to note how challenging in-flight experiments are and the difficulty to properly control timing of measurements. Studies using simulated microgravity models on Earth may first be needed to obtain round the clock data on multiple parameters and disentangle these relationships.

In this context, it is further important to accurately estimate the energy requirements in space.

ENERGY EXPENDITURE DURING SPACEFLIGHT AND SIMULATED WEIGHTLESSNESS

When energy balance is stable, energy needs equal energy expenditure. Changes in total energy expenditure can result from modifications in one or more of these main components (Pinheiro Volp et al., 2011):

- Resting metabolic rate, energy necessary to maintain basal body functions at rest, thermoneutrality, and fasting;
- Diet-induced thermogenesis, energy allocated to the processing of ingested food (i.e., energy needed to process nutrients after a meal for use and storage);
- Energy cost of thermoregulation, energy allocated to maintain the body at steady temperature;
- Energy consumed in any body movement, which includes non-exercise (or daily life activities) and structured exercise energy expenditure. Physical activities, both spontaneous and structured or planned, can be of very low intensity including sedentary activities, low, moderate, and vigorous intensity. Intensity, duration, and frequency of the bouts of activity, define the volume of activity and impact energy expenditure related to physical activity. Physical activity energy expenditure is the most variable component of total energy expenditure.

Stein et al. (1999a) objectively measured inflight free-living total energy expenditure with the gold standard method of double-labeled water during the life and microgravity sciences (LMS) 16-day mission. He reported an energy expenditure of 0.9 ± 0.014 MJ/kg/day. He further estimated that total energy expenditure equals $1.4 \times$ RMR + energy cost of structured physical exercise, where RMR is resting metabolic rate (MJ/d) and 1.4 an activity factor. This activity factor is the physical activity level defined as the ratio of total energy expenditure over resting metabolic rate. On Earth, it varies from 1.3 to 1.4 for sedentary and inactive individuals to 1.8–2.0 for sportive people, and can go up to 2.3–2.5 for world athletes (Westerterp, 2018). Non-exercising astronauts therefore have energy requirements close to sedentary and inactive adults in the general population but also to bed-rested participants. The 6° head-down tilt bed rest is a ground model of microgravity used on Earth to study physiological adaptations to weightlessness and test new countermeasures (Hargens and Vico, 2016). Using this model during a 42-day head-down tilt bed-rest study (Blanc et al., 1998), we estimated energy requirements for men to be $1.47 \times$ RMR + energy cost of exercise. In another 2-month bed-rest studies, we further showed that energy requirements for women were $1.45 \times$ RMR + energy cost of exercise (Bergouignan et al., 2010). Although resting metabolic rate has never been directly measured in space, data obtained during bed-rest studies showed a decrease in resting metabolic rate essentially due to fat-free mass loss from ambulatory conditions to bed rest (Blanc et al., 1998; Bergouignan et al., 2006, 2010). This reduction in metabolic rate, however, accounts for a somehow minor change in total energy expenditure, i.e., about 4% or 53 kCal in women (Bergouignan et al., 2010). Although no objective measurement has been reported in space, no change in diet-induced thermogenesis has been observed during bed-rest studies. It is, however, possible that a reduction in postprandial thermogenesis occurs in space, as foods are not consumed under the same solid nature and with the same nutritional density than on Earth. Indeed, a study conducted on Earth has demonstrated that the energy cost of food processing is higher after a solid compared to a liquid meal (Habas and Macdonald, 1998). At rest, the core temperature of the astronauts is 1°C above the core temperature measured on Earth (Stahn et al., 2017) probably because of the impaired convective heat transfer and evaporation process to cool down the body, low-grade pro-inflammatory responses to weightlessness, psychological stress-induced hyperthermia, and strenuous exercise protocols leading to this "space fever" (Fortney et al., 1998; Polyakov et al., 2001; Stahn et al., 2017). On Earth, body core temperature is positively correlated with energy expenditure (van Marken Lichtenbelt et al., 2002), but how changes in body core temperature influence 24 h energy expenditure in space is unknown. Based on all these data, it is probably the large decrease in physical activity due to muscle disuse that is responsible for the decrease in total energy expenditure. Altogether these data are showing that energy needs are similar on the ground for inactive individuals to those in space – the difference being mainly the energy cost of exercise. Why 24-h total energy expenditure is not matched by 24-h energy intake in space remains to be determined.

ENERGY EXPENDITURE, RATHER THAN ENERGY INTAKE, MAY DRIVE BODY WEIGHT CONTROL IN SPACE

To understand the regulation of energy balance in space, it is important to appreciate the coupling between energy expenditure and intake on Earth. A large body of data suggests that fat-free mass is a strong determinant of food intake (Blundell et al., 2012; Weise et al., 2014). This appears to be due to an increase in resting metabolic rate, as basal energy requirements are higher when fat-free mass is greater (Caudwell et al., 2013; Blundell et al., 2015a; Hopkins et al., 2016, 2018). Therefore, the decrease in fat-free mass due to muscle disuse consistently observed during spaceflight may partly explain the lower food intake of astronauts. However, this relationship seems to be more subtle and depends on energy status. While a positive relationship between fat-free mass and energy intake exists when individuals are at or close to stable energy balance, it is disrupted under energy imbalance situations (positive or negative). On Earth, in response to energy deficit, as it has been observed in astronauts, the associated decrease in fat-free mass and subsequently, resting metabolic rate, leads to an increase in energy intake rather than to a reduction, possibly as an attempt to restore fat-free mass (Dulloo et al., 2017; Stubbs et al., 2018). This compensatory effect is most likely

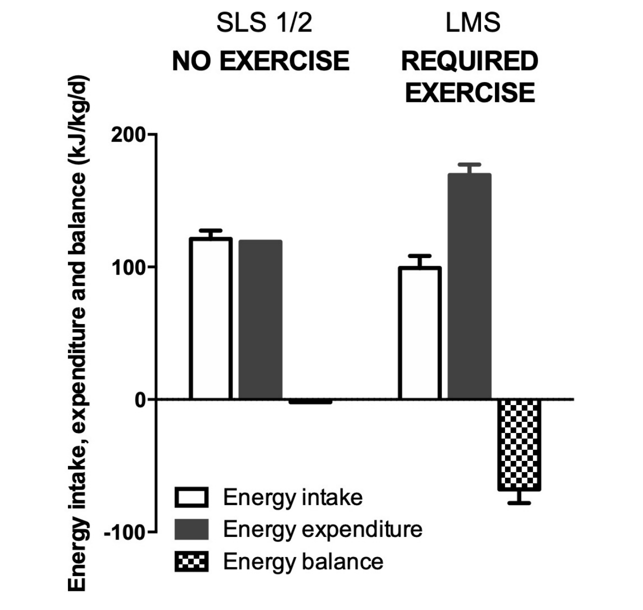

FIGURE 2 | Energy intake, energy expenditure, and energy balance measured in space missions with or without exercise countermeasure. Adapted from Stein (2000).

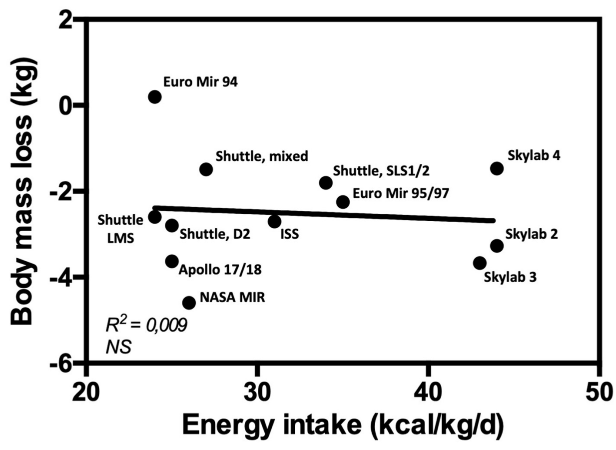

FIGURE 3 | Correlation between body mass loss and energy intake.

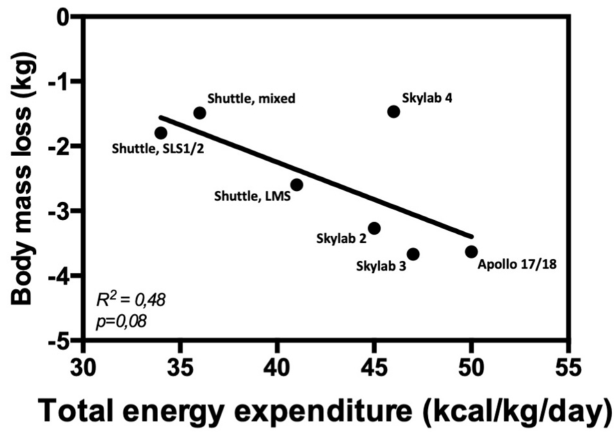

FIGURE 4 | Correlation between body mass loss and total energy expenditure.

true in the acute phase of energy deficit but as soon as a new steady-state in fat-free mass is reached the positive correlation between fat-free mass and energy intake may be reestablished. Over the long term, the lower fat-free mass in astronauts may therefore lead to lower energy intake. This scenario would need to be confirmed in space, but would explain the decrease in energy intake. The problem is that the decrease in energy intake is more pronounced than the reduction in the energy requirements leading to body mass loss.

A recent elegant clinical study on Earth has suggested that 24-h energy expenditure, rather than resting metabolic rate or fat-free mass, is the main predictor of energy intake (Piaggi et al., 2015). In space, Stein (2000) has shown that during a mission in which no exercise countermeasure was required, energy intake matched energy expenditure thus keeping energy balance stable. The nitrogen balance was also stable indicating a maintenance of fat-free mass. Surprisingly, during a mission in which exercise was prescribed as a countermeasure against body deconditioning, energy intake was not matching energy expenditure leading to a negative energy balance (**Figure 2**). This was also associated with a negative nitrogen balance, suggesting a loss of muscle mass. Altogether, these data suggest that the increase in energy expenditure induced by physical exercise is not accompanied by compensatory changes in energy intake to match energy requirements, resulting in negative energy balance. This may further explain why there is no relationship between energy intake and body mass loss (**Figure 3**), but a positive association between total energy expenditure and total mass loss during spaceflights (**Figure 4**). When publishing these data, Stein (2000) suggested that the negative energy balance observed in presence of exercise was the result of the adverse effects of exercise on energy intake. They assumed that this negative feedback on energy intake was due to problems in disposing of the metabolic by-products produced during exercise. Given the impaired efficiency of the thermo-regulatory mechanisms in space, heat and CO_2 produced during exercise would exacerbate the effects of higher body temperature, altered blood flow, and hypercapnia on appetite and energy intake. However, as we discussed it above, these factors may influence appetite but likely to a small extent. An alternative interpretation is that in space 24-h energy expenditure is the main driver of body mass changes, because energy intake cannot match it. This would be contrary to what is observed on the Earth where body weight loss is essentially reached by decreasing food intake (without spontaneous concomitant reduction in 24-h energy expenditure) rather than by increasing energy expenditure (Donnelly and Smith, 2005; Franz et al., 2007; Swift et al., 2018). Altogether these observations question the role of exercise in the regulation of energy balance in space and suggest that energy expenditure plays a key role in body mass control. These results further challenge the dogma of must-do exercise countermeasure, at least in its current form. To fully understand how exercise induces energy deficit in space, it is important to understand the respective impact of exercise on energy intake and expenditure, and the interaction between the different components of energy balance, both in space and on Earth.

ROLE OF NON-EXERCISE ACTIVITY ENERGY EXPENDITURE IN THE REGULATION OF ENERGY BALANCE ON EARTH AND IN SPACE

Because physical activity is the most variable component of energy expenditure, it is thought that the greater moderate-to-vigorous intensity activity (including mainly exercise) is, the higher is total energy expenditure. However, this relationship may not be as straightforward. The different components of energy expenditure seem to interact with one another and play a role in the regulation of total energy expenditure and energy balance in a coordinated manner. The concept of an "activity-stat" was first introduced by TW Rowland in 1998. This concept suggests the existence of a biological control center regulating energy expenditure to a particular set point (Rowland, 1998). Since then, some evidence supporting this theory have been reported. Recently, Pontzer (2015) proposed the concept of constrained total energy expenditure in humans. Based on this concept, energy expenditure increases with physical activity at low activity levels but plateaus at higher activity levels as the body adapts to maintain total energy expenditure within a narrow range. The authors hypothesized that high activity levels may be offset by decreases in the other components of total energy expenditure, i.e., resting metabolic rate and diet-induced thermogenesis. This model has been used to explain why physical activity often has little impact on weight-loss strategies.

What is missing in this hypothesis is that, in addition to resting metabolic and diet-induced thermogenesis, activity energy expenditure can be subdivided in two other sub-components. It is composed of energy expended during structured exercise (i.e., exercise energy expenditure, ExEE, mostly related to moderate to very vigorous intensity activities) and non-exercise activities (i.e., non-exercise activity related energy expenditure, NExEE, including mostly light, and to some extent moderate intensity physical activities). On Earth, NExEE represents the energy expended in any body movement during daily life activities such as walking, taking the stairs, gardening, etc. Early measurement of energy expenditure in respiratory chambers indicated that NExEE accounts for a large amount of calorie expenditure even in sedentary individuals and may therefore constitute a buffering reservoir in case of exercise-induced increase in total energy expenditure (Ravussin et al., 1986). A recent review by Melanson (2017) compiled evidence indicating that NExEE decreases in both men and women during an exercise training program. We showed this is particularly true in overweight/obese individuals who spontaneously decrease NExEE in response to increased ExEE (Lefai et al., 2017). Therefore, rather than

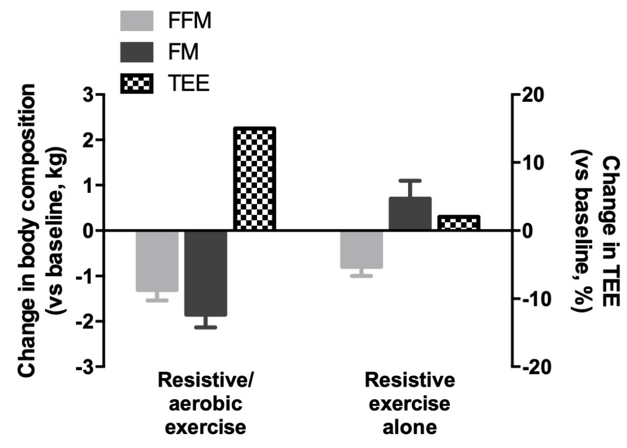

FIGURE 5 | Effect of exercise countermeasure programs combining resistive and aerobic exercise versus resistive exercise alone on fat mass, fat-free mass, and total energy expenditure during bed-rest studies. FM: fat mass; FFM: fat-free mass; TEE: total energy expenditure.

reductions in resting metabolic rate, the absence of increase in energy expenditure with structured physical activity is likely due to decreased NExEE and/or reductions in the energy cost of physical activity.

This regulatory process may, however, be different in space. Because of muscle disuse and reduced cost of locomotion in microgravity, the energy cost of daily activities is much lower, thus reducing NExEE. NExEE is, however, not null as indicated by the activity factor of 1.4 estimated by Stein et al. (1999a) in four non-exercising astronauts. This has two main implications. On the one hand, activity energy expenditure is mainly equivalent to the energy expended during exercise and extravehicular activity, and to a much lesser extent to NExEE. On the other hand, while engaging in the high volume of exercise prescribed as countermeasure, NExEE cannot be used to restore energy balance. Indeed, while the reduction in NExEE during space flights partly compensates for the increase in ExEE, this decrease is not sufficient to fully compensate for the high levels of the exercise prescribed as a countermeasure. This is because NExEE is the result of mandatory workload that cannot be 'compressed'. Bed-rest studies have provided insights on the regulation of energy balance in microgravity conditions.

EFFECT OF EXERCISE ON TOTAL ENERGY EXPENDITURE IN MICROGRAVITY CONDITIONS

Data we and others have obtained over the last 10 years during 10 to 90-day bed-rest studies provided some evidence supporting the hypothesis that exercise countermeasure may be the primary factor responsible for the negative energy balance during spaceflight (Bergouignan et al., 2010; Rudwill et al., 2013, 2015; Scott et al., 2014). Indeed, when subjects were fed either *ad libitum* or when energy intake was linked to requirements without exercise training, no significant change in fat mass was observed, reflecting a stable energy balance (Blanc et al., 1998). In contrast, when an exercise program combining resistive and aerobic exercise was performed, similar to the exercise countermeasure prescribed during spaceflights on the ISS, fat mass was strongly reduced reflecting a significant negative energy balance (Bergouignan et al., 2010) (**Figure 5**). In this study, resistance training was performed at maximal effort on a flywheel ergometer to train the thigh muscle groups using supine squat exercises during 35-min training sessions every 3 days. Aerobic training was performed three to four times per week with intensities varying from 40 to 80% of maximal oxygen uptake for 50 min. Importantly, despite this high volume of exercise and the combination of two types of exercise, this countermeasure protocol did not fully protect subjects from the loss of fat-free mass (Bergouignan et al., 2010). However, a training protocol based on resistive exercise only (flywheel ergometer, 35 min/day, 3–4 days/week) allowed to maintain fat-free mass at the baseline values during a 2-month bed rest in male subjects (Bergouignan et al., 2006), with no concomitant decrease in fat mass. Interestingly, while the resistive exercise protocol had a minor impact on total energy expenditure (+2%), the combined resistive and aerobic exercise countermeasure increased total energy expenditure by 15% (Bergouignan et al., 2010) (**Figure 5**). These data strongly suggest that energy expended during exercise is an important determinant of negative energy balance and weight loss during simulated microgravity in bed rest. Another important factor to consider is the cost of physical activity. Available data are conflicting. On the one hand, the cost of body movement is likely decreased in space compared to on Earth given the lower energy needed for weight-bearing muscle and muscle disuse. On the other hand, the only study conducted in space showed that the mechanical efficiency of walking and running on a treadmill was as low as 11% in space compared to 20% on Earth (Convertino, 1990), suggesting that the cost of activity is higher in space. These data have, however, to be considered with caution, as the subject loading during treadmill exercise is lower in space than on Earth. Oxygen consumption is therefore reduced, which is associated with a lower energy cost of exercise and/or metabolic efficiency. Another parameter to take into account is the metabolic efficiency that seems to be reduced, at least in simulated conditions (Greenleaf, 1989). Because the energy cost of exercise influences energy requirements, especially when large volumes of exercise and extra vehicular activities (EVAs) are prescribed, direct measurements of the efficiency of work and metabolism along with energy cost of activity are required to precisely evaluate the energy needs of astronauts.

Altogether these data support the hypothesis that a decrease in NExEE, rather than an increase in energy intake, is used primarily to buffer energy deficit induced by a high volume of exercise and represents a key component of energy balance control. Because this component is reduced in space due to the very nature of microgravity conditions, NExEE cannot be used (or only to a small extent) to restore energy balance when a high volume of exercise is prescribed as a countermeasure (**Figure 6**). The fact that energy intake cannot match energy expenditure when exercise is performed during spaceflight suggests a further negative feedback of exercise on appetite and energy intake.

EFFECT OF THE EXERCISE COUNTERMEASURE ON FEEDING BEHAVIOR AND ENERGY INTAKE

When energy balance was evaluated with a reference technique, as the difference between energy intake and total energy expenditure measured by the double-labeled water method during a 60-day bed-rest study, energy deficit was more pronounced in subjects following a protocol combining aerobic and resistive exercise than in the non-exercising group (Bergouignan et al., 2010). In this study, energy intake was calculated to counterbalance energy requirements, therefore maintaining a stable energy balance. Surprisingly, exercising subjects spontaneously reduced their energy intake below the prescribed values that accounted for the energy cost of exercise. This suggests that exercise impacts feeding behavior and hence food intake. Studies conducted on the ground have reported that aerobic exercise transiently suppresses appetite (Blundell et al., 2003; Broom et al., 2007), and this effect could be mediated, at least in part, by an increase in plasma satiety hormone PYY after aerobic exercise but not after resistance exercise (Broom et al., 2009). In addition, an increase in GLP-1 plasma concentration, a satiety hormone, has also been described after aerobic exercise sessions (Martins et al., 2007; Chanoine et al., 2008). A recent meta-analysis concluded that exercise induces a short-term energy deficit, as food intake is altered during the few hours following exercise (Schubert et al., 2013). It is possible that the increase in fat-free mass generated by resistive exercise is responsible for an increase in hunger to meet the increased energy requirements (Blundell et al., 2015b). In contrast, aerobic exercise has been associated with increased sensitivity of appetite control mechanisms (Blundell et al., 2015b). Clearly the influence of exercise on appetite is complex given it does not only depend on the type of exercise but also on the intensity. Contrasting results have indeed been published, suggesting that appetite-suppressing hormones are greater after high intensity exercise than after moderate-intensity aerobic exercise (Hazell et al., 2016). However, these studies mostly described effects of an acute exercise session and more work is clearly needed to assess the impact of changes in circulating anorexigenic hormone levels after exercise on subsequent food intake, and long-term appetite responses. In support of this, during a 60-day bed-rest study, combined aerobic and resistive exercise significantly increased fasting plasma GLP-1 concentration in women, which was associated with lower desire for food consumption. This later was itself positively associated with changes in energy intake (Bergouignan et al., 2010).

These data obtained in clinical and bed-rest studies are showing that exercise affects feeding behavior with an acute anorexic phenomenon which could exaggerate the loss of appetite and thus the negative energy balance. However, on Earth, over time, energy intake increases in response to greater energy expenditure induced by exercise training (Westerterp et al., 1992;

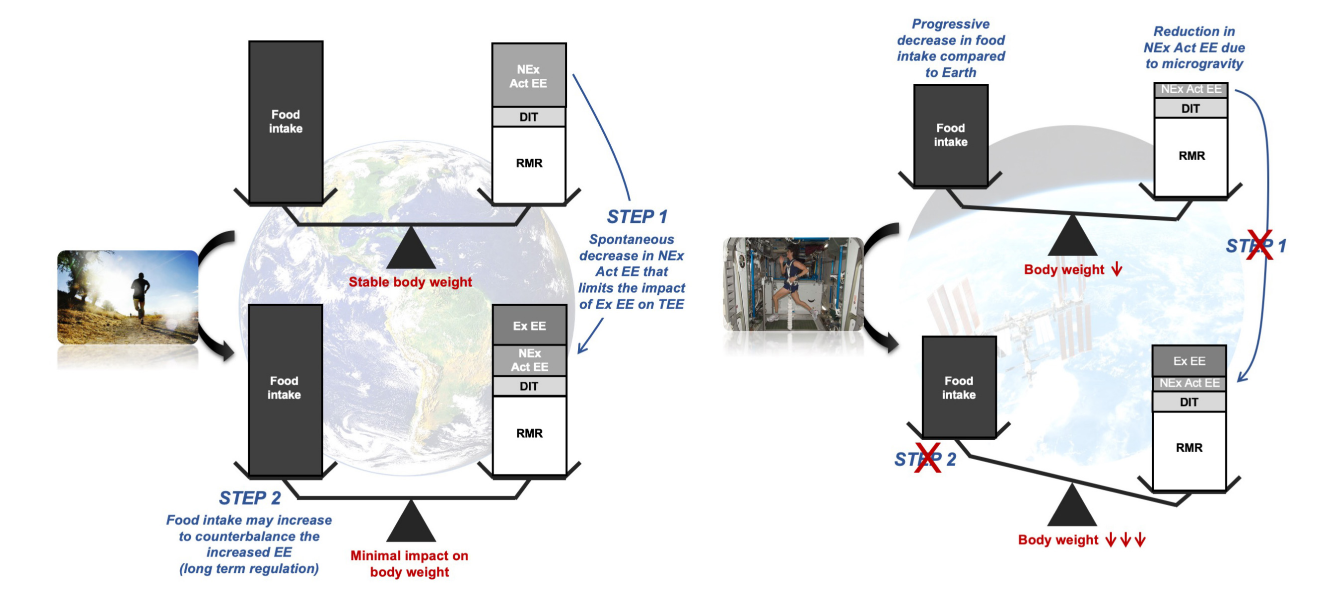

FIGURE 6 | General model of energy balance regulation on Earth and in Space in response to exercise. EE: energy expenditure; TEE: total EE; NEx Act EE: non-exercise activity EE; Ex EE: exercise EE; DIT: diet-induced thermogenesis; RMR: resting metabolic rate.

Charlot and Chapelot, 2013). Most recent data obtained on the ISS suggest it may be the same in space. In addition, inter-individual variability may occur regarding the ability of astronauts to compensate the energy deficit. For example, Stein et al. showed that astronauts who were the most fit were those who experienced the most pronounced deconditioning and lost more weight (Matsumoto et al., 2011; Stein, 2013). Regardless of the time frame needed to adjust energy intake to energy expenditure, all these findings are important to consider when defining future exercise countermeasures, and an exercise countermeasure with minimum impact on appetite should be favored.

WHERE DO WE GO FROM HERE?

A striking point when reviewing all this evidence is the fact that the importance of exercise during spaceflight has never been assessed under actual microgravity conditions. No trial has never been performed to rigorously evaluate the effect of the exercise countermeasure in space. This is an important point, as a large inter-individual variability in body weight loss has been observed and seems to be related to the energy cost of the exercise countermeasure. Furthermore, the adaptations of the body to microgravity *per se* (i.e., without any exercise countermeasure) remain a fundamental scientific question. This has been studied in bed-rest protocols on Earth, but the regulation of energy balance in simulated and actual microgravity is likely to be different. Studying the physiological impact of spaceflight without exercise countermeasure (extravehicular activities will obviously have to be sustained) would, however, provide with crucial information on whether, when, and how the body actually adapts to the space environment. Such a research study, however, raises important concerns; would it be ethical to ask astronauts to not perform exercise during spaceflight? A potential approach would be to run the study during the first period of the space flight, and instruct the astronauts to perform exercise during the last months of the mission in order to restore muscle and cardiovascular fitness before astronauts return to Earth. Although we believe this fundamental research question is important, we do not recommend against exercise countermeasure, but rather to rethink it.

As we reviewed it here, exercise, as currently prescribed, can negatively impact energy balance and other physiological systems. While exercise was likely of particular importance during early spaceflights to re-establish a certain level of physical activity, it may be less important for modern space missions during which astronauts are highly solicited for all type of tasks that involve more body movements. Therefore, we recommend that future studies evaluate energy requirements in astronauts and the energy cost of exercise in space as well as of the intense EVA. In order to better understand the in-flight regulation of energy balance and estimate daily energy requirements, the contribution of different components of energy balance (i.e., energy intake, total energy expenditure, ExEE, NExEE, resting metabolic rate, and diet-induced thermogenesis) should be evaluated along with the energy cost of activity. Because of its complexity, understanding how energy balance is regulated in space is of paramount importance to the health of astronauts and their mission success in future long-term missions. It will also be important from an economic and practical point of view considering the high cost of food transport and storage in a space station. For an individual estimated total energy expenditure of 12 MJ/day, a crew of six astronauts on a 3-year mission to Mars would require about 22 T of hydrated food, excluding water and the extra energy cost of exercise

(Schoeller and Gretebeck, 2000). Even if water is to be totally recycled and food partially dehydrated, the cost of transport would be tremendously significant (20,000 Euros per kilogram), emphasizing the need to derive accurate energy requirements. On the other hand, a small underestimation of the energy requirements could impact health and survival of the astronauts.

Altogether, these data support the need to renew the discussion of the current exercise countermeasure program, especially in the context of planning for planetary exploration. Exercise countermeasures that effectively prevent body deconditioning from microgravity while having a limited effect on total energy expenditure needs to be developed. Others have previously raised this issue and started to test different exercise types to address this question (Matsuo et al., 2012). We specifically propose the use of an exercise countermeasure program that has minimum impact on total energy expenditure, that does not induce a loss of appetite and a reduction in energy intake, while benefiting muscle mass, protecting from muscle fiber type switch, preserving bone mass, intermediary metabolism, cardiovascular function, and aerobic fitness. Among the possibilities, resistive exercise could help prevent muscle mass and function without inducing a large increment on energy expenditure. However, its effect on the cardiovascular system would not be expected to be adequate in counteracting cardiovascular deconditioning (Belin de Chantemele et al., 2004). Interestingly, a large body of data generated on Earth shows that high intensity interval training (HIIT) fulfills all these needs (Alves et al., 2017; Winding et al., 2018). The benefits of HIIT to cardiometabolic health have been extensively studied during the past decade and detailed in many reviews (Bird and Hawley, 2012; Gibala et al., 2012, 2014; MacInnis and Gibala, 2017; Wormgoor et al., 2017). Importantly, HIIT has been proven efficient in protecting bone (de Jong et al., 2004; Aboarrage et al., 2018) and skeletal muscle mass loss (Osawa et al., 2014; Bell et al., 2015; Garcia-Pinillos et al., 2017; Taylor et al., 2017), improving metabolic health (Roberts et al., 2013; Little et al., 2011, 2014; Jelleyman et al., 2015; Madsen et al., 2015; de Souza et al., 2017) and cardiovascular function (Sloth et al., 2013; Hussain et al., 2016; Hannan et al., 2018), sometimes to a greater extent than traditional endurance exercise training (Kessler et al., 2012; Milanovic et al., 2015; Ramos et al., 2015; Karlsen et al., 2017; MacInnis and Gibala, 2017; Xie et al., 2017; De Strijcker et al., 2018). In addition, HIIT has a lower impact on total energy expenditure than continuous aerobic exercise (Matsuo et al., 2012) and requires a lower time commitment than endurance training (Gibala, 2007; Gibala and McGee, 2008; Gillen et al., 2016), which represents a major advantage in the context of an astronaut's busy schedule during a mission. Testing the efficacy of a HIIT program in combination or not with sessions of resistive exercise as a countermeasure for future space missions therefore appears to be warranted. It will also be important to evaluate the frequency at which exercise needs to be performed: should astronauts perform a single bout of exercise once a day, or would it be more effective to fragment exercise into smaller bouts throughout the day? Studies conducted on Earth have demonstrated that exercise-related health benefits, especially with respect to glucose control and insulin resistance, are improved when subjects exercise regularly throughout the day rather than when a single longer bout of exercise is performed (Healy et al., 2008; Peddie et al., 2013). Additionally, HIIT relies primarily upon carbohydrate as fuel rather than fat, which may partially limit the loss of fat mass (De Jong et al., 2019). Another point to address will be to identify the best time to exercise. Indeed, a large body of research has shown that circadian rhythms impact exercise efficiency on Earth (Winget et al., 1985; Carrier and Monk, 2000; Teo et al., 2011). As these rhythms are unsettled during spaceflight due to the 90-min day/night cycle, studies should be performed to evaluate the best timing for exercising in space. Perhaps, exercise should be administered during every 90-min day-night cycle? While planet exploration programs are preparing to be launched, we should therefore approach with caution. Our knowledge of the relationship of exercise on human health in space remains to be fully understood. We are therefore entering a very exciting phase in space science research.

AUTHOR CONTRIBUTIONS

CL and AB wrote the first draft of the manuscript. All the authors edited it, approved the final version of the review, and contributed to the ideas presented in it.

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Conflict of Interest Statement: 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 Physiology

MINI REVIEW
published: 11 April 2019
doi: 10.3389/fphys.2019.00396

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Benefits of Motor Imagery for Human Space Flight: A Brief Review of Current Knowledge and Future Applications

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Motor imagery (MI) is arguably one of the most remarkable capacities of the human mind. There is now strong experimental evidence that MI contributes to substantial improvements in motor learning and performance. The therapeutic benefits of MI in promoting motor recovery among patients with motor impairments have also been reported. Despite promising theoretical and experimental findings, the utility of MI in adapting to unusual conditions, such as weightlessness during space flight, has received far less attention. In this review, we consider how, why, where, and when MI might be used by astronauts, and further evaluate the optimum MI content. Practically, we suggest that MI might be performed before, during, and after exposure to microgravity, respectively, to prepare for the rapid changes in gravitational forces after launch and to reduce the adverse effects of weightlessness exposition. Moreover, MI has potential role in facilitating re-adaptation when returning to Earth after long exposure to microgravity. Suggestions for further research include a focus on the multi-sensory aspects of MI, the requirement to use temporal characteristics as a measurement tool, and to account for the knowledge-base or metacognitive processes underlying optimal MI implementation.

Keywords: mental practice, weightlessness, motor performance, mental processes, microgravity

OPEN ACCESS

Edited by:
Tobias Weber, European Space Agency (ESA), France

Reviewed by:
Tadej Debevec, University of Ljubljana, Slovenia
Maria Stokes, University of Southampton, United Kingdom

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Specialty section:
This article was submitted to Environmental, Aviation and Space Physiology, a section of the journal Frontiers in Physiology

Received: *30 November 2018*
Accepted: *21 March 2019*
Published: *11 April 2019*

Citation:
Guillot A and Debarnot U (2019) Benefits of Motor Imagery for Human Space Flight: A Brief Review of Current Knowledge and Future Applications. Front. Physiol. 10:396. doi: 10.3389/fphys.2019.00396

INTRODUCTION

One main unique aspect of spaceflight is that astronauts do not feel the effects of gravity and therefore experience a weightlessness sensation, also called zero gravity, or microgravity. Technically, escaping the bonds of gravity, which can be simulated in parabolic flights, is known to disrupt both vestibular and proprioceptive systems with symptoms including confusion in the sense of up and down affecting the body schema (Grabherr et al., 2007), the body orientation (Massion et al., 1998; Lackner and Dizio, 2000), and motor control (Papaxanthis et al., 1998; Lackner and Dizio, 2000). Furthermore, additional long-term consequences of extended missions in space include bones weakening (osteoporosis), loss of muscle mass, strength, and endurance (Fitts et al., 2000; Williams et al., 2009), and decrease of blood volume and immunodeficiency (White and Averner, 2001; Williams et al., 2009). Neural studies further revealed changes in the patterns of brain activation after long missions in space (Van Ombergen et al., 2017). For instance, Roberts et al. (2017) reported narrowing of the central sulcus and the cerebrospinal fluid spaces at the vertex, in addition to an upward shift of the brain, which may cause visual impairment and intracranial pressure syndrome. Interestingly, when asking astronauts to either perform pure motor imagery (MI) or visuospatial imagery, Demertzi et al. (2016) observed greater activation of the supplementary motor area post-flight during MI. These results provide evidence that exposure to microgravity might not only affect the human physiology but also the human brain.

Research comparing motor performance in normogravity and microgravity contexts has accumulated in the past 25 years (for a recent review, see Macaluso et al., 2018). Divergent findings have emerged with some studies reporting alteration of movement accuracy and control (Bock et al., 1992; Papaxanthis et al., 1998; Bringoux et al., 2012), in addition to movement speed (Carriot et al., 2004; Crevecoeur et al., 2010). On the other hand, others studies failed to find significant differences in motor control and movement patterns (Papaxanthis et al., 2005; Bringoux et al., 2012). In a recent study, Macaluso et al. (2018) provided evidence that humans might be able to maintain the performance of functional goal-directed actions in weightlessness by successfully managing the spatiotemporal constraints of the movement through postural strategies reducing the displacement of the center of mass.

In sum and with the caveat that the findings have been inconsistent, the detrimental effects of microgravity on human sensorimotor skills must be taken into account both before and during the exposure to a weightlessness condition. In order to counteract these effects, astronauts are usually subjected to intense preparation including practice in simulators, training under water, and parabolic flights (Loehr et al., 2015; Kalicinski et al., 2017), and further have an allocated physical exercise program during their mission in space (e.g., Petersen et al., 2016). Active body mobilization remains, however, limited in space whereby astronauts are confronted with a shortage of time to complete such programs. A cost-effective, and non-invasive adjunct to complement physical training to both prepare the astronauts before a spaceflight and compensate for the detrimental effects of weightlessness exposure is MI. MI has demonstrated to enhance physical practice both in terrestrial (Schuster et al., 2011) and astronaut populations (Papaxanthis et al., 2003; Chabeauti et al., 2012; Bock et al., 2015). Finally, there is a paucity of research investigating the effect of MI when returning to normogravity while a strong theoretical basis would support ergogenic effects.

THE MULTIFACETED NATURE OF MOTOR IMAGERY

Motor imagery is a dynamic mental state during which the representation of a movement is rehearsed without engaging in the corresponding overt execution (Jeannerod, 1994). MI is a multimodal construct which consists of either recalling previously perceived images or envisaging forthcoming events through different sensory modalities. MI has multiple applications in both sport sciences and physical rehabilitation, and there is now converging evidence that MI enhances motor learning (Driskell et al., 1994; Munzert and Zentgraf, 2009; Schuster et al., 2011) and promotes motor recovery (de Vries and Mulder, 2007; Malouin et al., 2013). Interestingly, MI has been shown to improve motor performance both through *online* learning processes, since they occur as a *direct* consequence of practice, and *offline* learning processes (delayed performance improvement), which *indirectly* result from practice (for an extensive review, see Di Rienzo et al., 2016).

Understanding the neural correlates of goal-directed actions, whether executed or imagined, as well as the functional neuroanatomical networks associated with expertise in MI, has been an important achievement in cognitive brain research since the advent of neuroimaging techniques. Accumulated experimental evidences suggest that movement execution and MI share substantial overlap (albeit incomplete) of active brain regions (e.g., Jeannerod, 1994; Munzert and Zentgraf, 2009; Guillot et al., 2012a; Hétu et al., 2013; Hardwick et al., 2018), hence highlighting the functional equivalence between these two forms of practice. The principle of functional equivalence suggests that "motor imagery ... should involve, in the subject's motor brain, neural mechanisms similar to those operating during the real action" (Jeannerod, 2001, pp. S103–S104). Executed movements and simulation (i.e., MI) of the corresponding action engage comparable patterns of connectivity between cortical motor regions (Gao et al., 2011). MI therefore represents an efficient method to stimulate brain motor networks mediating skill acquisition and consolidation (Di Rienzo et al., 2016). Covert and overt practice of the corresponding movement share other similarities. Firstly, the time course of mentally simulated actions has been found to be highly correlated with that of the executed movement (e.g., Decety et al., 1989; Papaxanthis et al., 2002). Certain systematic distortions occur in this temporal relationship influenced by several external factors including action complexity and duration (for reviews, see Guillot and Collet, 2005; Guillot et al., 2012b). Secondly, the peripheral activity of the autonomic nervous system shows similar responses prior and during both MI and actual practices (for review, see Collet et al., 2013). Finally, MI has also been shown to be influenced by biomechanical and motor constraints (Munzert and Zentgraf, 2009). Taken together, these similarities between actual and imagined movements promote MI as a relevant alternative and/or complementary approach to physical practice.

Few studies to date have specifically investigated the specific relationship between MI and microgravity (for review, see Grabherr and Mast, 2010; **Table 1**). One exception by Papaxanthis et al. (2003) showed that cosmonauts performed and imagined movements with similar durations before and after exposure to microgravity. Interestingly, both MI and actual times were longer 2 days after return to Earth, and returned to pre-flight values 6 days after landing. Their findings strongly support that MI process replicates the neural modifications occurring during the re-adaptation of the motor system on Earth's gravito-inertial environment. Based on these findings, MI is therefore predicted to accurately mimic motor execution in the microgravity context. Consequently, MI should ideally be performed before, during,

TABLE 1 | Previous studies considering the effects of microgravity or zero gravity on motor imagery.

Authors	Type of paper	Main results
Chabeauti et al., 2012	Experimental	Actual durations are significantly longer than motor imagery durations in a weightlessness condition, with imagined durations being similar in normo- and microgravity. Changes elicited by microgravity might therefore hinder the updating of the internal models of action.
Bock et al., 2015	Review/theoretical	Theoretical guidelines of motor imagery training pograms designed to reach an optimal level of preparation before exposure to microgravity, and improve performance of astronauts upon return to Earth, before landing.
Grabherr and Mast, 2010	Review/theoretical	By considering the effects of microgravity on the ability to perform mental and motor imagery, the authors highlighted the lack of research investigating the effects of weightlessness on imagined movements, in particular during exposure to microgravity.
Kalicinski et al., 2017	Review/theoretical	Motor imagery of actions which are impossible on Earth (full body floating task) remains possible - although being degraded - and might thus be beneficial for preparing astronauts before their missions and space flights.
Papaxanthis et al., 2003	Experimental	Actual and motor imagery durations were strictly similar both before and after exposure to microgravity. Interestingly, these durations likewise increased 2 days after return to Earth, before returning to approximate pre-flight values 6 days after landing.

and after exposure to microgravity, respectively, to prepare for the sudden lack of gravity after launch, reduce the adverse effects of weightlessness exposition, and facilitate re-adaptation when returning from long exposure to microgravity.

Performing Motor Imagery Before Microgravity

As earlier outlined by Bock et al. (2015), MI should be performed before exposure to microgravity, for at least three main reasons: (i) enhancing the ability to perform MI and the quality of the MI experience, (ii) preparing for exposure to the weightlessness condition, and specifically prepare astronauts for the sudden lack of gravity after launch, and (iii) providing relevant pre-adaptation of MI practice which is likely to be degraded during microgravity exposure.

Preventing the negative effects of microgravity on MI during exposure to microgravity is of particular interest. A study of such detrimental effects was reported by Chabeauti et al. (2012), who provided evidence that actual durations were significantly longer than imagined durations in a weightlessness condition, and that imagined durations did not differ when comparing data collected in normogravity and microgravity. These results suggest that changes elicited by microgravity are likely to hinder the updating of the internal models of action, hence altering the ability to preserve the temporal congruence between actual and MI performance. Based on these findings, developing MI *before* exposure to microgravity, and notably the ability to decrease MI speed, might contribute to preserve the internal models of action, and therefore promote the ability to preserve the temporal equivalence between MI and physical practice during the subsequent flight. In particular, performing slow-motion imagery is known to facilitate a more in-depth and detailed analysis of motor skills being imaged (Jenny and Hall, 2013), which may be useful when anticipating the effects of microgravity on actual performance speed.

While not directly reflecting the influence of microgravity *per se*, Kalicinski et al. (2017) recently designed a study investigating the ability to imagine a movement which is not possible to perform under the presence of gravity (i.e., in a floating position). Although MI remained possible, they found that the elaboration and the control of mental images were degraded, and therefore postulate that MI of vestibular challenging movements might be relevant for astronauts, during their pre-flight training. Specific accurate MI exercises might thus be designed with a focus on the forthcoming lack of gravity. In this particular situation, external visual imagery, which requires to be dissociated from the action itself, might be particularly relevant. Concurrently, developing the ability to imagine the movement mainly from a visual perspective, i.e., without integrating the feeling of the sensations and balance elicited by the action during kinesthetic imagery, may contribute to prepare astronauts for exposure to microgravity.

Motor Imagery to Reduce the Adverse Effects of Microgravity During the Flight

As mentioned previously, converging evidence supports the contention that MI improves motor performance and facilitates motor learning in a similar way (i.e., functionally equivalent) to actual practice of the corresponding movement. Neuroimaging studies provided evidence that the cerebral plasticity occurring during the incremental acquisition of a motor sequence through actual practice was also reflected during MI (Lafleur et al., 2002; Jackson et al., 2003). In a seminal study, Pascual-Leone et al. (1995) reported an enlargement of the cortical representation of target muscles controlling a motor sequence learnt by MI, thus providing clear evidence of neuroplasticity from MI practice. Interestingly, in recent years, researchers investigated how optimally combining embedded MI and physical practice of the same movement in order to achieve peak performance. Allami et al. (2014) provided evidence that MI may replace up to 75% of the physical training if a minimal ratio of physical practice is delivered. Similarly, Reiser et al. (2011) reported strength gains after different ratios of MI and physical practice. In clinical settings, Malouin et al. (2004) observed that one session of rehabilitation including 15% of MI and 85% of physical practice resulted in comparable motor performance gains to 3 weeks of physical therapy. The same authors reported that prior MI practice might reduce by four the amount of physical practice required to reach the same level of performance (Malouin et al., 2009). Taken together, these findings emphasize the importance of embedding MI during physical practice training programs. MI is particularly useful when this physical practice training is restricted, for example, during spaceflights. As suggested by Kalicinski et al. (2017), MI exercises during space flight should also be performed with a focus on adjusting to gravitational forces to prepare astronauts for daily activities after landing. While MI must be seen as a complement to physical practice, rather than being an alternative, MI may need to be the predominant form of training at certain times during long flights, when there is limited space for exercise equipment.

Another important reason to consider the use of MI in weightlessness conditions is its expected beneficial effects on the limitation of strength loss. There is a general consensus that MI contributes to improve strength (Yue and Cole, 1992; Ranganathan et al., 2004; Yao et al., 2013), muscle activation and force performance (Di Rienzo et al., 2015; Grosprêtre et al., 2017). More importantly, MI has been shown to limit the loss of strength in patients with motor disorders and persons suffering from immobilization (Newsom et al., 2003; Lebon et al., 2012; Clark et al., 2014). As physical exercise and active mobilization are limited when facing weightlessness conditions, MI appears to be a plausible alternative to physical practice which may compensate for the lack of actual muscle contractions, which are known to affect the sensorimotor representations of the immobilized body parts (Meugnot et al., 2014). Specifically, the slowdown of the sensorimotor processes may be counteracted by kinesthetic imagery practice, while these beneficial effects would not systematically appear with visual imagery (Meugnot et al., 2015).

Overall, it is important to keep in mind that the nature and the quality of MI (i.e., the ability to preserve the temporal equivalence between imagined and actual times) during exposure to microgravity should be thoroughly controlled as MI is likely to be degraded in weightlessness conditions. Assessing and developing the individual MI ability before the mission therefore appears another critical prerequisite to maintain its accuracy during the flight.

Performing Motor Imagery After Microgravity

To our knowledge, no study has investigated the selective effects of MI after exposure to microgravity in order to specifically determine whether it may facilitate re-adaptation to normogravity. Experimental studies including MI trials after microgravity were mainly designed to compare with data collected before spaceflights. Interestingly, Papaxanthis et al. (2003) showed that on the second day post-flight, both actual and MI durations increased compared to pre-flight measurements, before returning to approximate pre-flight values 6 days after landing. Data therefore revealed similar evolutions for both types of practice, hence highlighting that dynamics of the motor system are appropriately reflected during MI.

Practically, astronauts exhibit pronounced long-term microgravity-related effects requiring weeks to months of rehabilitation for complete recovery. As MI has been shown to promote recovery and functional rehabilitation in patients with motor disorders (Malouin et al., 2013), specific MI exercises may be performed to facilitate re-adaptation and therefore limit the harmful consequences of long exposure to microgravity. Based on findings by Papaxanthis et al. (2003) and predictions derived from simulation theory (Jeannerod, 2006), MI would be expected to have a priming effect on expected physical changes when returning from a weightlessness period. Practically, astronauts spend weeks engaged in hypertrophy training to rebuild muscle and repairing bone after a long mission. Post-flight MI exercises might thus be practiced to promote strength (re)gains and facilitate fluid and effective movement execution of complex motor and balance tasks.

CONCLUSION: HOW TO IMPLEMENT MI INTO THE PREPARATION AND MISSION OF THE ASTRONAUTS

Motor imagery should ideally be performed before, during, and after exposure to microgravity to prepare for the lack of gravity, counteract the effects of weightlessness and promote the re-adaptation to normogravity. A quite similar theoretical viewpoint had been nicely proposed by Bock et al. (2015), who more specifically focused on the preparation period few days before landing. These authors developed two phases of individual MI training program to reach an optimal level of preparation before exposure to microgravity. In the first phase, astronauts should familiarize with MI and develop their MI ability, concurrently with physical practice. Practically, programs might incorporate MI of exercises related to conditions encountered during the forthcoming flight. The second step would be scheduled a few days just before landing and improve performance of astronauts upon return to Earth. Whereby MI might be used and provide before landing and improve performance of astronauts upon return to Earth benefits such as during and after the flight should certainly be extended at other times.

MI is a multimodal construct and should ideally combine the different imagery modalities, including visual imagery through the first and third-person perspectives, as well as kinesthetic imagery. As mentioned previously, this latter form of imagery practice, which requires to feel sensations usually elicited by the action, including force and balance, may be of particular interest during and after the flight, while external visual imagery may be more relevant before the flight. There is further converging evidence that including kinesthetic imagery into MI programs specifically contributes to enhance motor performance and limit strength loss. These benefits may thus be of particular interest to further limit strength loss during the flight and promote strength (re)gains after the flight. Another critical issue relates to the timing of mentally simulated movements. As the ability to achieve temporal congruence between imagined and actual practice is likely to be altered during exposure to microgravity, it is important to develop such capacity before the launch, and to carefully control it while practicing during the flight. Based on data reported by Chabeauti et al. (2012), voluntarily modulating MI speed may therefore be punctually relevant, in order to compensate for the time distortion induced by zero gravity and the corresponding lack of updating of internal models. This remains a working hypothesis awaiting experimental research, as previous data in the field of sport provided strong evidence that voluntarily decreasing imagery speed might similarly affect subsequent actual speed. Finally, few experimental studies highlighted the influence of circadian rhythms on MI accuracy, most especially on MI temporal features (Gueugneau et al., 2009, 2017; Gueugneau and Papaxanthis, 2010; Debarnot et al., 2012; Rulleau et al., 2015). Based on these findings providing evidence of harmful effects of time-of-day on accuracy of motor predictions, MI exercises should ideally be performed within the same period of the day. To account for the above dimensions of imagery in an applied context, interventions would need to include specific training on the metacognitive aspects of MI. Specifically, knowledge-based training on how to apply MI optimally would support any interventions (MacIntyre et al., 2014). Overall, future experimental studies are certainly needed and encouraged to confirm all expected and theoretical beneficial effects discussed in the present paper. Developing MI ability might be relevant for ongoing space tourism or personal spaceflight projects, which begin to appear for leisure or business purposes.

AUTHOR CONTRIBUTIONS

AG and UD participated to the writing of the manuscript and reading to the final version of the manuscript.

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Conflict of Interest Statement: 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 Physiology

MINI REVIEW
published: 16 May 2019
doi: 10.3389/fphys.2019.00584

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Optimization of Exercise Countermeasures for Human Space Flight: Operational Considerations for Concurrent Strength and Aerobic Training

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OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: *21 January 2019*
Accepted: *26 April 2019*
Published: *16 May 2019*

Citation:
Jones TW, Petersen N and Howatson G (2019) Optimization of Exercise Countermeasures for Human Space Flight: Operational Considerations for Concurrent Strength and Aerobic Training. Front. Physiol. 10:584. doi: 10.3389/fphys.2019.00584

The physiological challenges presented by space flight and in microgravity (µG) environments are well documented. µG environments can result in declines muscle mass, contractile strength, and functional capabilities. Previous work has focused on exercise countermeasures designed to attenuate the negative effects of µG on skeletal muscle structure, function, and contractile strength and aerobic fitness parameters. Exposure to µG environments influences both strength and aerobic type physical qualities. As such, the current exercise recommendations for those experiencing µG involve a combination of strength and aerobic training or "concurrent training." Concurrent training strategies can result in development and maintenance of both strength and aerobic capabilities. However, terrestrial research has indicated that if concurrent training strategies are implemented inappropriately, strength development can be inhibited. Previous work has also demonstrated that the aforementioned inhibition of strength development is dependent on the frequency of aerobic training, modality of aerobic training, the relief period between strength and aerobic training, and the intra-session sequencing of strength and aerobic training. While time constraints and feasibility are important considerations for exercise strategies in µG, certain considerations could be made when prescribing concurrent strength and aerobic training to those experiencing human space flight. If strength and aerobic exercise must be performed in close proximity, strength should precede aerobic stimulus. Eccentric strength training methods should be considered to increase mechanical load and reduce metabolic cost. For aerobic capacity, maintenance cycle and/or rowing-based high-intensity intermittent training (HIIT) should be considered and cycle ergometry and/or rowing may be preferable to treadmill running.

Keywords: microgravity, strength training, aerobic training, exercise recovery, neuromuscular adaptation

EXERCISE COUNTERMEASURES DURING HUMAN SPACE FLIGHT AND MICROGRAVITY

Human space flight and microgravity (μG) environments present numerous physical challenges (Petersen et al., 2016). A common, yet troublesome symptom of μG environments is the decline in skeletal muscle mass and strength (Riley et al., 2000; Fitts et al., 2010). This decline is attributable to μG rendering the body and other objects weightless, negating the requirement for muscular contractile forces to elicit movement of the body or external objects (Lackner and DiZio, 1996). Strength qualities are important for situations such as emergency egress, in flight maneuvers and returning to weight-bearing terrestrial environments (Laughlin et al., 2015). In addition, aerobic capabilities are required to sustain functional capacities and conduct activities such as prolonged space walks (Hackney et al., 2015; Hayes, 2015). As such, strategies are needed to maintain both strength and aerobic type physical qualities in μG environments.

Early work examined the effects of resistance exercise strategies on the maintenance of muscle integrity in crew members experiencing imposed bed rest. It was reported that strength training methods resulted in maintenance of muscle integrity during prolonged periods of bed rest (Brannon et al., 1963). These findings lead to subsequent work on exercise in actual or simulated μG, rather than using bed rest as a proxy (Zamparo et al., 1992; Murthy et al., 1994). Initially, exercise strategies for those experiencing μG involved a combination of continuous aerobic exercise *via* loaded cycling and running and walking on a treadmill with numerous bungee cords and restraints. Rudimentary strength training strategies using bungee cords were also prescribed (Kozlovskaya et al., 1995). While it was reported that such strategies could promote maintenance of muscle quality, subsequent work demonstrated that this may not always be the case. Trappe et al. (2009) documented the exercise program undertaken by crew members aboard the International Space Station (ISS) and examined its effectiveness for preserving calf muscle characteristics. It was reported that during the 6-month period, crew members engaged in ~5 days week^{-1} of moderate aerobic exercise and 3–6 days week^{-1} of resistance training. After 6 months, crew members experienced reduction in calf muscle mass and performance, indicating that the strength and aerobic stimuli reported here were insufficient to maintain muscle integrity. Following this work, it was proposed that future long duration space missions should modify exercise prescription. Subsequently, the Integrated Resistance and Aerobic Training protocol (SPRINT) was constructed. The SPRINT protocol was based on previous work into exercise and muscle fiber function in those experiencing bed rest (Trappe et al., 2004, 2008). The SPRINT protocol is notably different to the previous μG exercise prescriptions and is characterized by alternative days of strength and continuous aerobic exercise and interval type aerobic exercise (Murach et al., 2018). It is apparent that those preparing for and experiencing human space flight are required to train concurrently for the development and maintenance of strength and aerobic qualities. Furthermore, if these concurrent training strategies are to be delivered efficiently to maximize strength and aerobic development, certain program variables need to be considered.

CONCURRENT STRENGTH AND ENDURANCE TRAINING AND ITS "INTERFERENCE EFFECT"

Training for the maintenance and/or development of both strength and aerobic physical qualities is termed "concurrent training" and has been associated with suboptimal strength adaptations when compared with strength training performed in isolation (Hickson, 1980; Methenitis, 2018; Murlasits et al., 2018). While combining strength and aerobic training does not appear problematic in untrained populations, challenges are presented in well-trained individuals such as crew members. Previous work has reported crew members to possess good strength capabilities (lower body power = ~2,000 W, upper body power = ~1,000 W, lower body maximum isometric force ~2,200 N, and vertical jump = ~40 cm) (Loehr et al., 2011; English et al., 2015; Mulavara et al., 2018). In addition, it has been reported that crew members also exhibit heightened aerobic capabilities (aerobic capacity index = ~4.0 L min^{-1} for males and ~2.5 L min^{-1} for females) (Moore et al., 2015).

The muted strength development associated with concurrent strength and aerobic training is termed "interference effect" (Hickson, 1980). Combining strength and aerobic training is potentially challenging as there is requirement for crew members to train concurrently in μG environments in order to maintain muscle mass and contractile strength. This presents a potential issue for the crew members operating in μG environments where the strength training stimulus can be compromised by the aerobic type stimulus. Crew members have limited time to perform exercise regimens; therefore, it is essential that any exercise training performed has a positive influence on the individual's functional capabilities. As concurrent training might elicit suboptimal strength adaptations, it is reasonable to suggest that concurrent training is not as effective as separated training sessions, and may not always be appropriate for crew members seeking to maintain physical performance in μG. However, in the reality of space flight, most daily exercise sessions are preferably performed within the same session by crew members, in order to remain time efficient for their duties on board the space station.

Previous work investigating concurrent training and the interference effect has indicated that the presence and magnitude of any blunted strength adaptations are influenced by program variables including volume, frequency, and modality of aerobic training and the order of strength and aerobic stimulus (Wilson et al., 2012; Jones et al., 2013, 2016; Eddens et al., 2018). **Figure 1** summarizes how program variables can contribute to interference characteristics.

It is also worth noting that a large body of evidence has demonstrated that strength training can positively affect endurance performance. Augmented performance is typically

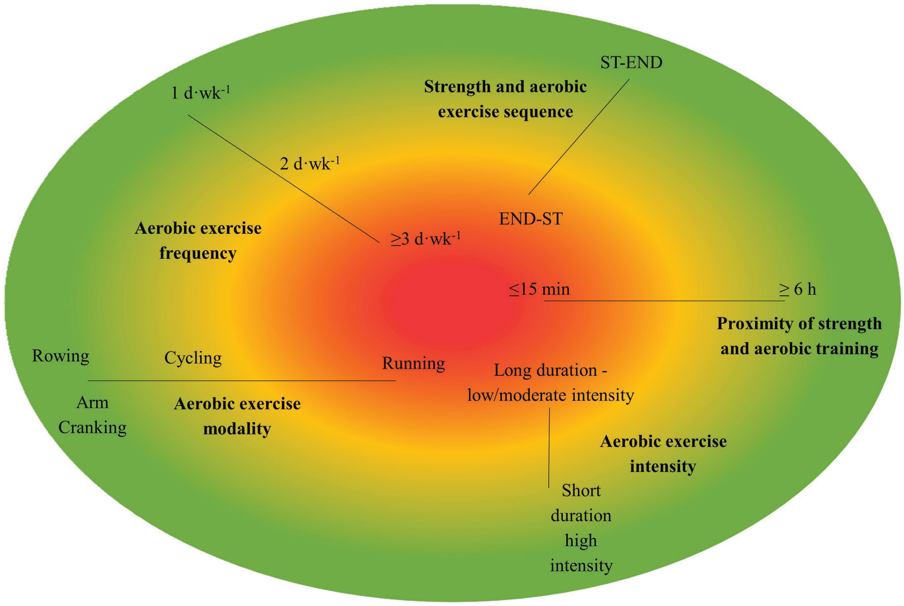

FIGURE 1 | Heat map of program variables and their contributions to the interference effect. Green, not likely to result in interference; amber, possible to result in interference; red, likely to result in interference; ST-END, strength before endurance training; END-ST, endurance before strength training.

via improvements in economy/efficiency (Mikkola et al., 2007; Barnes et al., 2013; Barnes and Kilding, 2015). Conversely, a recent review has suggested that if aerobic training is repeatedly performed under strength training-induced residual fatigue, aerobic type performance may be compromised (Doma et al., 2019). While this may be problematic, it is reasonable to suggest that if a sufficient recovery period is permitted between training modalities, any potential negative effect of strength training on aerobic adaptation may be avoided.

PROGRAM VARIABLES

Training Volume

The volume and frequency of aerobic training performed within a concurrent training regimen may be key program variables that influence any impaired strength development and/or maintenance (Wilson et al., 2012; Jones et al., 2013, 2016), volume being the total time of aerobic training and frequency being the number of aerobic sessions. Higher volumes of aerobic training tend to result in more pronounced inhibition of strength development. Research employing differing ratios of strength and aerobic training reported strength development to be similar in those who performed strength training alone and concurrent training at a ratio of 3:1 in favor of strength training (Jones et al., 2013, 2016). By contrast, those who performed equal frequencies of strength and aerobic training (three sessions per week of both strength and aerobic training) experienced smaller increases in maximal strength than those who performed strength training alone and those who performed three strength sessions per week and one aerobic session (ratio of 3:1). This impact of aerobic training frequency on strength development was observed following both isolated limb (Jones et al., 2013) and multi-joint (Jones et al., 2016) training interventions. Following the multi-joint intervention, those who performed three strength and three aerobic sessions per week not only experienced impaired strength development but also elevations in basal cortisol levels (Jones et al., 2016). It is reasonable to suggest that the muted strength development following higher frequencies and volumes of strength and aerobic training may be attributable to elevated physical stress.

A meta-analysis has indicated that longer durations of aerobic stimulus can result in greater inhibition of strength development (Wilson et al., 2012). However, there is a caveat to this fact. Previous work has reported that the soleus muscle is highly susceptible to unloading due to its oxidative nature (Gallagher et al., 2005; Trappe et al., 2008); it was also reported that to maintain integrity of the soleus muscle, higher volumes of stimulation are required. As such, it appears that the role of volume in interference and the maintenance of physical qualities may be specific to individual muscle groups.

The current guidelines for exercise during human space flight involve concurrent strength and aerobic training, with strength training contributing to 54% of the total training volume for European Space Agency (ESA) Crews (Petersen et al., 2016). However, these relative contributions may depend on the individual training protocol and also may vary between crew members of different space agencies. Separate work has also indicated that these concurrent strategies are high in frequency, with two (one strength and one aerobic) sessions a day being performed 6 days week^{-1} (Loehr et al., 2015). Combined, this may indicate that the current situation on ISS of predominantly concurrent training during long duration missions might result in impaired maintenance of contractile strength and muscle function.

Despite the current prescriptions, it is reasonable to suggest that, from a strength perspective, crew members might benefit from reducing the volume of aerobic training in order to provide adequate stimulus to attenuate losses in aerobic capacity and maintain strength. The benefits of this would allow physical qualities to be maintained and reduce the need to consume increased oxygen to train aerobically and of course reduce the consequent production of CO_2; as a consequence, the burden of regulating ambient CO_2 levels would be reduced.

Training Modalities

Aboard ISS, the use of two devices for aerobic training (treadmill and cycle ergometer) might seem appropriate and provide a variety of aerobic stimuli. It is not only aerobic exercise volume/frequency that impacts on the magnitude of the interference effect. A meta-analysis has indicated the modality of aerobic exercise stimulus influences interference characteristics (Wilson et al., 2012). The meta-analysis of 21 studies reported running to negatively impact on strength development but not cycling (Wilson et al., 2012). As such, it is logical that in μG environments, cycle ergometry would be more conducive to maintaining strength than treadmill running. Furthermore, there is no evidence to suggest that continuous or intermittent rowing results in any inference characteristics. In fact, recent work has indicated that resistance training using a gravity-independent flywheel and aerobic training *via* continuous and intermittent rowing was able to preserve several key muscle characteristics during 70 days of bed rest (Murach et al., 2018). It should also be noted that Murach et al. (2018) observed a combination of eccentric strength training and intermittent rowing successfully preserved muscular integrity of the soleus.

As previously stated, the soleus responds differently to other muscle groups to μG and exercise exposures (Gallagher et al., 2005; Trappe et al., 2008). It is possible that mechanical loading-based aerobic exercise like running can better maintain the qualities of the soleus in μG. An additional meta-analysis has indicated that if running is performed as high-intensity intermittent training (HIIT), then inference characteristics can be avoided (Sabag et al., 2018). As such, in some cases, HIIT running may be a viable aerobic training strategy.

The current time allocation for exercise aboard the ISS is 2.5 h day^{-1}. However, in future human exploration missions, it is possible that greater restrictions will be placed on exercise time. If this is the case, it is imperative that any exercise performed does not inhibit the maintenance of other physical qualities. Irrespective of whether exercise time on long duration missions is reduced, to maintain physical health and functionality, crew members will still be required to perform strength and aerobic training. If time available to exercise is reduced, the nature of the training, would of course, needs to be streamlined. From a strength perspective, the implementation of eccentric training methods (given that the injury risk remains low) may be beneficial. Eccentric muscle actions have the potential to produce high forces (when compared with concentric contractions) with low metabolic costs (McHugh et al., 2002) and hence reduce the increase oxygen cost. Furthermore, the nature of eccentric training methods could be well suited to μG environments. Data pooled from nine studies have indicated that iso-inertial flywheel resistance training involving eccentric overload triggers greater skeletal muscle adaptations (strength, power, and muscle mass) compared to gravity-dependent resistance training paradigms (Maroto-Izquierdo et al., 2017). As eccentric training elicits higher forces with greater skeletal muscle adaptation, it could be argued that maintenance of strength type qualities in μG environments could be achieved more efficiently with eccentric strength training methods. Furthermore, there is no evidence that eccentric strength training methods combined with aerobic training results in muted strength development. Concurrent training studies involving primarily or ideally exclusively eccentric training methods would provide useable inferences for practitioners supporting crew members who experience μG environments. In addition, there is also evidence that acute eccentric training improves mitochondrial calcium homeostasis and may stabilize mitochondrial respiratory function (Rattray et al., 2013). This could suggest that concurrent training with eccentric strength training may have additional benefits.

Currently, during long duration missions, crew members perform a combination of steady-state and interval aerobic training (Loehr et al., 2015). If time available to exercise is reduced, HIIT strategies could be considered. Previous work has indicated that HIIT can be equally effective as continuous training for improving aerobic capacity, despite HIIT duration and volume being much lower than that of continuous training (Tabata et al., 1996; Gibala et al., 2006). Furthermore, when matched for total volume, HIIT has been reported to improve aerobic capacity to a greater extent that moderate-intensity training (Helgerud et al., 2007). Not only does HIIT appear to be a viable option for aerobic exercise under greater time constraints, there is also no evidence that short duration HIIT results in impaired strength responses in concurrent training regimens.

Scheduling of Strength and Aerobic Training

In addition to frequency, volume, and modality of aerobic type stimulus, the order in which strength and aerobic training are performed can also influence the adaptations to concurrent training. A recent meta-analysis examined whether intra-session concurrent exercise sequence modulates strength-based outcomes associated with the interference effect (Eddens et al., 2018). The analysis indicated that strength followed by aerobic exercise is more favorable for improving dynamic strength than *vice versa*. It is likely that this is due to strength training being more effective when performed in a non-fatigued state (i.e., not following prior aerobic exercise) (Sporer and Wenger, 2003). In addition, it is unlikely that aerobic training involving the lower body musculature impacts upper body strength (Jones et al., 2016). Due to the nature of human space flight and long duration missions, it is inevitable that any exercise performed will be placed under strict time constraints. It has been reported that during human space flight, strength and aerobic training can take place "back-to-back" or in close proximity with minimal relief period between training modalities (Petersen et al., 2016). Previous work has indicated that the relief period between strength and aerobic training (even when strength is conducted prior to aerobic training) can influence both acute and chronic strength performance and adaptations (Docherty and Sporer, 2000; Sporer and Wenger, 2003; Robineau et al., 2016). Previous work has indicated that strength and aerobic stimuli should be separated by ≥6 h if impairments in strength development are to be avoided (García-Pallarés and Izquierdo, 2011; Robineau et al., 2016). This suggestion is supported by recent work indicating that combined strength and continuous and intermittent rowing conducted with a 4-h relief period resulted in maintenance of muscle characteristics during 70 days of bed rest (Murach et al., 2018). These data indicate that if time constraints are a concern, a 4-h relief period between strength and aerobic stimuli is permissible. It is also perhaps reasonable to suggest that aerobic training primarily involving the lower body musculature (e.g., cycling) could be followed by upper body strength training.

RECOMMENDATIONS FOR PROGRAMMING AND FUTURE RESEARCH

To conclude, it appears that the volume, frequency, order, and modality of strength and aerobic training can influence the responses to combined strength and aerobic training. Based on what is known about combining strength and aerobic training in terrestrial environments, evidence-based programming recommendations can be made regarding concurrent training in μG. It should however be noted that these are general recommendations and may not necessarily apply to all muscle groups.

The aim of these recommendations is to promote maintenance of strength and aerobic qualities, while minimizing the potential confounding factors associated with concurrent training:

- If strength and aerobic exercise must be performed in close proximity, strength should precede the aerobic stimulus. However, if possible, a 4-h relief period should be permitted.
- For aerobic capacity maintenance, cycle ergometry and/or rowing may be preferable to treadmill running.
- Eccentric strength training methods should be considered to increase mechanical load and reduce metabolic cost.
- For aerobic capacity, maintenance cycle and/or rowing-based HIIT should be considered.

The effects of differing concurrent training strategies in μG environments have not been investigated, and there are limited opportunities to perform controlled intervention studies in a μG environment. This is because flight rules and medical requirements on the ISS stipulate that crewmembers must conduct exercise strategies designed to counteract the negative effects of μG (and no crew wants to take the risk of serious deconditioning). Therefore, the opportunities to manipulate program variables and have individuals performing different exercise strategies within the same long-duration mission are limited. As such, presently we must refer to what we know about combining strength and aerobic training in terrestrial environments and apply these to μG paradigms. It is also not unreasonable to speculate that the elevated physical stress associated with μG environments may result in a more pronounced interference effect. As such, future work should perhaps compare the current exercise prescription of exercise in μG against a concurrent strength and aerobic regimen specifically designed to avoid any interference characteristics.

Future research into exercise countermeasure for human space flight may seek to address the following questions:

- Do high volumes of aerobic training result in inhibited strength development/maintenance in μG?
- Do frequency, order, and modality of strength and aerobic training influence any inhibited strength development/maintenance in μG?
- Are eccentric training methods compatible with aerobic training in μG environments?

AUTHOR CONTRIBUTIONS

TJ and GH wrote the initial drafts with NP reviewing drafts.

FUNDING

The publication fees of this article are funded by the European Space Agency.

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Conflict of Interest Statement: 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 Physiology

MINI REVIEW
published: 22 May 2019
doi: 10.3389/fphys.2019.00581

High-Intensity Interval Training: A Potential Exercise Countermeasure During Human Spaceflight

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High-intensity interval training (HIT) is an effective approach for improving a range of physiological markers associated with physical fitness. A considerable body of work has demonstrated substantial improvements in cardiorespiratory fitness following short-term training programmes, while emerging evidence suggests that HIT can positively impact aspects of neuromuscular fitness. Given the detrimental consequences of prolonged exposure to microgravity on both of these physiological systems, and the potential for HIT to impact multiple components of fitness simultaneously, HIT is an appealing exercise countermeasure during human spaceflight. As such, the primary aim of this mini review is to synthesize current terrestrial knowledge relating to the effectiveness of HIT for inducing improvements in cardiorespiratory and neuromuscular fitness. As exercise-induced fitness changes are typically influenced by the specific exercise protocol employed, we will consider the effect of manipulating programming variables, including exercise volume and intensity, when prescribing HIT. In addition, as the maintenance of HIT-induced fitness gains and the choice of exercise mode are important considerations for effective training prescription, these issues are also discussed. We conclude by evaluating the potential integration of HIT into future human spaceflight operations as a strategy to counteract the effects of microgravity.

Keywords: high-intensity interval training, cardiorespiratory fitness, neuromuscular fitness, human spaceflight, microgravity, physical performance, exercise countermeasure

OPEN ACCESS

Edited by:
Jun Sugawara,
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Reviewed by:
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Specialty section:
This article was submitted to Exercise Physiology, a section of the journal Frontiers in Physiology

Received: *01 February 2019*
Accepted: *25 April 2019*
Published: *22 May 2019*

Citation:
Hurst C, Scott JPR, Weston KL and Weston M (2019) High-Intensity Interval Training: A Potential Exercise Countermeasure During Human Spaceflight. Front. Physiol. 10:581. doi: 10.3389/fphys.2019.00581

INTRODUCTION

The prolonged exposure to microgravity (μG) and the space environment associated with human spaceflight necessitates effective countermeasures to manage the multi-system adaptation that occurs. These adaptations are both short term, including headache, drowsiness, nausea, vomiting, and dizziness, collectively referred to as "space motion sickness" (Ortega and Harm, 2008), and longer term, including fluid redistribution and reductions in maximal oxygen uptake (VO_{2max}), muscle size and strength, and bone mineral density (BMD) (Demontis et al., 2017).

Exercise training is a fundamental strategy for managing adaptation to spaceflight; however, the potential physical (size and internal dimensions of vehicle/habitats), logistical (supply of food and water and device maintenance/repair), and operational (time for exercise, interference with other crewmembers' work) constraints of future space exploration missions highlight a need for alternate approaches to counteracting μG-induced changes (Scott et al., 2019). High-intensity interval training (HIT), involving repeated bouts of intense exercise, interspersed with periods of rest or lower intensity active recovery, is a widely used training approach with demonstrated efficacy for inducing physiological adaptation across a range of outcomes. As an exercise countermeasure, HIT may offer several operational advantages, including; (1) substantial physiological stimulus possible in a short time period; (2) the potential to impact multiple components of fitness simultaneously; (3) is typically performed using a single exercise mode; (4) an ability to target upper- and lower-body function. This mini-review aims to highlight the potential for HIT as an exercise countermeasure during human spaceflight by summarizing the terrestrial evidence base relating to its effectiveness and considering exercise programming variables in the context of spaceflight.

HIGH-INTENSITY INTERVAL TRAINING

Despite intensifying scientific enquiry over the last 15–20 years, HIT is not a new approach to exercise training (Billat, 2001). Although terminology varies, HIT can be: high-intensity interval training (HIT), performed at "near maximal" or "submaximal" intensity (≥80% maximal heart rate), or sprint interval training (SIT), often described as low-volume HIT, characterized by efforts performed at "all out" or "supramaximal" intensity (≥100% VO_{2max}) (Weston et al., 2014a; MacInnis and Gibala, 2017). Despite broad protocol dichotomization, HIT exists on a continuum, encompassing a wide spectrum of exercise intensities, with longer duration HIT intervals (e.g., Wisloff et al., 2007) at the lower end and SIT (e.g., Gibala et al., 2006) at the upper end. As exercise intensity is a key mediator of training adaptation (Shephard, 1968), it may be the intense stimulus induced by HIT is a potent catalyst for physiological remodelling (MacInnis and Gibala, 2017). Despite a predominant focus on VO_{2max} improvement, the intensity of HIT places considerable demands on both the aerobic and anaerobic energy systems and the neuromuscular system (Buchheit and Laursen, 2013a,b), suggesting potential for adaptation across multiple physiological systems.

EFFECTIVENESS OF HIGH-INTENSITY INTERVAL TRAINING

Cardiorespiratory Fitness

Numerous interventions (e.g., Helgerud et al., 2007; Burgomaster et al., 2008; Matsuo et al., 2014; Astorino et al., 2017) demonstrated HIT as a potent strategy for improving VO_{2max}. These experimental findings have been corroborated in several meta-analyses in healthy (Bacon et al., 2013; Sloth et al., 2013; Weston et al., 2014b; Milanovic et al., 2015) and clinical populations (Weston et al., 2014a; Liou et al., 2016). Compared with moderate intensity continuous training (MICT), HIT may elicit adaptations of a similar (Gibala et al., 2006; Burgomaster et al., 2008; Scribbans et al., 2014) or even greater magnitude (Helgerud et al., 2007; Daussin et al., 2008; Matsuo et al., 2014), despite a substantially reduced time commitment. Previous work has reported large improvements in VO_{2max} following HIT (Mean ± SD; 22.5 ± 12.2%) and SIT (16.7 ± 11.6%), compared with a moderate improvement (10.0 ± 8.9%) following continuous training (Matsuo et al., 2014), while a recent meta-analysis demonstrated a possibly small beneficial effect for HIT on VO_{2max} (1.2 ml kg^{-1} min^{-1}; 95% confidence limits ±0.9 ml kg^{-1} min^{-1}) when compared with continuous endurance training (Milanovic et al., 2015). It may be that the underlying physiological mechanisms differ between HIT and MICT (Daussin et al., 2008), although this remains to be fully determined.

Exercise at both ends of the intensity continuum, and that representing the middle ground (e.g., Little et al., 2010), can induce substantial (e.g., 10–15%) improvements in VO_{2max} following short-term training programmes (MacPherson et al., 2011; Metcalfe et al., 2012; Matsuo et al., 2014). Nevertheless, participant-related factors (e.g., baseline fitness; Weston et al., 2014b) and protocol-related factors (e.g., repetition duration; Bacon et al., 2013) moderate responses, suggesting that effective manipulation of programming variables is necessary to maximize physiological adaptation (Buchheit and Laursen, 2013a). While mechanisms responsible for HIT-induced improvements in cardiorespiratory fitness remain elusive, both peripheral (e.g., increased mitochondrial content and function) and central adaptations (e.g., increased cardiac output) may contribute to increased VO_{2max} (Daussin et al., 2007; Burgomaster et al., 2008; Jacobs et al., 2013; Astorino et al., 2017).

Neuromuscular Fitness

The intensity of HIT induces a substantial acute neuromuscular load (Buchheit and Laursen, 2013a) and high levels of muscle fiber recruitment (Sale, 1987), therefore providing a stimulus for neuromuscular adaptation (Creer et al., 2004; Martinez-Valdes et al., 2017). Although resistance training represents the primary strategy for improving muscle morphology, previous investigations demonstrated HIT-induced increases in lean- or fat-free mass (Gillen et al., 2013; Robinson et al., 2017; Sculthorpe et al., 2017) and muscle cross-sectional area (Osawa et al., 2014). Increases in protein synthesis (Bell et al., 2015) and satellite cell activity (Nederveen et al., 2015) may contribute to these observed changes. These findings are not universal however (Nybo et al., 2010), and the potential for HIT to increase muscle mass remains largely unknown.

Substantial improvements in mean and peak power output (PPO) of ~5–20% have been observed following SIT (Burgomaster et al., 2005, 2006; Astorino et al., 2011; Zelt et al., 2014; Sculthorpe et al., 2017), potentially mediated by changes in anaerobic enzyme activity (MacDougall et al., 1998; Rodas et al., 2000).

However, power output determined during short-duration cycling bouts (e.g., Wingate test) may primarily represent metabolic not neuromuscular power. Nonetheless, emerging evidence suggests that HIT increases explosive muscular power, assessed *via* leg extension (Hurst et al., 2018) and standing broad jump (Buckley et al., 2015). Improvements in muscle strength following HIT also occur (McRae et al., 2012; Buckley et al., 2015; Martinez-Valdes et al., 2017) with small-moderate increases (~7%) in knee extensor strength following six sessions of cycle-based HIT performed at 100% PPO (Martinez-Valdes et al., 2017). These findings reaffirm the potential for HIT as a training strategy capable of improving cardiorespiratory and neuromuscular fitness simultaneously.

PROGRAMMING CONSIDERATIONS FOR HIGH-INTENSITY INTERVAL TRAINING DURING SPACEFLIGHT

While HIT can simultaneously improve cardiorespiratory and neuromuscular fitness, acute training responses and subsequent adaptations are determined by the interaction of several programming variables (Buchheit and Laursen, 2013a,b; MacInnis and Gibala, 2017). The following section discusses programming considerations relevant to the operational use and potential advantages of HIT during spaceflight.

Exercise Volume

Low-volume HIT, typically involving four to six repetitions of 30–60 s exercise performed at "all-out" intensity, induces substantial improvements in cardiorespiratory fitness (Sloth et al., 2013; Weston et al., 2014b) and may offer potential for rapid fitness gains in a short time period. However, despite the potent effects of this training stimulus, the intensive nature of this exercise protocol necessitates substantial recovery periods between intervals (~4 min), meaning that session duration is often ~30 minutes. Reducing the volume of exercise does not necessarily lessen the magnitude of adaptation following SIT, and improvements in VO_{2max} can be enhanced with fewer repetitions (Vollaard et al., 2017). For example, a protocol of 3 × 20 s all out cycle sprints performed three times per week for 6 weeks (Gillen et al., 2014) or 12 weeks (Gillen et al., 2016) increased peak oxygen uptake (VO_{2peak}) by 12 and 19%, respectively. Reducing exercise volume further, improvements of 10–15% in VO_{2peak} can occur following 6 weeks of three sessions per week involving only 2 × 20 s all out sprints (Metcalfe et al., 2012, 2016). Importantly, a reduced exercise volume does not appear to have a detrimental effect on anaerobic, as well as aerobic performance, given that improvements in PPO were not different following 2–4 weeks of SIT intervals of either 15 or 30 s (Zelt et al., 2014) or 10 or 30 s (Hazell et al., 2010) duration. Even with a reduced exercise volume, HIT maintains the potential to induce rapid fitness gains.

Exercise training programmes typically involve a combination of resistance and endurance training and are termed "concurrent" (Fyfe et al., 2014) or "combined" training (Hurst et al., 2019). Although resistance and endurance training represent effective strategies for improving muscular and cardiorespiratory fitness respectively, concurrent training may induce an "interference effect" whereby improvements in muscular fitness are attenuated compared with performing resistance training alone (Fyfe et al., 2014). Incorporating SIT into a concurrent training programme may help to mitigate any observed interference effects (Cantrell et al., 2014), as these may largely be exercise volume rather than intensity dependent (Fyfe et al., 2016).

Differentiation of High-Intensity Interval Training

As HIT incorporates a broad spectrum of intensities, performing exercise across this range is an effective strategy to induce a differential adaptive response (Barnes et al., 2013; Rønnestad et al., 2015). Exercise bout duration represents a key programming variable because of the inverse relationship between duration and intensity (i.e., shorter intervals typically involve higher intensity exercise). Therefore, manipulating exercise duration alters energy system contribution (Gastin, 2001) as well as the degree of neuromuscular loading (Buchheit and Laursen, 2013b). Shorter (30 s) compared with long duration cycle-based intervals (300 s) have been demonstrated to result in a higher training intensity (363 ± 32 W vs. 324 ± 42 W) and lead to significant increases in VO_{2max} (8.7 ± 5.0%) and PPO (8.5 ± 5.2%) (Rønnestad et al., 2015). Furthermore, following uphill running-based HIT, improvements in aerobic fitness and performance variables were optimal around the middle intensity (100% velocity at VO_{2max}; 10% gradient; 1:2 work:rest ratio) with increases in neuromuscular measures (e.g., peak power, maximum rate of force development) greatest at the highest intensity (Barnes et al., 2013). Repeated-sprint training (RST), typically defined as a series of short sprints (3–7 s in duration), separated by recovery periods of less than 60 s (Buchheit and Laursen, 2013a), is another HIT derivative at the highest end of the intensity spectrum. As with SIT, RST induces considerable acute metabolic and neuromuscular demands (Buchheit and Laursen, 2013b), thereby highlighting potential as a multicomponent training tool. This supposition was supported in a recent meta-analysis that reported clear beneficial effects of RST on measures of countermovement jump height, sprint times, repeated sprint ability, and high-intensity running performance (Taylor et al., 2015). Manipulating HIT exercise intensity therefore promotes a differential training response, with these findings further demonstrating potential for HIT as a combined training tool for inducing adaptation across multiple physiological systems. Ultimately, varied HIT prescription within a training programme (e.g., Wright et al., 2016) is necessary to maximize metabolic and neuromuscular adaptations (Buchheit and Laursen, 2013a,b).

Maintenance of High-Intensity Interval Training-Induced gains

Although short-term fitness gains are well documented following HIT, maintaining fitness over an extended time period represents another challenge. To date however, only a limited number of studies evaluated the effects of manipulating session frequency on the maintenance of HIT-induced fitness improvements. Following a 2-week SIT intervention, which increased VO_{2max} (3%) and high-intensity intermittent running performance (17%), participants completed a single weekly SIT session for 5 weeks (Macpherson and Weston, 2015). Interestingly, this maintenance phase induced a 4.2% improvement in VO_{2max}, indicating that reduced training frequency can be an effective strategy to maintain SIT-induced fitness improvements (Macpherson and Weston, 2015). In another investigation, performing 24 HIT sessions at either moderate frequency (MF; three sessions per week) or high frequency (HF; eight sessions per week) led to a 10.7% increase in VO_{2max} in the MF group with no statistically significant improvement (3.0%) in the HF group (Hatle et al., 2014). Following the intervention, participants completed a 9-week detraining period involving no training with both groups demonstrating increased VO_{2max} at 12 days post-intervention and a return to baseline 4 weeks after highest measurement (Hatle et al., 2014). These data support the idea that lower frequency training may be as effective as higher frequency training for maintaining fitness, although there remains only limited evidence to support this assertion, particularly in well-trained individuals.

Exercise Mode

Traditionally, HIT has been delivered using a single exercise mode with treadmill walking/running and cycle ergometry, the most commonly used approaches. However, despite the logistical advantages of this approach, these exercise modes deliver a predominantly lower-body training stimulus. In the context of spaceflight, this is likely to be suboptimal because the performance profile of astronauts necessitates a synergy of upper- and lower-body fitness. Recently, however, there has been an increased desire to move beyond the exercise modes typically associated with HIT. Alternative exercise modes for performing HIT include body-weight resistance exercise (McRae et al., 2012), non-weight bearing all-extremity ergometers (Hwang et al., 2016), hydraulic resistance machines (Hurst et al., 2018), a combination of strength and endurance exercises (Buckley et al., 2015), and high-intensity circuit-type training (Sperlich et al., 2017). These modes provide a whole-body training stimulus, inducing substantial improvements in VO_{2peak} (~8%), lower-body muscle power (6–15%), upper- and lower-body 1RM strength (27%), and muscular endurance (40–280%) (McRae et al., 2012; Buckley et al., 2015), following short-term training programmes.

As well as the need for upper- and lower-body fitness, exercise interventions delivered using a single exercise mode are desirable because of physical constraints during spaceflight. Performing combined upper- and lower-body HIT using a hydraulic resistance machine for 12 weeks improves explosive leg power (~10%) and predicted VO_{2max} (8.4%) (Hurst et al., 2018), while 8 weeks of HIT performed using a non-weight-bearing ergometer improves aerobic fitness (11%) and cardiac systolic function (Hwang et al., 2016). While these findings are encouraging, it should be noted that both of these studies involved older adults with relatively low baseline fitness who typically demonstrate greater training-induced improvements. Collectively, however, these data highlight potential for innovative approaches to training delivery and should encourage researchers to explore alternative exercise modes.

INTEGRATION INTO CURRENT AND/OR FUTURE HUMAN SPACEFLIGHT OPERATIONS

Interval exercise during spaceflight is not new, having been previously used during Shuttle missions and on the Mir Space Station. More recently, several interval-type protocols have been routinely used on the International Space Station (ISS) since Expedition 1 (Loehr et al., 2015). The intensity of these treadmill-based protocols was initially limited by technological constraints (e.g., maximal belt speed); however, the availability of the "T2" treadmill and cycle ergometry protocols from Expeditions 20–25 onwards enabled exercise at higher intensities (Loehr et al., 2015). The maximum intensity of cycle-based protocols is currently 90% VO_{2max} – characterizing them as HIT rather than SIT. However, the within-session exercise intensity varies (60 to 90% VO_{2max}), thereby differing from typical experimental HIT protocols where prescribed intensity within a session remains constant. Despite the routine use of interval exercise during spaceflight, NASA's SPRINT study (National Aeronautics and Space Administration [NASA], 2018) is the only controlled investigation involving HIT in μG to date. Notwithstanding positive initial findings, the experimental design and limited available data from this study (Goetchius et al., 2019) make it impractical to draw definitive conclusions about the effectiveness of this training approach.

Maximal intensity exercise, in the form of maximal oxygen uptake (VO_{2max}) assessment, was first incorporated during Shuttle Missions (Levine et al., 1996; Moore et al., 2001) with tests performed on ISS since 2009 (Moore et al., 2014) and used operationally without incident since 2016. This could provide a framework for the use of HIT at intensities up to 100% VO_{2max} during flight, which have been delivered with low risk across a range of healthy and clinical terrestrial populations (Rognmo et al., 2012). While SIT protocols (≥100% VO_{2max}) may represent low risk in terrestrial populations, the physiology of astronauts is altered (although not apparently compromised, e.g., maximum heart rate; Moore et al., 2014) in microgravity, and therefore, the use of SIT for countermeasure exercise requires additional consideration.

Although HIT session duration is often ≥30 minutes, this is consistent with current continuous and interval-type protocols used on ISS and would fit within the current time allowance for aerobic exercise (60 min) (Loehr et al., 2015). However, as HIT achieves significant benefits when interval duration and/or number is reduced, time savings may well be realized. Moreover, if HIT can induce neuromuscular changes, this reduces current and future reliance on resistance training, potentially achieving further time savings. In addition to potential time savings, lower energy expenditure and elevations in metabolism from HIT compared with continuous protocols (Matsuo et al., 2012) offer significant operational benefits over the course of a long mission. Specifically, reduced energy requirements (i.e., provision of food, which represents additional mass) and reduced burden on the environmental management systems (i.e., removal of CO_2, moisture, heat). The effectiveness of short-term low-volume HIT programmes might also facilitate the intermittent use of countermeasure exercise to achieve further savings in resources and by-product management. In this approach, informed by systematic tests of function (e.g., VO_{2max}), a degree of adaptation could be allowed with periods of HIT interspersed to manage the magnitude of change.

Finally, the potential effectiveness of HIT across different exercise modes offers an advantage for exploration. Vehicle/mission constraints make it likely that only one exercise device will be available to crew and current concepts do not include treadmill running (National Aeronautics and Space Administration [NASA], 2017; The Danish Aerospace Company, 2018). However, they do envisage multiple modes of exercise, including cycling, rowing, and upper- and lower-body resistance-type exercise, all of which could accommodate HIT/SIT protocols.

CONCLUSION

Collective evidence suggests that HIT could offer a range of operational and physiological benefits during spaceflight making it a viable tool within the exercise countermeasure programme. Substantial terrestrial findings support the efficacy of HIT as a time-efficient tool for cardiorespiratory fitness improvement with emerging data indicating potential beneficial effects on the neuromuscular system. The potential for HIT to impact other physiological markers affected by μG (e.g., BMD) remains largely unknown however and further investigation is warranted. Furthermore, despite encouraging terrestrial evidence, there remains no rigorous evaluation of HIT in μG and the efficacy of HIT during spaceflight is still unknown. Finally, consideration of astronaut-specific physiology (e.g., μG-induced fluid shifts) as well as logistical constraints (e.g., provision of appropriate exercise devices) and exercise programming variables is needed to maximize the potential application of HIT.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Conflict of Interest Statement: JS is employed by KBRwyle GmbH, Cologne, Germany.

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.

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MINI REVIEW
published: 04 July 2019
doi: 10.3389/fphys.2019.00837

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State-of-the-Art Exercise Concepts for Lumbopelvic and Spinal Muscles – Transferability to Microgravity

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Edited by:
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Specialty section:
This article was submitted to
Environmental, Aviation and
Space Physiology,
a section of the journal
Frontiers in Physiology

Received: 10 April 2019
Accepted: 17 June 2019
Published: 04 July 2019

Citation:
Hides J, Hodges P and Lambrecht G
(2019) State-of-the-Art Exercise
Concepts for Lumbopelvic and
Spinal Muscles – Transferability
to Microgravity.
Front. Physiol. 10:837.
doi: 10.3389/fphys.2019.00837

Low back pain (LBP) is the leading cause of disability worldwide. Over the last three decades, changes to key recommendations in clinical practice guidelines for management of LBP have placed greater emphasis on self-management and utilization of exercise programs targeting improvements in function. Recommendations have also suggested that physical treatments for persistent LBP should be tailored to the individual. This mini review will draw parallels between changes, which occur to the neuromuscular system in microgravity and conditions such as LBP which occur on Earth. Prolonged exposure to microgravity is associated with both LBP and muscle atrophy of the intrinsic muscles of the spine, including the lumbar multifidus. The finding of atrophy of spinal muscles has also commonly been reported in terrestrial LBP sufferers. Studying astronauts provides a unique perspective and valuable model for testing the effectiveness of exercise interventions, which have been developed on Earth. One such approach is motor control training, which is a broad term that can include all the sensory and motor aspects of spinal motor function. There is evidence to support the use of this exercise approach, but unlike changes seen in muscles of LBP sufferers on Earth, the changes induced by exposure to microgravity are rapid, and are relatively consistent in nature. Drawing parallels between changes which occur to the neuromuscular system in the absence of gravity and which exercises best restore size and function could help health professionals tailor improved interventions for terrestrial populations.

Keywords: counter-measures, trunk muscles, anti-gravity, space flight, back pain

INTRODUCTION

Exposure to microgravity induces rapid alterations in multiple physiological systems. This mini review focuses on neuromuscular and sensorimotor systems. One of the primary changes in the neuromuscular system in response to microgravity is skeletal muscle atrophy, which occurs especially in muscles that maintain posture while upright on Earth (anti-gravity or postural muscles) (Chang et al., 2016). Changes are greater in the lower body than the upper body, with muscle losses documented in the muscles spanning the trunk, hip, knee, and ankle (Mulavara et al., 2018).

In addition, bone mineral density decreases by 1–2% per month (LeBlanc et al., 2000). Back pain among astronauts has a documented incidence rate of 52 (Kerstman et al., 2012) and 70% (Pool-Goudzwaard et al., 2015). Exercise is the only countermeasure available to mitigate declines in muscle size and function, bone density, and is routinely used in spaceflight to protect health of crews and to effectively manage back pain (Kerstman et al., 2012). The NASA roadmap projects that humans will be sent to Mars by the 2030s. Details concerning how exercise can be optimized to limit atrophy are currently inadequate, and development of countermeasures for long duration missions is required. A recent study reported that lessons learned from development of exercise strategies on Earth could inform programs for long duration missions. In particular, programs developed for people with low back pain (LBP) may have application as inflight exercise countermeasures (Hides et al., 2017). Since the last review was written in 2017, there have been considerable advancements in knowledge in the field of LBP research. For example, the mechanisms underpinning the changes in paraspinal muscles observed in people with LBP are only just beginning to be understood. An increased understanding of these changes may inform improved design and timing of exercise interventions. Despite there being a small amount of data for astronauts, and a large amount of data for people on Earth with LBP, studying astronauts provides valuable data as exposure to microgravity provides a discrete perturbation to the system and produces relatively consistent and predictable responses. On Earth, LBP and the accompanying changes in the paraspinal muscles might take decades to occur and have many contributing factors. With astronauts, it is possible to plan longitudinal studies and conduct measures pre-and post- exposure to the discrete modification of microgravity and evaluate the effectiveness of different interventions. Conducting prospective research trials on Earth is difficult, as it requires assessment of a very large pool of individuals, waiting for LBP to develop, and accounting for the multiple contributing variables. Additional information may be gained from Earth-based analogue studies, such as exercise interventions for people following prolonged bed rest.

EARTH-BASED ANALOGUE STUDIES AND TRUNK MUSCLES

Bed rest and dry immersion are models commonly used to simulate microgravity and create a terrestrial model of space flight with the advantage of being able to manipulate research conditions (Parry and Puthucheary, 2015; Ploutz-Snyder et al., 2018; Tomilovskaya et al., 2019). In bed rest, participants follow a strict protocol of lying down in bed at a 6° head down tilt for days to months. In dry immersion, a waterproof elastic fabric is used to immerse subjects into a deep bath up to the neck level in a supine position (Tomilovskaya et al., 2019). These trials are used to understand the implications of muscle disuse/physical inactivity, to simulate the axial unloading experienced by the sensorimotor system in space and in the case of dry immersion, to simulate a lack of support (Reschke et al., 2009; Tomilovskaya et al., 2019).

In the trunk region, muscles that have been studied include the multifidus, lumbar erector spinae, quadratus lumborum, abdominal wall muscles (transversus abdominis, and obliquus internus and externus abdominis) and psoas. Bed rest studies have shown that preferential atrophy of antigravity muscles occurs in response to this stimulus (Bloomfield, 1997), and there is evidence of progressively greater decrements in muscle size over time (Parry and Puthucheary, 2015). In dry immersion, a significant decrease in the transverse stiffness of the back extensor muscles has been noted (Rukavishnikov et al., 2017). This is interpreted to indicate decreased extensor muscle activity and produce a flexed posture as an acute response to transition to weightlessness (Tomilovskaya et al., 2019). In response to bed rest, the rate of muscle atrophy in the lumbo-pelvic region was greatest in the multifidus (L4 and L5 vertebral levels) and the lumbar erector spinae (at L1 and L2) muscles, where both muscles are known to have their greatest cross section area. A 5-day dry immersion study also found decreased cross-sectional area area of the quadratus lumborum, multifidus, and erector spinae muscles at the L4-L5 vertebral level on MRI (Rukavishnikov et al., 2018). Bed rest induced a contrasting increase in size of the abdominal flexor and psoas muscles (Hides et al., 2007; Belavy et al., 2011). Some of the changes induced in prolonged bed rest studies are long lasting in nature. Changes observed in the lumbar multifidus muscles remained evident 90 days following re-ambulation and return to full pre-bed rest levels of activity (Belavy et al., 2008).

In addition to changes in muscle size, bed rest, and dry immersion have been found to affect the passive structures of the spine. This includes increased disc volume, spinal length, and loss of the lower lumbar lordosis (Belavy et al., 2011; Rukavishnikov et al., 2018). Although these Earth-based analogue studies provide valuable insights, some responses may not be observed in microgravity. For example, no changes in lumbar inter-vertebral disc height or disc water content were found on pre- to post- space flight imaging (Chang et al., 2016; Bailey et al., 2018) and the occurrence of LBP on Earth during bed rest is different from LBP in microgravity in relation to pain intensity and duration (Pool-Goudzwaard et al., 2015). Innovations including use of in-flight ultrasound imaging are being evaluated as a way to monitor changes occurring during space flight to understand the mechanisms for these differences (Garcia et al., 2018; Harrison et al., 2018).

CHANGES IN TRUNK MUSCLES ASSOCIATED WITH LOW BACK PAIN AND SPINAL CONDITIONS

Low back pain is a complex condition with multiple contributors to both the pain and associated disability, including psychological factors, social factors, biophysical factors, comorbidities, and pain-processing mechanisms (Hartvigsen et al., 2018). This mini review will address biophysical factors, namely trunk muscle changes. Changes in trunk muscles have been observed in people with LBP. In those with acute LBP, localized muscle atrophy of the multifidus muscles has been demonstrated (Hides et al., 1996). In subacute LBP, there is adipose accumulation without atrophy (Battie et al., 2012), whereas chronic LBP is characterized by more diffuse atrophy (Hides et al., 2011), fibrosis and fatty infiltration (Zhao et al., 2000). A recent systematic review examined the association between LBP and morphology of paraspinal muscles including the erector spinae, multifidus, psoas, and quadratus lumborum muscles (Ranger et al., 2017). Results showed evidence for a negative association between cross-sectional area (CSA) of the multifidus muscles and LBP (smaller muscle as related to worse LBP). Results were conflicting for the other muscles (Ranger et al., 2017). CSA of the multifidus muscles was predictive of LBP for up to 12 months in men (Ranger et al., 2017) and CSA of the multifidus and erector spinae muscles at the L4 and L5 vertebral levels predicted low back disability (Ranger et al., 2018). Fatty infiltration of paraspinal muscles may result in loss of muscle function and impaired strength (Lang et al., 2010). Although higher levels of MRI defined fat infiltration have been observed in people with LBP (Kjaer et al., 2007; Pezolato et al., 2012), there are conflicting results regarding the relationship between fatty infiltration of the multifidus muscles and LBP (Ranger et al., 2017). The mechanisms underpinning the changes in the paraspinal muscles in people with LBP are complex and time dependent and only beginning to be understood. In the acute phase, animal studies show reduced neural drive to the multifidus muscles (consistent with inhibition) immediately after injury (Hodges et al., 2009). However, this appears to shift to fibrotic, adipose and muscle fiber-type changes (fast-to-slow fiber transformation) in the multifidus muscles mediated by dysregulated inflammatory pathways in the muscle in the subacute period (Hodges et al., 2015), which is thought be related to activity of pro-inflammatory macrophages (James et al., 2018b). In animals, this has been shown following experimental injury to intervertebral disc despite no direct injury to the muscle (Hodges et al., 2009), and after spontaneous intervertebral disc degeneration (James et al., 2018a, 2019). In this latter study, dysregulation of the inflammatory pathways was related to the severity/extent of the disc degeneration and changes were prevented by physical activity (James et al., 2018a). Exercise also prevented the accumulation of fibrosis (James et al., 2019). In addition to these effects, exercise also polarizes macrophages to the anti-inflammatory subtype (Leung et al., 2015) in addition to other effects such as preventing central sensitization (Sluka et al., 2013), as well as effects on muscle fiber types and metabolism. Together, exercise represents a clinical strategy with diverse effects on muscle health, supporting the concept of 'exercise as medicine' (Ploutz-Snyder et al., 2018). In the chronic phase, more generalized changes appear consistent with disuse.

Findings of a pro-inflammatory response in the multifidus muscles may also be very relevant for systemic inflammatory conditions affecting the spine such as axial spondyloarthritis (axSpa) and for critically ill patients who are immobilized. Although axSpa is a systemic disease, the initial inflammatory changes occur in the lumbo-pelvic region, and the lumbar paraspinal muscles are therefore a target for any primary or secondary pathological changes. Studies using MRI have demonstrated decreased CSA of the multifidus muscles, as well as changes in composition of the muscles (Akgul et al., 2013; Resorlu et al., 2017). Although exercise is beneficial in diseases such as axSpa, the mechanisms are not known. The effects could be mediated by the complex physiology of cytokines and associated molecular pathways. For instance, cytokines including interleukin 6 (IL-6) are released by muscles on contraction (Ostrowski et al., 2000). IL-6 has both pro- and anti-inflammatory effects and can act in a hormone like manner to produce anti-inflammatory effects, such as increasing IL-10, while decreasing TNF-α (Starkie et al., 2003). On this foundation, it has been proposed that the benefits of exercise on axSpa may be mediated *via* decreasing inflammation (Sveaas et al., 2017). Regarding critically ill patients, immobility also increases the production of pro-inflammatory cytokines and reactive oxygen species with subsequent muscle proteolysis promoting overall muscle loss (Winkelman, 2009; Puthucheary et al., 2010).

EXERCISE AND LOW BACK PAIN

There are many forms of exercise therapy for low back pain (LBP). Over the last three decades, changes to key recommendations in clinical practice guidelines for management of LBP have placed greater emphasis on self-management and exercise programs targeting functional improvement (Foster et al., 2018). Many approaches for management of LBP focus on modifying motor control, which refers to motor, sensory, and central processes for control of posture and movement (Hides et al., 2019). A common assumption of motor control training (MCT) is that the manner in which an individual loads their spine (e.g. posture, movement, and muscle activation strategies) can contribute onset, persistence, and recovery of symptoms. MCT considers sensory and motor aspects of spine function, and each individual's management program is tailored to the suboptimal features identified on assessment. The MCT approach aims to identify and modify the suboptimal features of motor control, with integration into function. Although there is limited evidence to suggest that MCT is more effective for LBP than other forms of exercise in the general population (Macedo et al., 2014; Smith et al., 2014; Saragiotto et al., 2016), MCT has been considered to be an important component of post-mission neuromuscular reconditioning of astronauts post spaceflight, especially with respect to regaining postural alignment and axial loading (Evetts et al., 2014).

It has been demonstrated that MCT can remediate changes in trunk muscles associated with LBP, but the effects and design of exercise will depend on the timing, and the underlying mechanisms. In the acute phase, when neural inhibition explains the rapid muscle atrophy, MCT achieved restoration of CSA of the multifidus muscles (Hides et al., 1996) and reduced recurrence of symptoms (Hides et al., 2001) with precise gentle activation. In athletes with more persistent symptoms, MCT decreased pain along with increases in the CSA of the multifidus muscle (Hides et al., 2008). Several studies have shown that in the chronic phase, adequate loading of the muscles is necessary to induce muscle hypertrophy (Danneels et al., 2001; Schoenfeld, 2010). Of note, individuals with LBP who have higher proportions of fatty infiltration into lumbar multifidus (at the L4/5 and L5/

S1 vertebral levels) are less likely to respond to exercise therapy. This may suggest that structural changes in muscles are more resistant to change (Hebert et al., 2018), or that further refinement of the exercise design is necessary to optimize effect in this group. Promisingly, there is preliminary evidence that fatty infiltration of the multifidus muscles can be reduced with exercise. A recent study showed that free weight-based resistance training decreased chronic LBP and disability, in conjunction with altered biomechanics of a squat exercise and reduced fatty infiltration of lumbar multifidus and lumbar erector spinae muscles at the L3/4 and L4/5 vertebral levels, but not at L5/S1 (Welch et al., 2015). The L5/S1 vertebral level had higher percentages of fatty infiltration pre-intervention, and the investigators proposed that muscles with a higher percentage of fatty infiltration may be more resilient to change in response to exercise, or alternatively that the loading may have been distributed unevenly with decreased loading on the multifidus muscle in that region.

EFFECTS OF MICROGRAVITY ON TRUNK MUSCLES

Recent work has investigated the effect of microgravity on active (Chang et al., 2016; Bailey et al., 2018; Burkhart et al., 2018) and passive structures of the spine (Garcia et al., 2018; Harrison et al., 2018). Both the size and composition of the paraspinal muscles and changes in the lumbar lordosis have been examined pre- and post-spaceflight and 6 months on the International Space Station (ISS) in three recent studies (Chang et al., 2016; Bailey et al., 2018; Burkhart et al., 2018). The lumbar spine was shown to flatten by 11%, and the size of the multifidus muscles decreased by 8–9% (at the L3-4 vertebral level) (Bailey et al., 2018). Of note, changes in multifidus CSA correlated with the changes in the lumbar lordosis. With respect to individual paraspinal muscles decreases in CSA (erector spinae: −4.6%, multifidus: −8.4%, quadratus lumborum: −5.9 to −8.8%) and increased intramuscular fatty infiltration of these muscles (and the psoas) have also been observed post-flight (Burkhart et al., 2018). However, CT scanning was conducted at the L1/L2 vertebral levels, so is possible that the changes observed may have been even greater at the lower lumbar levels, which were not measured in this study. Promisingly, results showed that more resistance exercise was associated with less decline in the CSA of the ES and MF muscles (Burkhart et al., 2018). A study employing MRI showed that paraspinal lean muscle mass at the L3-4 vertebral level decreased significantly post mission, but recovery was incomplete 46 days post-flight (Chang et al., 2016). It is currently unknown whether exercise countermeasures will be effective at preventing inflight paraspinal muscle atrophy in long duration missions (Chang et al., 2016).

CURRENT EXERCISE COUNTERMEASURES ON THE ISS

Since 2006, the European Space Agency (ESA) has built a multidisciplinary team that is responsible for astronaut preparation, inflight management while on the ISS and reconditioning after return to Earth. A recent clinical commentary has provided a detailed description of the physiotherapy (Lambrecht et al., 2017) and sports science (Petersen et al., 2016) programs. These were developed over nine long-duration missions. There is also work outlining the Russian countermeasure systems for adverse effects of microgravity on long-duration ISS flights (Kozlovskaya et al., 2015). The principles underlying the ESA astronaut program for lumbo-pelvic neuromuscular reconditioning post spaceflight have also been published (Evetts et al., 2014).

During pre-flight training, astronauts are familiarized with the Advanced Resistive Exercise Device (ARED), which is an exercise countermeasure on the ISS. This focuses on optimizing spinal posture during the exercise while on Earth, as maintaining a good spinal position in microgravity can be challenging due to the reduced awareness secondary to lesser proprioceptive feedback in the absence of gravitational load and muscle activation. In flight, astronauts perform 2 h of training each day to mitigate the known negative effects of microgravity on the neuro-musculoskeletal system. A comprehensive program including use of cycle ergometry, treadmill and ARED training is used in an attempt to maintain muscular and cardiovascular endurance, muscle strength, and provide axial loading of skeletal structures (Lambrecht et al., 2017). However, it is important to note that the vertical loading provided by a harness on the ISS treadmill only provides a load of approximately 50 to 70–80% of body weight (Petersen et al., 2016) and that previous work has shown peak forces experienced during walking and running on-orbit are markedly lower than those measured on Earth (Cavanagh et al., 2010). Astronauts are monitored using real-time feedback *via* an audio and video conference link with the ESA physiotherapist and sports scientist, to optimize performance and for safety (Lambrecht et al., 2017).

Longitudinal monitoring of size of trunk muscles in response to exposure to microgravity and reconditioning has shown that exercises performed using the ARED induce changes that differ between trunk muscles/muscle regions. Although the exercise program successfully maintained the size of the multifidus muscles at the L2-L4 vertebral levels, the multifidus muscle at the L5 level was still reduced post exposure to microgravity (Hides et al., 2016). The localized effect and recalcitrance to rehabilitation at this level parallels findings of some Earth based studies. The multifidus muscle at L5/S1 has been shown to be affected more than other vertebral levels in response to de-loading (Hides et al., 2007; Belavy et al., 2011), acute and chronic LBP (Hides et al., 1996, 2011) and in response to exercise interventions (Hides et al., 2008, 2012; Welch et al., 2015). The observation that size of the multifidus muscles at L4 and L5 predicts disability associated with LBP, reinforces the premise that these lower levels require special attention when prescribing exercise (Ranger et al., 2018). The position of the lumbo-sacral junction has been monitored closely in astronaut reconditioning to allow progression to weightlifting and endurance training for astronauts (Petersen et al., 2017). If the astronaut is unable to control their spinal alignment during exercise and function, they are encouraged to exercise with lower load, where optimal postural alignment can be maintained, prior to progression to greater load.

IMPLICATIONS FOR EXERCISE COUNTERMEASURES FOR FUTURE HUMAN EXPLORATION MISSIONS

One of the challenges for space travel beyond the ISS is the development of effective countermeasures for future exploration vehicles that are highly restricted in terms of the allocations for exercise hardware, volume, mass, and power (Ploutz-Snyder et al., 2018). Thus, large devices such as the ARED may not be available. NASA is currently developing small exercise devices that combine aerobic and resistance exercise in a single device (Ploutz-Snyder et al., 2018). When tested on bed-rest participants, 1 h per day preserved muscle, cardiovascular fitness and bone mass. This training time is shorter than daily exercise sessions performed on the ISS (Lambrecht et al., 2017), and the smaller size of the device could potentially be used in volume constrained spaceflight. Lower body negative pressure treadmill exercise has also been implemented on bed-rest participants, with findings suggesting this intervention partially counteracts deconditioning associated with simulated microgravity (Cao et al., 2005). It has been proposed that the proprioceptive system could be targeted by countermeasures given current spaceflight constraints (Layne and Forth, 2008; Yarmanova et al., 2015; Mulavara et al., 2018). Neurophysiological studies indicate that when vestibular information becomes unreliable, supplemental information such as proprioception is up-weighted to maintain control of posture and locomotion (Yates et al., 2000; Carriot et al., 2015). The addition of inflight proprioceptive countermeasures coupled with adequate resistance training could therefore help to mitigate the changes seen in response to prolonged exposure to microgravity (Bloomberg et al., 2015). The multifidus muscle is dense with muscle spindles (Nitz and Peck, 1986), and plays an important role in proprioception of the lumbo-pelvic region and control of the lumbar lordosis.

One disadvantage of the ARED is that it only involves movement in one dimension, but humans are designed to move in three dimensions. Elastic bands, such as Theraband, could be used to perform exercises in three dimensions. In addition, axial loading through the use of skinsuits is a possibility (Carvil et al., 2017). Different combinations of exercise countermeasures would be possible, for example, astronauts could perform exercises while wearing skinsuits, and while using technology based solutions already developed on Earth for conditions such as LBP. Virtual reality-based technology has successfully been used to administer LBP interventions (Park et al., 2013; Kim et al., 2014), where patients see themselves as a projected avatar. This could be used to monitor and correct posture, provide customized rehabilitation programs in order to strengthen muscles and increase endurance (Su et al., 2015). In addition, if astronauts were experiencing LBP on long duration missions and having difficulty with activation of the multifidus muscle, ultrasound imaging could be used to provide feedback and enhance MCT (Hides et al., 2012). Ultrasound imaging has been successfully used by crew on the ISS to provide examinations of the spine (Garcia et al., 2018), and ultrasound imaging could be a viable option for inclusion on long duration flights, due to the extremely compact nature of recently developed equipment.

CONCLUSION

Exposure to microgravity is associated with LBP and an elevated risk of disc herniation on return to Earth. Understanding the mechanisms by which the exposure to microgravity affects the spine is important. This information is likely to guide in flight countermeasures. Understanding the effects of microgravity on the spine can provide new and potentially important information which could be used to design future interventions for people on Earth. As we move towards long-term missions, this reciprocal knowledge transfer could benefit both astronauts and people with chronic conditions such as LBP on Earth.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

ACKNOWLEDGMENTS

The authors wish to thank their colleagues from the European space Agency for their continued collaboration, acknowledge previous funding from the European space Agency, the astronauts who have answered questionnaires regarding low back pain and allowed them to measure their paraspinal muscles permitted us to report the findings, and the co-ordinators and participants from the Berlin Bed Rest Studies.

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Conflict of Interest Statement: 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 Physiology

SYSTEMATIC REVIEW
published: 24 July 2019
doi: 10.3389/fphys.2019.00864

Re-examination of 1- vs. 3-Sets of Resistance Exercise for Pre-spaceflight Muscle Conditioning: A Systematic Review and Meta-Analysis

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OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Environmental, Aviation and Space Physiology,
a section of the journal Frontiers in Physiology

Received: 30 January 2019
Accepted: 20 June 2019
Published: 24 July 2019

Citation:
Ralston GW, Kilgore L, Wyatt FB, Dutheil F, Jaekel P, Buchan DS and Baker JS (2019) Re-examination of 1- vs. 3-Sets of Resistance Exercise for Pre-spaceflight Muscle Conditioning: A Systematic Review and Meta-Analysis. Front. Physiol. 10:864. doi: 10.3389/fphys.2019.00864

Background: Recommendations on resistance training (RT) set-volume protocols in preparation for spaceflight muscular strength conditioning remains equivocal. A meta-analysis was performed on the effects of single-set (S), or three-set (M3) RT on muscular strength per exercise for different body segments and joint types (multi-joint and single-joint).

Methods: Computerized searches were performed on PubMed, MEDLINE and SPORTDiscus^{TM}. Twelve studies were considered appropriate according to pre-set eligibility criteria. Outcomes analyzed were pre-to-post-muscular strength change on; multi-joint and single-joint combined; upper body only; lower body only; multi-joint exercises only; single-joint exercises only.

Results: Upper body exercise analysis on combined subjects and untrained subjects only reported greater but not significant strength gains with M3 (ES 0.37; 95% CI 0.09–0.82; $P = 0.11$ and ES 0.35; 95% CI–0.49 to 1.19; $P = 0.42$). Trained only subjects reported superior strength gains with M3 (ES 0.63; 95% CI 0.34–0.92; $P = <0.0001$). Lower body exercise on combined subjects and untrained subjects only reported superior strength gains with M3 (ES 0.35; 95% CI 0.10–0.60; $P = 0.006$ and ES 0.49; 95% CI 0.14–0.83; $P = 0.005$). Trained subjects only observed greater but not significant strength gains with M3 (ES 0.18; 95% CI −0.23 to 0.58; $P = 0.39$). Multi-joint exercise on combined subjects reported greater strength gains with M3 (ES 0.83; 95% CI 0.14–1.51; $P = 0.02$). Trained only subjects reported greater strength gains with M3 (ES 0.52; 95% CI 0.10–0.94; $P = 0.02$). Single-joint exercise on combined subjects and untrained only observed greater strength gains for M3 (ES 0.49; 95% CI 0.26–0.72; $P = <0.0001$ and ES 0.56; 95% CI 0.21–0.91; $P = 0.002$). Trained only subjects reported greater but not significant strength gains with M3 (ES 0.37; 95% CI −0.01 to 0.75; $P = 0.06$).

Conclusion: For astronauts in space-flight preparation, the findings suggest that M3 training appears to be preferable over S for developing muscular strength. Nevertheless, depending on the physical conditioning of the crew member or tight pre-flight scheduling, S is still able to provide a positive strength training stimulus.

Keywords: resistance training and muscular strength, resistance training and training volume, single vs.multiple-sets, one vs.multiple-sets and muscular strength, one vs.three-sets and muscular strength

INTRODUCTION

Recent advances in space technology, space medicine and collaboration among international space agencies, have contributed significantly toward sending humans deeper into interplanetary space. It is predicted that future crewed missions will focused on deeper space transit; however, at present, this has not transpired due to the significant demands placed on the human body. Governments and space agencies, however, are determined to achieve long duration space exploration and for this to be achieved the astronauts in-flight physical conditioning must be optimal for mission functionality. Astronauts, as part of pre-flight preparation, follow appropriate resistance training (RT) protocols that prepare them for microgravity (μG) environments. Currently, astronauts live and work in extreme environments but significant differences between low-earth orbit operations and exploring interplanetary space exist. Astronauts presently perform low-earth orbit operations in extreme environments including μG, confinement, radiation exposure, and social isolation. These extreme conditions significantly alter the physiological demands experienced by International Space Station (ISS) astronauts relative to terrestrial dwelling. Spaceflight poses unique physiological deconditioning and maladaptation due to prolonged exposure to μG, including significant muscle degradation and impaired skeletal functioning (Convertino, 1990; Stein, 2013; Bloomberg et al., 2016).

Exposure to a μG environment has been shown to have significant adverse effects on skeletal muscle tissue including changes in expression of structural, metabolic, and contractile proteins that adjust the function of tissue (LeBlanc et al., 1996; Fitts et al., 2001; Trappe et al., 2001; Adams et al., 2003; Carpenter et al., 2010). A reduction in muscle strength also leads to a reduction in applied mechanical forces to bones that may intensify the loss of bone mineral content that occurs due to the lack of ground reaction forces in a μG environment. As a result, astronauts will be physically weaker with bones more fragile when they land. These extreme effects of μG on muscle tissue in humans raised concerns by the National Aeronautics and Space Administration (NASA) about the structural and functional deconditioning in muscles that led to astronauts having; (1) loss of strength to perform emergency egress when landing in partial μG and; (2) the inability to perform and endure occupational activities in μG which vary in the magnitude of work-related loading and intensity (Adams et al., 2003). Widrick et al. (1999) suggested that exposure to two and a half weeks of μG led to an overall eight per cent reduction in fiber diameter or up to 15% in the cross-sectional area of slow twitch muscle fibers of the human soleus. LeBlanc et al. (2000) reported that during a 17 day mission significant post-flight changes occurred in muscle volume of between three-to-ten per cent in all muscle regions except hamstrings compared to baseline. LeBlanc and colleagues also observed significant decreases in muscle volume of between 5 and 17% in all muscle groups except the neck during Mir missions of 16–28 week durations. In addition, Trappe et al. (2009) reported losses of muscle strength and approximately two per cent muscle volume per month and five per cent in peak muscle power per month. Similarly, Gopalakrishnan et al. (2010) stated that up to four per cent loss of strength at the knee per month and a loss of approximately three per cent in elbow strength per month. This reduction in muscle activity during spaceflight compromises muscle mass and strength and could have significant consequences related to the success of long duration space exploration.

These decremental changes have driven the pursuit of adequate pre-spaceflight physical training protocols and suitable countermeasures, which has included electrical stimulation, artificial gravity, nutritional therapy, pharmacologic, and various forms of exercise interventions (Lang et al., 2017). Convertino and Sandler (1995) state that physical exercise is central to inhibit unloading-induced remodeling of the muscular and skeletal system. However, sustaining muscle and skeletal bone health remains a significant obstacle in human space exploration. Current pre-flight prescription of RT is primarily established from evidence-driven terrestrial RT and experience gained during previous missions. This has led to disparities in the physical conditioning of astronauts as no such established exercise prescription has been employed that would sustain in-flight muscle strength and functioning. Unfortunately, there does not appear to be a collectively accepted method regarding pre-flight RT prescription that all space agencies adhere too in preparation for space transit. With the daily set-volume, resistance loading, exercise type, and training frequency vary from the space agency to space agency.

Abbreviations: ACSM, American College of Sports Medicine; Chi^2, Chi-square; CI, 95% confidence intervals; d.f., Degrees of freedom; ES, Effect size; I^2, I-squared index test; ISS, International Space Station; IV, Inverse variance; M, Mean; M3, Three-set; MVC, Maximum voluntary contraction; NASA, National Aeronautics and Space Administration; *n*, Sample size number; *P*, Probability; PEDro, Physiotherapy evidence database; PRISMA, Preferred reporting items for systematic reviews and meta-analyses; Q, Cochran Q; RAN, Randomized trials; RCTs, Randomized control trials; RevMan, Review manager; RT, Resistance training; S, One-set; SD, Standard deviation; SE, Standard error; SEM, Standard error of measurement; SMD, Standardized mean difference; Tau^2, Tau-square; μG, Microgravity; 1RM, One repetition maximum.

The European Space Agency strategy for astronaut's pre-flight preparation focus on individualized training approaches that incorporate three stages (Kozlovskaya et al., 1995); (1) adaptation phase that acquaints individuals with ISS exercise hardware; (2) main phase that counteracts physiological adaptation to μG and; (3) preparation for re-entry and terrestrial landing. The RT prescription comprises of both multi-joint and single-joint exercises (squats, deadlifts, bench press, crunches, and heel raises) altering from training session to training session (Hackney et al., 2015). The Japan Aerospace Exploration Agency implements a pre-flight programme that consists of individualized programmes that are related to the anticipated mission tasks that crew members would perform (Loehr et al., 2015). The Canadian Space Agency uses a three-block approach with each stage lasting 4 weeks with set-volume for strength between two-to-five sets (Loehr et al., 2015). NASA implement increased set-volume (MS) with astronauts performing both concentric and eccentric actions that are prescribed by the American College of Sports Medicine (Garber et al., 2011).

Garber et al. (2011) constructed the position statement that provides direction on the prescription of exercise for apparently healthy adults. In the 2011 position statement, multiple-sets are cited for experienced trainees and competitive athletes that are comparable to astronauts' fitness status at the end of pre-flight conditioning. However, Stein (2013) argues that astronauts at their physical peak may have more to lose during in-flight unloading because of μG. Matsumoto et al. (2011) reported that astronauts who performed walking as part of the pre-flight protocol lost less body weight than those that performed intense exercise protocols. It could be debated that if astronaut's pre-flight physical conditioning is in an over-compensated state, they may experience more significant weight loss during spaceflight that may be detrimental. Consequentially, the set-volume training dose needed for astronauts to be in optimal condition requires further investigation. Daily RT set-volume has been an often-contested issue, established from different recommendations that support MS programming. However, in preparation for spaceflight with μG environments, it is perhaps more advantageous to implement S programming in which to develop functional strength that does not facilitate the same level of in-flight deconditioning and weight loss.

Published RT meta-analytical evidence is equivocal on what set-volume elicits superior strength improvements, with disparity existing in the recommendations (**Table 1**). Several meta-analytical studies have been performed that support the use of multiple-sets (MS) programmes compared to single-set (S) per exercise on untrained and trained subjects (Rhea et al., 2002b, 2003; Peterson et al., 2004; Wolfe et al., 2004; Krieger, 2009; Fröhlich et al., 2010). However, due to the absence of available studies, most meta-analytical evidence is drawn from S and MS (two-eight-sets per exercise) that does not fully quantify a dose-response relationship. Several meta-analyses that support increased set-volume (Rhea et al., 2002b, 2003; Peterson et al., 2004; Wolfe et al., 2004) include small ESs that potentially drifted toward greater set-volume. For example, Wolfe et al. (2004) inferred that athletes should perform eight-sets per muscle group to develop strength. This was established from only six effect sizes (ES) and data obtained came from one study and any conclusions derived concerning the direct impact of eight-sets compared to any other number would be unreliable. Besides, none have provided a specific set number for strength development and have pooled findings from studies that have combined different exercise types to generate ES. This, unfortunately, produces issues with daily RT set-volume recommendations, as most meta-analytical evidence have pooled data from studies that have combined exercise types (multi-joint and single-joint exercises) from different population groups (untrained and trained) utilizing a broad age ranges (18–65).

Although meta-analyses regarding the effects of S vs. MS have been published (Rhea et al., 2002b, 2003; Peterson et al., 2004; Wolfe et al., 2004; Krieger, 2009; Fröhlich et al., 2010), with support given for the application of MS to develop strength or muscular hypertrophy. Disagreement remains regarding the need to perform additional sets for increasing muscular strength. Published critical reviews (Smith and Bruce-Low, 2004; Winett, 2004; Otto and Carpinelli, 2006; Carpinelli, 2012; Fisher, 2012), have examined the validity of published meta-analyses on set-volume, concluding that reported data do not fully support a dose-response relationship between the additional number of sets and strength gains. These reviews identified confounding factors including the presence of low-quality studies, variations in subject characteristics and inconsistencies in experimental designs that generate spurious inferences regarding muscular strength increases.

Currently, no meta-analytical evidence is available that examines the effect of daily set-volume on body segmentations (upper or lower body) or specific joint types (MJ and SJ) on muscle strength change. In the context of pre-flight RT, it is critical that the magnitude of daily RT set-volume is examined to prepare astronauts for space transit. The purpose of this review and meta-analysis, therefore, was four-fold: (1) to re-examine the effects of RT volume (S or M3) of ST on muscular strength per exercise; (2) to determine if specific set-volume (S vs. M3) produce different strength gains when multi-joint exercises are compared with single-joint exercises; (3) to investigate if the magnitude of strength gain differs between multi-joint and single-joint exercises by population group (trained vs. untrained) and body segmentations (upper vs. lower body). The final objective; (4) is to provide a perspective on developing muscular strength that provides recommendations on daily RT set-volume for pre-flight strength development. Based on previous evidence (Rhea et al., 2002b, 2003; Peterson et al., 2004; Wolfe et al., 2004; Krieger, 2009), we hypothesized that there would be superior pre-to-post-training strength gains with M3 RT compared to S.

METHODS

Literature Search

This meta-analysis was performed using the recommendations and criteria defined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati et al., 2009). Computer-aided searches were conducted using the following databases: MEDLINE (PubMed),

TABLE 1 | Summary of previous meta-analyses on set-volume and strength development.

References	Study objective	Exercise type	Summary findings
Rhea et al., 2003	Identify a dose-response relationship for intensity, frequency, and volume of training	MJ and SJ comb	Untrained and trained subjects should perform four-sets per muscle group.
Peterson et al., 2004		MJ and SJ comb	Athletes should perform eight-sets per muscle group for athletes.
Peterson et al., 2005	Review of recent evidence on strength development research	MJ and SJ comb	Untrained subjects should perform four-sets per muscle group. Trained subjects should perform eight-sets per muscle group.
Wolfe et al., 2004	Examination of single-set vs. multiple-set on muscle strength	MJ and SJ comb	MS (two-five sets) elicit superior strength gains for trained subjects. Untrained subjects should perform S initially.
Krieger, 2009	Comparison of the effects S-vs.-MS per exercise have on strength	MJ and SJ comb	Maximal strength gains are elicited with two-three-sets per exercise than S, in both untrained and untrained subjects.
Fröhlich et al., 2010	Comparison of the effects of S-vs.-MS for increasing maximal strength levels	MJ and SJ comb	S regimes are equivalent to MS training for increasing strength in the initial period. MS training is superior overextended periods.

N, number; MJ, multi-joint; SJ, single-joint; comb, combined; MS, multiple-sets; S, single-joint.

SWETSWISE, EMBASE, and SPORTDiscus™. The period of search history assessed was inclusive to August 2018. An extensive manual search and cross-referencing of journals, reference lists, was also performed with citations and abstracts from studies published in foreign language journals and scientific conferences were excluded. Descriptive terms and keywords that were used to retrieve studies included: "resistance training and muscular strength," "resistance training and training volume," "single vs. multiple-sets," and "one vs. multiple-sets and muscular strength." Boolean operators, including AND, OR, and NOT, were used to focus literature searches with literature searches reduced to studies involving humans only.

As a result of systematic computerized database searches, journals were retrieved from 1960 to August 2014 in where S vs. M3 were examined, from different population demographics (trained, untrained, male, and female subjects). After preliminary literature searching, reference lists of articles were screened for additional studies of relevance on muscular strength development. During the first selection round, appropriate study titles were screened for relevance with the inclusion of either resistance training or training volume. In the second selection round, GR, LK, and DB read the abstracts and then selected the article if resistance training for muscle strength was evaluated before and after a minimum RT intervention period of 4-weeks. This minimum time course was chosen due to reports of muscular adaptations in response to RT (Stock et al., 2016). In the third selection round, full articles were read.

Eligibility Criteria

Studies were deemed eligible in this review if they met the following conditions; (a) human subjects free from chronic disease, muscular, or orthopedic injuries, or physical limitations; (b) trained and untrained adult male or female subjects between 18 and 45 years; (c) subject's descriptive characteristics included in the report (height, weight, training status, and training experience); (d) subjects training at least one primary muscle group-pectoralis major, deltoids (anterior, lateral, posterior); bicep brachii, or tricep brachii; latissimus dorsi; quadriceps (vastus medialis, vastus intermedius, vastus lateralis, rectus femoris); hamstrings (bicep femoris, semitendinosus, semimembranosus; (e) at least one performed pre-to-post measure of muscular strength; (f) studies that compared S vs. M3 performing resistance exercise only (active control group); (g) training protocols lasting a minimum of 4-weeks; (h) and appropriate information to calculate training ES. This meta-analysis included both randomized trials (RAN) and randomized control trials (RCTs) that observed the intervention treatments using stratified resistance exercises with S vs. M3. RAN allocation ensures no systematic variances between the intervention groups; however, no control group may influence the assessment of outcomes (Schünemann et al., 2013). RCTs are a more specific method for defining a cause-effect relationship between treatments and outcomes.

Search Strategy

Titles and abstracts of retrieved journal articles were independently evaluated for content relevance by three reviewers (GR, LK, and DB). Abstracts that contained the necessary information regarding the pre-set inclusion and exclusion criteria were retrieved and independently evaluated for full-text eligibility. Potential studies that did not have descriptive data tables but presented pre- to post-primary strength data in the form of figures resulted in extraction using WebPlot-Digitiser (Web Plot Digitiser V.3.11. Texas, USA: Ankit Rohatgi, 2017). Where differences between reviewers (GR, LK, and DB) occurred then additional dialogue and agreements were made by consensus. Ten randomly selected studies underwent *post-hoc* reassessment with the extracted results compared. For each reviewer coder drift was set at <10% in all cases, and inter-rater (GR and DB) reliability was >95%. Studies were read and individually coded for the following variables; (1) subject's descriptive characteristics, including age, training experience, and sample size; (2) programme characteristics including training frequency, number of sets performed per exercise, the number of reps performed per exercise; (3) measurement of pre-post-strength outcome(s) and; (4) treatment effects of mean (M) and SD values of changes in pre- and post-strength outcomes for RT intervention and control groups.

Assessment of Methodological Quality of Studies

Internal validity of retrieved studies was evaluated using the Physiotherapy Evidence Database (PEDro) scale. The PEDro scale (Verhagen, 1998; Maher et al., 2003) has 11 measures, with a maximum score of ten. However, a maximum score from the PEDro scale, in this case, was eight, as the therapists, assessors and technicians conducting the interventions cannot be blinded. Studies were included in this analysis if they had a PEDro score of ≥ four, as this was considered as having acceptable internal validity. Methodological quality was independently assessed by reviewers (GR, LK, and DB). Variances of judgement concerning the scoring of the journal articles were agreed between reviewers through consensus.

Calculation of Effect Size

Descriptive statistics were calculated to describe and summarize the results of the systematic review process. Data of individual study characteristics were entered into a spreadsheet (Microsoft, Redmond, WA, USA) to compare pre-post-strength outcomes

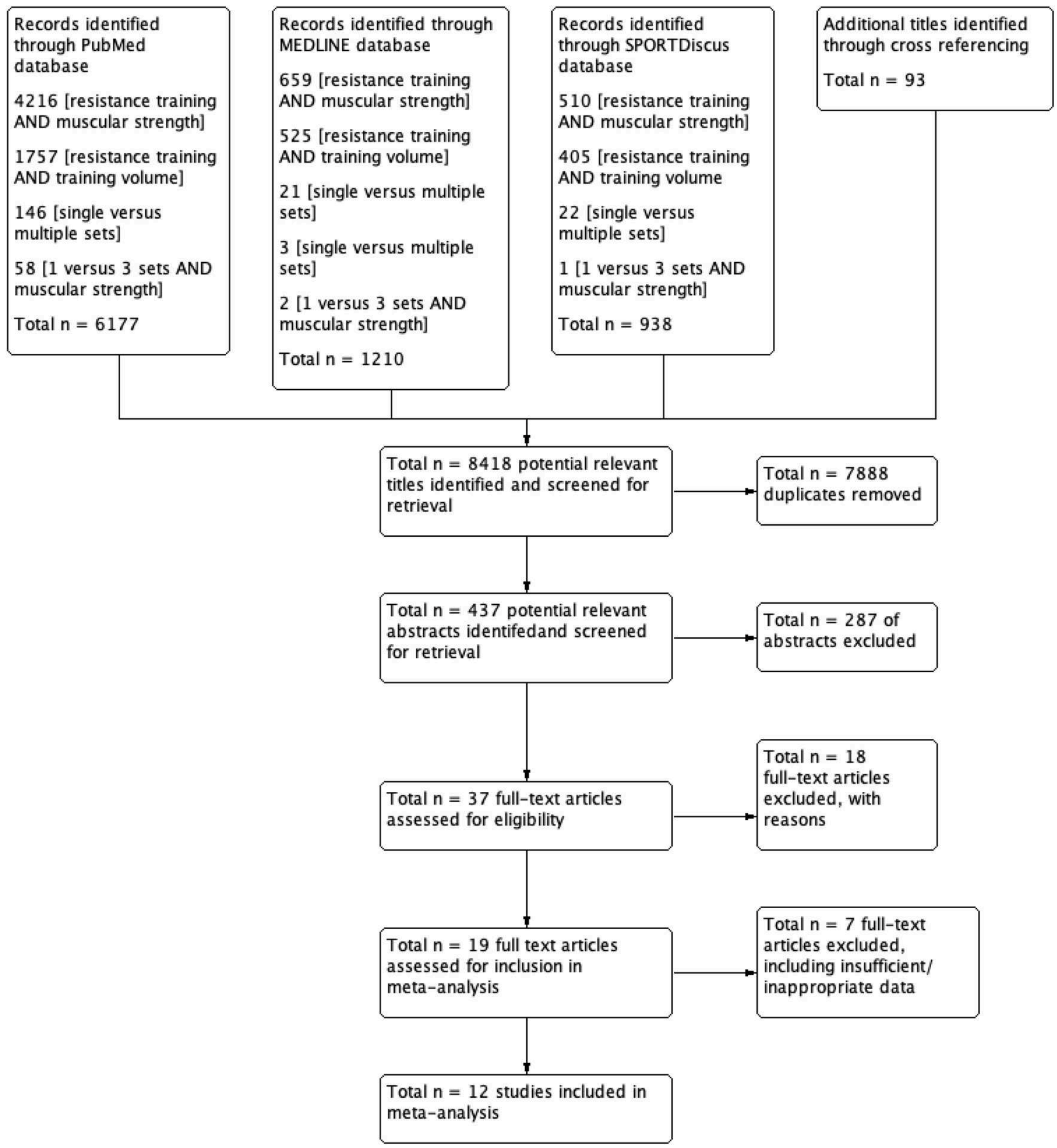

FIGURE 1 | The flow of journal articles through the systematic review process.

of each study for coding, review and data reference. Descriptive statistics containing sample size (n), mean (M) and SD were extracted from each study. This provided data for the mean differences in pre- to post-intervention between groups (e.g., S and M3) on several strength outcomes. Muscular strength was deemed a continuous data variable; therefore, the standardized mean difference (SMD) with 95% confidence intervals (95% CI) were used to establish the ES measures. For each strength outcome variable, a SD score was calculated by using Cohen's d index of a single ES (di = [M1–M2]/SDpi) (Cohen, 1998), where d = ES, i = individual study, M1 = pre-intervention mean, M2 = post-intervention mean, and SDp = pooled standard deviation. The SD was calculated by summing the extracted pre-intervention and post-intervention SDs and dividing by two. If the standard error of measurement (SEM) of the mean was specified, the SD was calculated using the formula (SD = SEM*square root of N) (Howell, 2012). Separate ES was weighted to account for individual sample sizes. If a study reported, exact *P*-values for a change of strength, the SD of change was calculated. Studies that did not report, exact *P*-values, the SD of change was calculated using the pre- and post-intervention SDs. Due to diverse population demographics and methods with the included studies, a random-effects inverse variance (IV) using the DerSimonian-Laird method (DerSimonian and Laird, 1986) was applied with the effects measure of SMD. If a study had numerous time-periods, only the pre- to post-intervention strength outcomes were extracted and entered for analysis. The data was then used to compute ES estimates and CI. For each strength measure, an ES was calculated as the pre- to post-intervention change, divided by the pre-intervention SD (Morris and DeShon, 2002).

Meta-Essentials (Suurmond et al., 2017) was initially used to input pre-post-strength outcome data with each row denoted as an individual ES for a treatment group. If treatment groups had multiple ES, then each ES was coded in a separate row. This aided with the computation of ES, SEM, and study size to allocate appropriate weight to each study, and estimate a study effect. To determine the significance of the ES, the chi-square (Chi^2) test was performed in each model used. For the statistical analyses, Review Manager (RevMan) version 5.3.5 was used to calculate the difference in SD of post-intervention strength outcomes and the generation of forest plots. Data needed were either; (1) means and SDs (pre- and post-strength change); (2) CI data for pre- to post-strength change for each treatment group (3) *P*-values for pre- to post-strength difference for each treatment group, or if only the level of significance was available, and; (4) default *P*-values (e.g., $P \leq 0.05$ becomes $P \leq 0.49$, $P \leq 0.01$ becomes $P \leq 0.0099$, and $P \geq$ not significant becomes $P \geq 0.05$).

The random-effects model was implemented to allow for variability between the studies due to high heterogeneity. A random-effects model conceptualized the existing series of studies under investigation to be a random sample selected from a larger population of studies. In the random-effects model meta-analysis, there are two sources of variability; (1) variability of the effect parameters, and; (2) sampling variability of experimental units (i.e., subjects) into studies. If individual parameter estimates of each study lead to high levels of heterogeneity, the random-effects analysis considers the "*true variance*" (or the remaining unmeasured random-effects between studies) in addition to the modeled between-study variances and sampling error typically assumed in fixed-effects models. It should be highlighted that the random-effects model typically gives less specific estimates and larger CIs.

Heterogeneity and Risk of Bias

To evaluate heterogeneity between studies, the *I*-squared (I^2) index test and Cochran Q (Q) heterogeneity statistic were applied. The I^2 test was used to assess the degree of heterogeneity for each outcome, with an $I^2 > 50\%$ applied to indicate heterogeneity. Non-significance signifies that the results of the different studies were similar ($P \geq 0.05$) and $P < 0.05$ denotes a statistically significant effect. The Q statistic uses the sum of squared deviations of each estimate resulting from the pooled estimate and weights the contribution of each study. The Q

TABLE 2 | Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
One or more muscle groups used duration intervention and appropriate strength assessment (i.e., single-joint exercises, e.g., leg curl)	Small subject sample groups (e.g., $n <$ six)
The minimum duration of the training intervention is 4-weeks; preferably longitudinal studies (>12-weeks)	The use of either legal or illegal ergogenic aids or supplementation prior to or during interventions
It would be desirable if there were an appropriate control group included within the research design with subjects randomly assigned to groups	Training order variation throughout the intervention
Training programme supervised throughout the intervention. Ensuring that interventions are of similar order and if applicable inter-set recovery periods standardized for multiple-sets	No quasi RCT or narrative studies/reviews to be included
The warm-up is standardized between treatment groups	Subjects below 18 or above 45 years of age
Appropriate criteria were specified regarding training loading (intensity) and subjects trained to volitional fatigue	Researchers did not report results adequately (pre-to-post-mean and standard deviation)
Subject groups comparing 1- vs. 3-sets per exercise per session	Investigated the effects of nutritional supplements in combination with resistance training
Subjects used resistance training as a means of training	Concurrent aerobic and strength training interventions
Studies published in the English language journals only	

TABLE 3 | Characteristics of excluded studies investigating 1-vs. 3-sets.

References	Design	Status	Sex	N	Age, y, mean ± SD or range	Frequency	Duration (wk)	Sets	Reps	Strength outcomes	The reasoning for exclusion from the current analysis
Kraemer, 1997	RAN	T	M	40	20 ± 2.3	3	12	1/3	8–12	1RM BP, 1RM LP	Excluded due to differences between groups, single circuit group performed forced reps at the end, and multiple circuit group did no forced reps
Borst et al., 2001	CT	U	C	31	37 ± 7	3	25	1/3	8–12	Sum of 1RM for CP and LExt	Excluded due to inadequate evidence of pre-and post-intervention training means and SDs to calculate an effect size
McBride et al., 2003	RCT	U	C	28	21.52 ± 1.3	2	12	1/3	6–15	1RM LP; 1RM BC	Excluded due to amount of sets subjects were performing
Galvão and Taaffe, 2005	RAN	U	C	28	65–78	2	20	1/3	8	Maximum isokinetic and isometric KExt strength	Excluded due to subjects age range
Munn et al., 2005	RCT	U	C	115	20.6 ± 6.1	3	6	1/3	6–8	1RM EFlex	Excluded due to the primary aim, which was the effects of contraction speed with one or three-sets at fast or slow speeds
Rønnestad et al., 2007	RAN	U	M	21	26.6 ± 0.1	3	11	1/3	7–10	1RM lower body (LP, LExt, LC); 1RM upper body (CP, Row, LatP, BC, SP)	Provided the subjects with nutritional supplementation (protein chocolate bar) and energy drinks during each exercise bout
Starkey et al., 1996	RCT	U	C	48	18–50	3	14	1/3	8–12	Maximal isometric KFlex; KExt	Study data identified as an outlier when observed using the Galbraith plot

N, number; y, years; SD, standard deviation; wk, weeks; Reps, repetitions; RAN, randomly assigned trial; T, trained; M, male; 1RM, 1 repetition maximum; BP, bench press; LP, leg press; CT, control trial; U, untrained; C, male and female subjects combined; CP, chest press; LExt, leg extension; SD, standard deviation; RCT, randomized controlled trial; BC, bicep curl; KExt, knee extensor; EFlex, elbow flexor; LC, leg curl; Row, seated row; LatP, latissimus pull-down; SP, shoulder press; KFlex, knee flexion.

TABLE 4 | Study and subject characteristics 1-vs. 3-sets.

References	Design	Status	Sex	N	Age, y, mean ± SD or range	Until failure	Frequency (sessions per wk)	Duration (wk)	Sets	Reps	Training loads (% 1RM)	Strength outcomes [strength measurement type]
Hass et al., 2000	RAN	T	C	42	39.2–40.1	Yes	3	13	1/3	8–12	67–80	[1RM] LExt, LC, CP, OP, BC
Rhea et al., 2002a	RAN	T	M	16	20–22	Yes	3	12	1/3	8–12	67–80	[1RM] BP, LP
Paulsen et al., 2003	RAN	U	M	18	20–30	Yes	3	6	1/3	7	83	[1RM] Sq, KExt, LC, BP, SP, Row, LatP
Kelly et al., 2007	RCT	T	C	40	22.2–25.3	Max effort	2	8	1/3	8	80	[Nm] KExt
Bottaro et al., 2009	RAN	U	M	24	19–25.4	Yes	2	12	1/3	8–12	67–80	[1RM] KExt, EExt
Baker et al., 2013	RAN	T	M	16	18–21	Yes	3	8	1/3	6	85	[1RM and Nm] BP, SP, BC
Sooneste et al., 2013	RAN	U	M	8	22.9–27.1	Yes	2	12	1/3	8	80	[1RM] SPC
Reid et al., 1987	RAN	U	M	34	18–35	Yes	3	8	1/2/3	3–18	63–93	[1RM] EFlex, EExt, KFlex, KExt, SFlex, SExt
Kramer et al., 1997	RAN	T	M	43	20.3 ± 1.9 [SEM]	Yes	3	14	1/3	8–12	67–80	[1RM] Sq
Schlumberger et al., 2001	RCT	T	F	27	20–40	Yes	2	6	1/3	6–9	65–77	[1RM] LExt, BP
Humburg et al., 2007	RCT	U	C	29	23.1–27.1	Yes	3	9	1/3	8–12	67–80	[1RM] BC, LP, BP
Radaelli et al., 2014	RCT	U	M	48	23.5–25.3	Yes	3	26	1/3/5	8–12	67–80	[5RM] BP, LP, LatP, SP
Total/mean ± SD				393			2.7 (± 0.49)	11.2 (± 5.4)		9.0 (± 1.7)	76.5 (± 7.5)	

N, number; y, years; SD, standard deviation; wk, weeks; Reps, repetitions; % 1RM, percentage of subjects one repetition maximum; RAN, randomly assigned trial; T, trained; C, male and female subjects combined; 1RM, 1 repetition maximum; LExt, leg extension; LC, leg curl; CP, chest press; OP, overhead press; BC, bicep curl; M, male; BP, bench press; LP, leg press; U, untrained; SEM, standard error of measurement; Sq, squat; KExt, knee extension; SP, shoulder press; Row, seated row; LatP, latissimus pull-down; RCT, randomized controlled trial; Nm, peak torque; 5RM, subjects five repetition maximum; EFlex, elbow flexion; KFlex, knee flexion; SFlex, shoulder flexion; SExt, shoulder extension; SPC, seated preacher curl; F, female.

heterogeneity test was applied to evaluate heterogeneity prior to estimating tau-square (Tau^2), then I^2 and Tau^2 statistics were calculated. Comparing the Q statistic with an X^2 distribution with k^{-1} degrees of freedom (where k denotes the number of included studies) allowed *P*-values to be attained. All analyses were conducted at the 95% confidence level. The ES of $\leq$0.2, $\leq$0.5, $\leq$0.8, and $\geq$0.8 were considered trivial, small, moderate and large, respectively (Cochran, 1954).

For the assessment and evaluation of publication bias, the use of funnel plot assessments with Duval and Tweedie's (2000) trim and fill correction was applied. The purpose of the "*trim and fill*" was to identify and correct for funnel plot asymmetry ascending from publication bias. This method is to; (1) remove the smaller studies causing funnel plot asymmetry; (2) apply the trimmed funnel plot to estimate the true "*centre*" of the funnel, then; (3) replace the removed or omitted studies around the center. Forest plots were produced to display the study-specific ES and the corresponding CI. All forest plots generated were visually examined against its standard error (SE) to account for publication bias also known as the "*file drawer problem*." This refers to the influence of the results of a study that introduces bias into the scientific literature by selective publication, primarily by the propensity to publish positive results but not to publish negative results (Scargle, 2000).

Separate subgroup analysis on ES was performed with the resulting moderators, including; (1) single-joint or multi-joint resistance exercise on 1RM strength gains (trained only subjects); (2) single-joint or multi-joint resistance exercise on 1RM strength gains (untrained only subjects). In the subgroup analysis, mean differences in ES were computed for each study to produce a study-level ES for the difference between S and M3 allowing for the generation of forest plots. Sensitivity analysis was performed, by identifying any studies that were highly influential which may bias the analysis. This was achieved for each model by eliminating one study at a time and then inspecting the set-volume predictor. Influential studies were removed if they caused a significant change in the magnitude of the coefficient or change from significant ($P \leq 0.10$) to non-significant ($P \geq 0.10$) or vice versa.

RESULTS

The procedure used for systematic literature search and retrieval is displayed in **Figure 1** from "*potentially relevant*" to article inclusion. The specific stages of the selection procedure for the meta-analysis are described as a flow diagram (**Figure 1**).

Study Selection

The initial examination generated 8,418 related abstracts and citations. Thirty-seven full-text articles were initially deemed to meet the inclusion criteria. A total of 19 potentially relevant journal articles met the pre-set inclusion and exclusion criteria (**Table 2**) and were further assessed for content applicability. Six studies (Kraemer, 1997; Borst et al., 2001; McBride et al., 2003; Galvão and Taaffe, 2005; Munn et al., 2005; Rønnestad et al., 2007) were rejected prior to data extraction, with Galbraith plot identifying one further article (Starkey et al., 1996) as an outlier and was omitted. Descriptions for the seven studies that were excluded are detailed in **Table 3**.

Resistance Training Study Characteristics

Following appraisal and sensitivity measures 12 full-text articles (Reid et al., 1987; Kraemer, 1997; Hass et al., 2000; Schlumberger et al., 2001; Rhea et al., 2002a; Paulsen et al., 2003; Humburg et al., 2007; Kelly et al., 2007; Bottaro et al., 2009; Baker et al., 2013; Sooneste et al., 2013; Radaelli et al., 2014) met pre-set inclusion criteria (**Table 2**). Journal articles included in this analysis had dates ranging from 1987 to 2014. In total, 12 studies provided data on 393 subjects (**Table 4**) with the both randomized control groups (RCT [$n = 4$]) and random assignment of treatment conditions (RAN [$n = 8$]) experimental designs included.

The mean age of the subjects was 25.2 (± 5.4 years). The training status of subjects included in the 12 studies was untrained ($n = 6$) and trained ($n = 6$). Assigned cohorts consisted of male ($n = 8$ [67%]), female only groups ($n = 1$ [12%]), and mixed-sex studies ($n = 3$ [25%]) which were included in the analysis. The RT period ranged from 6 to 26 weeks (mean = 11.2 [±5.4] weeks), weekly training frequency ranged from 2 to 3 days per week (2.7 [±0.49] per week), and the repetitions used ranged from 3 to 18 repetitions (9.0 [±1.7]) per week. The total number of sets per week ranged from two-to-three-sets (2.7 [±1.7]) for S and six-to-nine-sets for M3 (7.5 [±2.1]) per exercise. Also, training loads ranged from 63 to 90% 1RM (76.7 [±4.1]) with the subject's resistance training characteristics and weekly training volume specified in **Table 5**.

Sensitivity Analysis

The PEDro scale was based on the Delphi list (Verhagen, 1998) with column 1a not used in the calculation of the scores. Only criterion 2–11 are scored giving a total out of ten. Each column number corresponds to the following criteria on the PEDro scale (**Table 6**): 1[a] = eligibility criteria (1a = eligibility criteria specified [1= yes/0 = no]); 2 = subjects randomly allocated; 3 = allocation was concealed; 4 = groups similar at baseline; 5 = blinded subjects; 6 = therapists blinded; 7 = assessors blinded; 8 = follow-up measures obtained for >85% of subjects; 9 = intention to treat analysis; 10 = between groups statistical comparison; 11 = point measures and measures of variability. The included studies had PEDro scores that ranged from five through to six (**Table 6**). Though the maximum PEDro score is 11, it is problematic and unrealistic to achieve this total. Realistically the maximum score on PEDro was eight as it is problematic to blind both participants and researchers to an exercise intervention. Consequently, included journal articles had a common area of bias as subjects, therapists or researchers were not blinded. Galbraith plots were used to investigate for study heterogeneity and identification of potential outliers. Examination of Galbraith plots exposed no outliers (**Figure 2**). To assess for publication bias trim and fill funnel plot were also performed in all comparison models. This was to safeguard for overestimations of the ES of set-volume and strength outcomes in the included studies. The shape of the funnel plot did not expose any evidence of apparent asymmetry.

TABLE 5 | Resistance training characteristics and weekly training volume.

References	RT exercises performed	Total number of sets per exercise performed weekly	Total number of reps performed daily per exercise	Total number of reps performed weekly per exercise	Total number of reps (sets × reps × frequency × exercise) performed weekly
Hass et al., 2000	LExt, LC, PullO, ACross, CP, LatR, OP, BC, TriExt	S:3 M3:9	S: 8–12 M3: 8–12	S:24–36 M3:72–108	S = 216–324 M = 648–972
Rhea et al., 2002a	BP, LP. S performed additional exercises BC, LatP, AbC, BExt, Row	S:3 M3:9	S: 8–12 M3: 8–12	S:24–36 M3:72–108	S = 168–252 M3 = 144–216
Paulsen et al., 2003	Sq, KExt, LC, BP, SP, Row, LatP	S:3 M3:9	S: 7 M3: 7	S:21 M3:63	S = 147 M3 = 441
Kelly et al., 2007	KExt	S:2 M3:6	S: 8 M3: 8	S:16 M3:48	S = 16 M = 48
Bottaro et al., 2009	LP, PullO, KFlex, CP, BC, AbC	S:2 M3:6	S: 8–12 M3: 8–12	S:16–24 M3:48–72	S = 96–144 M = 288–432
Baker et al., 2013	BP, IncBP, DumF, BCbar, BCdumb, HammerC, SP, LatR, URow	S:3 M3:9	S: 6 M3: 6	S: 18 M3: 54	S = 162 M = 486
Sooneste et al., 2013	SPC	S:2 M3:6	S: 8 M3: 8	S:16 M3:48	S = 16 M = 48
Reid et al., 1987	LExt, LC, LP, CR, BP, MilPres, LatP, TriExt, BC	S:3 M3:9	S: 8 M3: 8	S:24 M3:72	S = 216 M = 648
Kramer et al., 1997	Sq, PushP, BP, AbC, PullTh, LC, BRow	S:3 M3:9	S: 8–12 M3: 8–12	S:24–36 M3:72–108	S = 168–252 M = 504–756
Schlumberger et al., 2001	LExt, LC, AbC, ShAdd, ShAbd, BP, LatP	S:2 M3:6	S: 6–9 M3: 6–9	S:12–18 M3:36–54	S = 84–126 M = 252–378
Humburg et al., 2007	BC, LP, BP	S:3 M3:9	S: 8–12 M3: 8–12	S:24–36 M3:72–108	S = 72–108 M = 126–324
Radaelli et al., 2014	BP, LP, LatP, LExt, SP, LC, BC, AbC, TriExt	S:3 M3:9	S: 8–12 M3: 8–12	S:24–36 M3:72–108	S = 216–324 M = 648–972

RT, resistance training; LExt, leg extension; LC, leg curl; PullO, pull-over; ACross, arm cross-over; CP, chest press; LatR, lateral raise; OP, overhead press; BC, bicep curl; TriExt, tricep extension; BP, bench press; S, one-set; M3, three-sets; LP, leg press; LatP, latissimus pull-down; AbC, abdominal curl; BExt, back extension; Row, seated row; Sq, squat; KExt, knee extension; SP, shoulder press; KFlex, knee flexion; IncBP, incline bench press; DumF, dumbbell flye; BCbar, bicep curl with bar; BCdumb, bicep curl with dumbbells; HammerC, hammer curl; URow, upright row; SPC, seated preacher curl; MilPres, military press; PushP, push press; PullTh, pull through; Brow, back row; SHadd, shoulder adduction; ShAbd, shoulder abduction.

Effects of 1- vs. 3- Sets on Multi-Joint and Single-Joint Exercise

Pre- to post-strength outcomes were assessed via a meta-analytic procedure for all included studies. Subgroup analysis was then performed with multi-joint and single-joint exercises combined into separate subdivision analysis. A random-effects model was incorporated into each strength measure due to the potential of pooled study data generating significant heterogeneity with I^2 used to evaluate heterogeneity.

The pooled mean ES estimates (untrained and trained) of multi-joint and single-joint data (**Tables 7**, **8**) comprised of 70 treatment groups from 12 studies (Reid et al., 1987; Kramer et al., 1997; Hass et al., 2000; Schlumberger et al., 2001; Rhea et al., 2002a; Paulsen et al., 2003; Humburg et al., 2007; Kelly et al., 2007; Bottaro et al., 2009; Baker et al., 2013; Sooneste et al., 2013; Radaelli et al., 2014). The random-effects model exposed a considerable amount of variability between studies. Heterogeneity prior to taking Tau^2 into consideration (Q heterogeneity test) was: Chi^2 = 131.56, d.f. = 11, $P < 0.00001$. The heterogeneity statistic I^2 (%) = 92 [interpreted as high, (Higgins et al., 2003)], and the tau^2 test (between-trials variance) = 0.74. When a random effect analysis was implemented, a large effect was detected for combined multi-joint and single-joint exercises on RT set training volume [mean effect size (ES) 0.93; 95% CI 0.41–1.45]. Pre- to post-intervention strength change was greater with M3 compared to S (ES difference 0.25) with the effect statistically significant ($P = 0.0005$). The mean for S was 0.64 (95% CI 0.44–0.84). The mean ES for M3 was 0.89 (95% CI 0.66–1.12).

Untrained Subjects' Effects of Single -vs. Three-Sets on Combined Exercises

Examination of the effects of pre- vs. post-training strength (untrained subjects only) categorized as either S or M3 from six studies (Reid et al., 1987; Paulsen et al., 2003; Humburg et al., 2007; Bottaro et al., 2009; Sooneste et al., 2013; Radaelli et al., 2014). The random-effects model exposed a considerable amount of variability between studies. Q heterogeneity test was: Chi^2 = 78.30, d.f. = 5, $P < 0.00001$. The heterogeneity statistic I^2 (%) = 94 [interpreted as high, (Higgins et al., 2003)], and the tau^2 test (between-trials variance) = 0.94. A large effect was observed on untrained only subjects for multi-joint and single-joint exercises combined (ES 1.20; 95% CI 0.39–2.01). Pre- to post-intervention strength change was greater when M3 was

TABLE 6 | Methodological quality of studies based on the PEDro score.

References	PEDro Scale item											Total
	1[a]	2	3	4	5	6	7	8	9	10	11	
Reid et al., 1987	1	1	0	1	0	0	0	1	1	1	1	6
Kramer et al., 1997	1	1	0	1	0	0	0	1	1	1	1	6
Hass et al., 2000	1	1	0	1	0	0	0	1	1	1	1	6
Schlumberger et al., 2001	1	1	0	1	0	0	0	1	1	1	1	6
Rhea et al., 2002a	1	1	0	0	0	0	0	1	1	1	1	5
Paulsen et al., 2003	1	1	0	1	0	0	0	1	1	1	1	6
Humburg et al., 2007	1	1	0	1	0	0	0	1	1	1	1	6
Kelly et al., 2007	1	1	0	1	0	0	0	1	1	1	0	5
Bottaro et al., 2009	1	1	0	1	0	0	0	1	1	1	1	6
Baker et al., 2013	1	1	0	1	0	0	0	1	1	1	1	6
Sooneste et al., 2013	1	1	0	1	0	0	0	1	1	1	1	6
Radaelli et al., 2014	1	1	0	1	0	0	0	1	1	1	1	6

PEDro, Physiotherapy Evidence Database. The PEDro scale is based on the Delphi list (Verhagen, 1998). Column 1a not used in the calculation of the scores. Only criterion 2–11 are scored giving a total out of ten. Column numbers correspond to the following criteria on the PEDro scale: 1[a] = eligibility criteria (1a = eligibility criteria specified [1= yes/0 = no]), 2 = random allocation, 3 = concealed allocation, 4 = groups similar at baseline, 5 = blinded subjects, 6 = blinded therapists, 7 = blinded assessors, 8 = follow-up measures obtained for > 85% of subjects, 9 = intention to treat analysis, 10 = between groups statistical comparison, 11 = point measures and measures of variability.

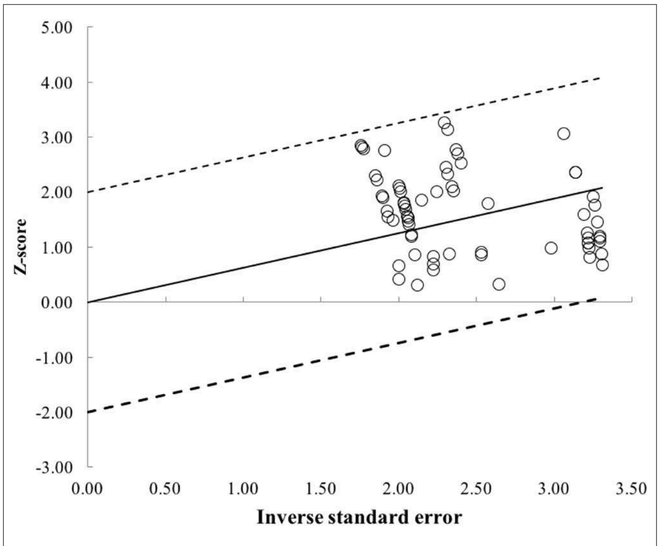

FIGURE 2 | Galbraith plot used to examine study heterogeneity (pre- vs. post-strength change). Each open circle represents one pre- vs. post-study data.

compared to S (ES difference 0.22) with statistical significance ($P = 0.004$). The mean for S was 0.60 (95% CI 0.34–0.85). The mean ES for M3 was 0.82 (95% CI 0.52–1.11).

Trained Subjects' Effects of Single -vs. Three-Sets on Combined Exercises

Separate subgroup examination on the effects of pre- vs. post-training strength (trained subjects only) categorized as either S or M3 from six studies (Kramer et al., 1997; Hass et al., 2000; Schlumberger et al., 2001; Rhea et al., 2002a; Kelly et al., 2007; Baker et al., 2013). The random-effects model exposed a considerable amount of variability between studies. Q heterogeneity test was: $\text{Chi}^2 = 29.21$, d.f. = 5, $P < 0.0001$. The heterogeneity statistic I^2 (%) = 83 (interpreted as high; Higgins et al., 2003), and the tau^2 test (between-trials variance) = 0.42. A moderate effect was observed on trained only subjects for multi-joint and single-joint exercises combined (ES 0.63; 95% CI 0.05–1.22). Pre- to post-intervention strength gain was greater when M3 was compared to S (ES difference 0.28) with statistical significance ($P = 0.03$). The mean for S was 0.68 (95% CI 0.35–1.01). The mean ES for M3 was 0.96 (95% CI 0.61–1.31).

Effects of 1-vs. 3-Sets on Upper Body Exercise

Examination of upper body exercises (multi-joint and single-joint exercises combined) comprised 10 studies (Reid et al., 1987; Hass et al., 2000; Schlumberger et al., 2001; Rhea et al., 2002a; Paulsen et al., 2003; Humburg et al., 2007; Bottaro et al., 2009; Baker et al., 2013; Sooneste et al., 2013; Radaelli et al., 2014) are displayed in the forest plot (**Figure 3**). The random-effects model exposed a large amount of variability between studies ($I^2 = 93\%$). Removal of Humburg et al. (2007) and Radaelli et al. (2014) data, resulted in moderate heterogeneity (Q heterogeneity test was: $\text{Chi}^2 = 21.71$, d.f. = 7, $P = 0.003$). The heterogeneity statistic I^2 (%) = 68 (interpreted as moderate heterogeneity, Higgins et al., 2003), and the tau^2 test (between-trials variance) = 0.27, and a small effect was observed (ES 0.37; 95% CI −0.09 to 0.82). Pre- to post-intervention strength change was greater when M3 was compared with S (ES difference 0.19) with no statistical significance ($P = 0.11$). The mean ES for S was 0.68 (95% CI 0.42–0.94). The mean ES for M3 was 0.87 (95% CI 0.61–1.14).

TABLE 7 | Pre- vs. post-strength analysis of multi-joint exercise.

References	*N*	*N* per group	Age (y) [range or mean ± SD]	Frequency/ duration	Testing modality	Sets (reps)	Training loads	Weekly sets per exercise	Pre- vs. post [mean ± SD]	Pre- vs. post % strength change	Reported *P*-value (Pre- vs. post)	ES
Hass et al., 2000	42	S:21	39.2–40.1	3 per wk for 13 wks	CP	1 (8–12)	8–12RM	S	1.9 ± 0.6 vs. 2.1 ± 0.5	10.5	≤0.05	0.36
		M3:21			CP	3 (8–12)		M3	2.1 ± 0.7 vs. 2.3 ± 0.6	9.5	≤0.05	0.31
Hass et al., 2000	42	S:21	39.2–40.1	3 per wk for 13 wks	OP	1 (8–12)	8–12RM	S	1.9 ± 0.4 vs. 2.0 ± 0.4	5.3	≤0.05	0.25
		M3:21			OP	3 (8–12)		M3	2.0 ± 0.6 vs. 2.3 ± 0.6	15.0	≤0.05	0.5
Rhea et al., 2002a	16	S:8	19–23	3 per wk for 12 wks	LP	1 (8–12)	8–12RM	S	269.0 ± 16.8 vs. 337.2 ± 69.0	25.4	≤0.05[a]	1.36
		M3:8			LP	3 (8–12)		M3	225.9 ± 25 vs. 343.5 ± 89.9	52.1	≤0.05[a]	1.78
Rhea et al., 2002a	16	S:8	19–23	3 per wk for 12 wks	BP	1 (8–12)	8–12RM	S	64.2 ± 8.9 vs. 76.7 ± 28.0	19.5	≤0.05[a]	0.60
		M3:8			BP	3 (8–12)		M3	66.8 ± 7.3 vs. 85.5 ± 20.8	28	≤0.05[a]	1.20
Paulsen et al., 2003	18	S:10	20–30	3 per wk 6 wks	Sq	1 (7)	7RM	S	129.5 ± 65.1 vs. 147 ± 67.4	13.5	≤0.01[b]	0.26
		M3:8			Sq	3 (7)		M3	122.5 ± 82.0 vs. 149.4 ± 82	22.0	≤0.01[b]/≤0.05[c]	0.33
Paulsen et al., 2003	18	S:10	20–30	3 per wk for 6 wks	BP	1 (7)	7RM	S	74.8 ± 22.1 vs. 82.3 ± 26.3	10	≤0.01[b]	0.31
		M3:8			BP	3 (7)		M3	77.8 ± 32 vs. 85.0 ± 36.5	9.3	≤0.01[b]/≤0.05[c]	0.21
Baker et al., 2013	16	S:8	18–21	3 per wk for 8 wks	BP	1 (6)	6RM	S	659.4 ± 112.7 vs. 776.2 ± 121.5	17.7	≤0.05 one tailed[a]	1.00
		M3:8			BP	3 (6)		M3	671.3 ± 131.3 vs. 789.9 ± 96.0	17.7	≤0.05 one tailed[a]	1.03
Baker et al., 2013	16	S:8	18–21	3 per wk for 8 wks	SP	1 (6)	6RM	S	412.6 ± 71.5 vs. 527.2 ± 74.5	27.8	≤0.05 one tailed[a]	1.57
		M3:8			SP	3 (6)		M3	418.5 ± 49.0 vs. 510.6 ± 62.7	22.0	≤0.05 one tailed[a]	1.64
Kramer et al., 1997	43	S:16	20.3 ± 1.9 [SEM]	3 per wk for 14 wks	Sq	1 (8–12)	8–12RM	S	101.9 ± 20.6 vs. 114.1 ± 18.7	12.0	/	0.62
		M3:14			Sq	3 (8–12)		M3	98.5 ± 27.7 vs. 123.7 ± 43.2	25.6	≤0.05[a]	0.69
		MSV3: 13			Sq	1–3(3–10)		MSV3	111.2 ± 25.6 vs. 135.7 ± 20.6	22.03	≤0.05[a]	1.05
Schlumberger et al., 2001	27	Con: 9	20–40	2 per wk for 6 wks	BP	Con (0)	6RM	Con	28.1 ± 2.4 vs. 27.2 ± 2.9	3.2	/	−0.34
		S:9			BP	1 (6–9)		S	31.7 ± 9.0 vs. 33.0 ± 9.3	4.1		0.14
		M3:9			BP	3 (6–9)		M3	26.9 ± 3.5 vs. 29.7 ± 4.6	10.4	≤0.05[a]	0.69

(Continued)

TABLE 7 | Continued

References	*N*	*N* per group	Age (y) [range or mean ± SD]	Frequency/ duration	Testing modality	Sets (reps)	Training loads	Weekly sets per exercise	Pre- vs. post [mean ± SD]	Pre- vs. post % strength change	Reported *P*-value (Pre- vs. post)	ES
Humburg et al., 2007	29	Con: 7	23.1–27.1	3 per wk for 9 wks	BP	Con (0)	8–12RM	Con	47.5 ± 15.7 vs. 48.2 ± 17.1	1.47	/	0.04
		S: 22			BP	1 (8–12)		S	56.1± 20.6 vs. 61.7 ± 21.7	10.0	≤0.05[a]	0.26
		M3: 22			BP	3 (8–12)		M3	54.9 ± 21.6 vs. 63.0 ± 23.0	14.8	≤0.05[a]	0.36
Humburg et al., 2007	29	Con: 7	23.1–27.1	3 per wk for 9 wks	LP right leg	Con (0)	8–12RM	Con	155.7 ± 23.1 vs. 149.8 ± 26.2	−3.80	/	−0.24
		S: 22			LP right leg	1 (8–12)		S	174.4 ± 44.7 vs. 188.1 ± 36.4	7.9	≤0.05[a]	0.34
		M3: 22			LP right leg	3 (8–12)		M3	172.7 ± 38.4 vs. 195.3 ± 44.7	13.1	≤0.05[a]	0.54
Humburg et al., 2007	29	Con: 7	23.1–27.1	3 per wk for 9 wks	LP left leg	Con (0)	8–12RM	Con	156.5 ± 31.5 vs. 149.7 ± 33.8	−4.35	/	−0.21
		S: 22			LP left leg	1 (8–12)		S	169.5 ± 40.2 vs. 183.1± 36.1	8.0	≤0.05[a]	0.36
		M3: 22			LP left leg	3 (8–12)		M3	165.4 ± 38.2 vs. 189.9 ± 44.9	14.8	≤0.05[a]	0.59
Radaelli et al., 2014	48	Con: 10	23.5–25.3	3 per wk for 6 months	BP	Con (0)	8–12RM	Con	68.3 ± 11.4 vs. 64.4 ± 8.8	−5.71	/	−0.38
		S:12			BP	1 (8–12)		S	64.5 ± 9.5 vs. 73.2 ± 9.9	13.5	≤0.05[a,c]	0.90
		M3:13			BP	3 (8–12)		M3	73.4 ± 9.4 vs. 86.1 ± 8.4	17.3	≤0.05[a,c]	1.42
		M5:13			BP	5 (8–12)		M5	89.6 ± 9.6 vs. 99.6 ± 5.5	11.2	≤0.05[a]	1.13
Radaelli et al., 2014	48	Con: 10	23.5–25.3	3 per wk for 6 months	LatP	Con (0)	8–12RM	Con	60.5 ± 6.8 vs. 62.2 ± 6.6	2.8	/	0.25
		S:12			LatP	1 (8–12)		S	57.9 ± 10.7 vs. 68.7 ± 9.5	18.7	≤0.05[a,c]	1.07
		M3:13			LatP	3 (8–12)		M3	62.5 ± 6.21 vs. 70.0 ± 4.76	12.0	≤0.05[a,c]	1.36
		M5:13			LatP	5 (8–12)		M5	74.2 ± 9.5 vs. 86.5 ± 6.5	16.6	≤0.05[a,c]	1.51
Radaelli et al., 2014	48	Con: 10	23.5–25.3	3 per wk for 6 months	SP	Con (0)	8–12RM	Con	26.1 ± 7.4 vs. 29.4 ± 7.6	12.6	–	0.44
		S:12			SP	1 (8–12)		S	31.6 ± 7.1 vs. 38.7 ± 9.3	22.5	≤0.05[a]	0.86
		M3:13			SP	3 (8–12)		M3	34.2 ± 7.5 vs. 42.3 ± 6.3	23.7	≤0.05[a,c]	1.17
		M5:13			SP	5 (8–12)		M5	41.5 ± 8.2 vs. 56.1 ± 11.9	35.2	≤0.05[a,c]	1.43
Radaelli et al., 2014	48	Con: 10	23.5–25.3	3 per wk for 6 months	LP	Con (0)	8–12RM	Con	157.8 ± 21.0 vs. 155.0 ± 25.0	−1.8	/	−0.12
		S:12			LP	1 (8–12)		S	170 ± 34.1 vs. 196.7 ± 15.5	15.7	≤0.05[a]	1.01
		M3:13			LP	3 (8–12)		M3	172.5 ± 30.1 vs. 199.2 ± 14.4	15.5	≤0.05[a,c]	1.13
		M5:13			LP	5 (8–12)		M5	178.5 ± 24.4 vs. 201.5 ± 25.4	12.9	≤0.05[a]	0.92

N, number of subjects; y, years; SD, standard deviation; Reps, repetitions; ES, effect size; S, one-set; M3 three-sets; LP, leg press; RM, repetition maximum; BP, bench press; Sq, squat; SP, shoulder press; MSV3, multiple-sets with changes in training volume; Con, control group; LatP, lateral pull-down; SP, shoulder press; CP, chest press; OP, overhead press.

[a] *Significantly greater than prior to training ($P \leq 0.05$).*

[b] *Significant differences from corresponding groups-exercise values ($P \leq 0.05$).*

[c] *Significantly greater prior to training ($P \leq 0.01$).*

TABLE 8 | Pre- vs. post-strength analysis on single-joint exercise.

References	*N*	*N* per group	Age (y) [range or mean ± SD]	Frequency/ duration	Testing modality	Sets (reps)	Training loads	Weekly sets per exercise	Pre- vs. post [mean ± SD]	Pre- vs. post % strength change	*P*-Value (Pre- vs. post)	ES
Hass et al., 2000	42	S:21	39.2–40.1	3 per wk for 13 wks	LExt	1 (8-12)	8–12RM	S	2.4 ± 0.4 vs. 2.7 ± 0.4	12.5	≤0.05	0.75
		M3:21			LExt	3 (8–12)		M3	2.6 ± 0.4 vs. 2.9 ± 0.4	11.5	≤0.05	0.75
Hass et al., 2000	42	S:21	39.2–40.1	3 per wk for 13 wks	LCurl	1 (8–12)	8–12RM	S	2.0 ± 0.3 vs. 2.1 ± 0.2	5	≤0.05	0.39
		M3:21			LCurl	3 (8–12)		M3	2.1± 0.2 vs. 2.3 ± 0.2	9.5	≤0.05	1.00
Hass et al., 2000	42	S:21	39.2–40.1	3 per wk for 13 wks	BC	1 (8–12)	8–12RM	S	1.0 ± 0.3 vs. 1.1 ± 0.3	10	≤0.05	0.33
		M3:21			BC	3 (8–12)		M3	1.1± 0.3 vs. 1.2 ± 0.3	9.1	≤0.05	0.33
Paulsen et al., 2003	18	S:10	20–30	3 per wk for 6 wks	KExt	1 (7)	7RM	S	125.8 ± 52.8 vs. 144 ± 45.5	14.5	≤0.01[a]	0.37
		M3:8			KExt	3 (7)		M3	117.8 ± 38.2 vs. 142.5 ± 25.2	21.0	≤0.01[a]/≤0.05[b]	0.76
Paulsen et al., 2003	18	S:10	20–30	3 per wk for 6 wks	LCurl	1 (7)	7RM	S	57.3 ± 30.4 vs. 64.8 ± 24.03	13.1	≤0.01[a]	0.27
		M3:8			LCurl	3 (7)		M3	55.9 ± 29.1 vs. 65.3 ± 37.1	16.8	≤0.01[a]/≤0.05[b]	0.25
Kelly et al., 2007	40	Con: 8	22.2–25.3	2 per wk for 8 wks	Con	Con (0)	8RM	Con	135.7 ± 77.1 vs. 127.1 ± 64.6	6.3	/	−0.12
		S:14			KExt	1 (8)		S	163.5 ± 56.4 vs. 171.2 ± 70	4.7	≤0.05	0.12
		M3:18			KExt	3 (8)		M3	171.4 ± 62.0 vs. 200.8 ± 111.1	17.2	≤0.05	0.33
Bottaro et al., 2009	24	S:13	22.2 ± 3.2	2 per wk for 12 wks	KExt	1 (8–12)	8–12RM	S	24.3 ± 3.0 vs. 25.3 ± 2.9	4.1	?	0.34
		M3:11			KExt	3 (8–12)		M3	20.9 ± 3.2 vs. 23.4 ± 2.3	12.0	≤0.05[c]	0.90
Bottaro et al., 2009	24	S:13	22.2 ± 3.2	2 per wk for 12 wks	EExt	1 (8–12)	8–12RM	S	51.4 ± 10.9 vs. 55.2 ± 10.2	7.4	≤0.05[c]	0.36
		M3:11			EExt	3 (8–12)		M3	45.6 ± 5.9 vs. 48.3 ± 8.2	5.9	≤0.05[c]	0.38
Baker et al., 2013	16	S:8	18–21	3 per wk for 8 wks	BC	1 (6)	6RM	S	402.8 ± 54.8 vs. 485.1 ± 48	20.4	≤0.05 one tailed[c]	1.60
		M3:8			BC	3 (6)		M3	421.4 ± 44.1 vs. 499.8 ± 77.4	18.6	≤0.05 one tailed[c]	1.24
Sooneste et al., 2013	8	S:8	25.0 ± 2.1	2 per wk for 12 wks	SPC	1 (8)	8RM	S	9.1 ± 1.6 vs. 10.9 ± 2.5	19.8	≤0.05[c]	0.86
		M3:8			SPC	3 (8)		M3	9.1 ± 1.6 vs. 11.9 ± 2.9	30.8	≤0.05[c]	1.20

(Continued)

TABLE 8 | Continued

References	*N*	*N* per group	Age (y) [range or mean ± SD]	Frequency/ duration	Testing modality	Sets (reps)	Training loads	Weekly sets per exercise	Pre- vs. post [mean ± SD]	Pre- vs. post % strength change	*P*-Value (Pre- vs. post)	ES
Reid et al., 1987	34	S:9	18–35	3 per wk for 8 wks	KFlex	1 (10–12)	6–12RM	S	34.2 ± 6.4 vs. 39.7 ± 8	16.1	≤0.05[c]	0.76
		M3:9			KFlex	3 (6)		M3	35.2 ± 5.3 vs. 40 ± 5.6	13.6	≤0.01[a]	0.88
Reid et al., 1987	34	S:9	18–35	3 per wk for 8 wks	KExt	1 (10–12)	6–12RM	S	80.5 ± 15.8 vs. 95.5 ± 17.8	18.6	≤0.01[a]	0.89
		M3:9			KExt	3 (6)		M3	90.0 ± 16.7 vs. 103.6 ± 16.4	15.1	≤0.01[a]	0.82
Reid et al., 1987	34	S:9	18–35	3 per wk for 8 wks	EFlex	1 (10–12)	6–12RM	S	39.3 ± 4.2 vs. 43.9 ± 6.3	11.7	≤0.01[a]	0.86
		M3:9			EFlex	3 (6)		M3	42 ± 5.2 vs. 45.5 ± 6.9	8.3	≤0.05[c]	0.57
Reid et al., 1987	34	S:9	18–35	3 per wk for 8 wks	EExt	1 (10–12)	6–12RM	S	28.5 ± 7 vs. 35 ± 10.8	22.8	≤0.01[a]	0.71
		M3:9			EExt	3 (6)		M3	33.4 ± 8.1 vs. 40.3 ± 10.3	20.7	?	0.74
Reid et al., 1987	34	S:9	18–35	3 per wk for 8 wks	SFlex	1 (10–12)	6–12RM	S	47.3 ± 10.7 vs. 58.3 ± 10.7	23.3	≤0.01[a]	1.03
		M3:9			SFlex	3 (6)		M3	52.9 ± 11.9 vs. 64.4 ± 9.8	21.7	≤0.05[c]	1.05
Reid et al., 1987	34	S:9	18–35	3 per wk for 8 wks	SExt	1 (10–12)	6–12RM	S	48.2 ± 11.1 vs. 54.8 ± 11.2	13.7	?	0.59
		M3:9			SExt	3 (6)		M3	51.8 ± 9.1 vs. 66.5 ± 11.1	28.4	≤0.01[a]	1.44
Schlumberger et al., 2001	27	Con: 9	20–40	2 per wk for 6 wks	LExt	Con (0)	6RM	Con	44.1 ± 7.7 vs. 44.0 ± 8.6	−0.23	/	−0.01
		S:9			LExt	1 (6–9)		S	44.8 ± 6.8 vs. 47.8 ± 7.9	6.7	≤0.05	0.41
		M3:9			LExt	3 (6–9)		M3	43.7 ± 6.1 vs. 50.6 ± 7.6	15.8	≤0.05	1.00
Humburg et al., 2007	29	Con: 7	23.1–27.1	3 per wk for 9 wks	BC	Con (0)	8–12RM	Con	25.9 ± 11.9 vs. 25.6 ± 12.1	−1.2	/	−0.02
		S: 22			BC	1 (8–12)		S	28.1 ± 9.4 vs. 30.0 ± 9.4	6.8	≤0.05	0.20
		M3: 22			BC	3 (8-12)		M3	26.4 ± 9.5 vs. 30.6 ± 9.4	15.9	≤0.05	0.44

N, number of subjects; y, years; SD, standard deviation; Reps, repetitions; ES, effect size; S, one-set; M3= three-sets; per week, number of days trained per week; LExt, leg extension; RM, repetition maximum; LCurl, leg curl; BC, bicep curl; KExt, knee extension; Con, control group; EExt, elbow extension; SPC, seated preacher curl; EFlex, elbow flexion; SFlex, shoulder flexion; SExt, shoulder extension.

[a] *Significantly greater than prior to training ($P \leq 0.05$).*

[b] *Significant differences from corresponding groups-exercise values ($P \leq 0.05$).*

[c] *Significantly greater than prior to training ($P \leq 0.01$).*

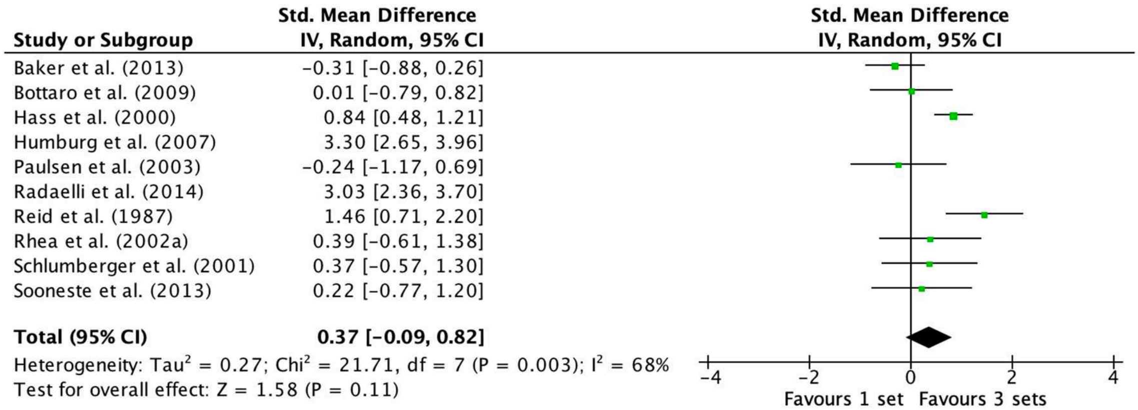

FIGURE 3 | Forest plot of 1 vs. 3-sets (trained and untrained subjects [upper body exercise] combined) with Humburg et al. (2007) and Radaelli et al. (2014) datum excluded.

Untrained Subjects' Effects of 1- vs. 3-Sets on Upper Body Exercise

Examination of upper body exercises (multi-joint and single-joint exercises combined) on untrained subjects comprised of six studies (Reid et al., 1987; Paulsen et al., 2003; Humburg et al., 2007; Bottaro et al., 2009; Sooneste et al., 2013; Radaelli et al., 2014). The random-effects model exposed a large amount of variability between studies ($I^2 = 94\%$). Removal of Humburg et al. (2007) and Radaelli et al. (2014) data, resulted in large heterogeneity (Q heterogeneity test was: $\text{Chi}^2 = 11.45$, d.f. = 3, $P = 0.010$). The heterogeneity statistic I^2 (%) = 74 (interpreted as high heterogeneity, Higgins et al., 2003), and the tau^2 test (between-trials variance) = 0.54, and a small effect was observed (ES 0.35; 95% CI −0.49 to 1.19). Pre- to post-intervention strength change was greater when M3 was compared with S (ES difference 0.23) with no statistical significance ($P = 0.42$). The mean ES for S was 0.81 (95% CI 0.67–0.95). The mean ES for M3 was 1.04 (95% CI 0.66–1.41). Subgroup examination of S vs. M3 pre- to post-intervention strength differences on trained only and untrained only subjects was not viable due to inadequate study data.

Trained Subjects' Effects of 1- vs. 3-Sets on Upper Body Exercise

Examination of upper body exercises (multi-joint and single-joint exercises combined) on trained subjects comprised of four studies (Hass et al., 2000; Schlumberger et al., 2001; Rhea et al., 2002a; Baker et al., 2013). Q heterogeneity test was: $\text{Chi}^2 = 3.09$, d.f. = 3, $P = 0.38$. The random-effects model exposed a low amount of variability between studies. The heterogeneity statistic I^2 (%) = 3 (interpreted as low, Higgins et al., 2003), and the tau^2 test (between-trials variance) = 0.00. When a random effect analysis was implemented, a moderate effect was detected on trained only subjects for upper body exercise resistance exercises (ES 0.63; 95% CI 0.34–0.92). Pre- to post-intervention strength change was greater when M3 was compared to S (ES difference 0.33) with statistical significance ($P < 0.0001$). The mean for S was 0.59 (95% CI 0.16–1.02). The mean ES for M3 was 0.92 (95% CI 0.53–1.31).

Effects of 1- vs. 3-Sets on Lower Body Exercise

Examination of lower body exercises (multi-joint and single-joint exercises combined) on untrained and trained subjects comprised of 10 studies (Reid et al., 1987; Hass et al., 2000; Schlumberger et al., 2001; Rhea et al., 2002a; Paulsen et al., 2003; Humburg et al., 2007; Kelly et al., 2007; Bottaro et al., 2009; Radaelli et al., 2014) are displayed in the forest plot (**Figure 4**). Q heterogeneity test was: $\text{Chi}^2 = 54.00$, d.f. = 9, $P < 0.00001$. The random-effects model exposed a high amount of variability between studies I^2 (%) = 83. Removal of Hass et al. (2000) and Humburg et al. (2007) data, resulted in no heterogeneity (Q heterogeneity test was: $\text{Chi}^2 = 4.05$, d.f. = 7, $P = 0.77$). The heterogeneity statistic I^2 (%) = 0 (interpreted as no heterogeneity, Higgins et al., 2003), and the tau^2 test (between-trials variance) = 0.00, and a small effect was observed (ES 0.35; 95% CI 0.10–0.60). Pre- to post-intervention strength change was greater when M3 was compared with S (ES difference 0.27) with statistical significance ($P = 0.006$). The mean ES for S was 0.60 (95% CI 0.36–0.84). The mean ES for M3 was 0.87 (95% CI 0.57–1.17).

Untrained Subjects' Effects of 1- vs. 3-Sets on Lower Body Exercise

Examination of lower body exercises (multi-joint and single-joint exercises combined) on untrained comprised of five studies (Reid et al., 1987; Paulsen et al., 2003; Humburg et al., 2007; Bottaro et al., 2009; Radaelli et al., 2014). Q heterogeneity test was: $\text{Chi}^2 = 34.99$, d.f. = 4, $P = < 0.00001$. The random-effects model exposed a high amount of variability between studies I^2 (%) = 89. Removal of Humburg et al. (2007) data, resulted in no heterogeneity (Q heterogeneity test was: $\text{Chi}^2 = 2.36$, d.f. = 3, $P = 0.50$). The heterogeneity statistic I^2 (%) = 0 (interpreted as no heterogeneity, Higgins et al., 2003), and the tau^2 test (between-trials variance) = 0.00, and a moderate effect was observed

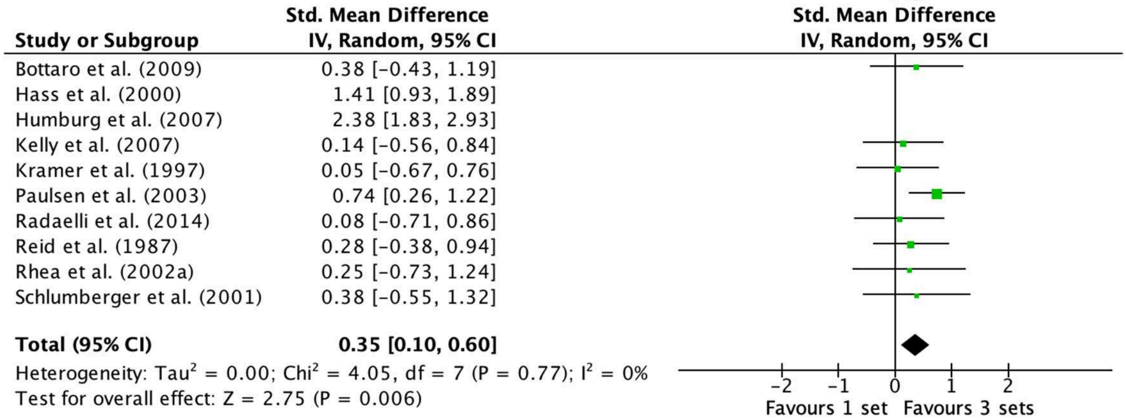

FIGURE 4 | Forest plot of 1 vs. 3-sets (untrained and trained subjects [lower body exercise] combined) with Hass et al. (2000) and Humburg et al. (2007) datum excluded.

(ES 0.49; 95% CI 0.14–0.83). Pre- to post-intervention strength change was greater when M3 was compared with S (ES difference 0.28) with statistical significance ($P = 0.005$). The mean ES for S was 0.75 (95% CI 0.30–1.2). The mean ES for M3 was 1.03 (95% CI 0.51–1.55).

Trained Subjects' Effects of 1- vs. 3-Sets on Lower Body Exercise

Examination of lower body exercises (multi-joint and single-joint exercises combined) on trained subjects comprised of five studies (Kramer et al., 1997; Hass et al., 2000; Schlumberger et al., 2001; Rhea et al., 2002a; Kelly et al., 2007). Q heterogeneity test was: $Chi^2 = 15.24$, d.f. $= 4$, $P = < 0.004$. The random-effects model exposed a high amount of variability between studies I^2 (%) $= 74$. Removal of Hass et al. (2000) data, resulted in no heterogeneity (Q heterogeneity test was: $Chi^2 = 0.34$, d.f. $= 3$, P-value $= 0.95$). The heterogeneity statistic I^2 (%) $= 0$ (interpreted as no heterogeneity, Higgins et al., 2003), and the tau^2 test (between-trials variance) $= 0.00$, and a trivial effect was observed (ES 0.18; 95% CI −0.23 to 0.58). Pre- to post-intervention strength change was greater when M3 was compared with S (ES difference 0.32) with no statistical significance ($P = 0.39$). The mean ES for S was 0.63 (95% CI 0.18–1.08). The mean ES for M3 was 0.95 (95% CI 0.43–1.47).

Effects of 1- vs. 3-Sets on Multi-Joint Only Exercise

Outcomes for S vs. M3 on multi-joint exercise (combined trained and untrained subjects) classified as S or M3 are displayed in the forest plot (**Figure 5**). The forest plot includes the mean ES and CIs for strength change separated for interventions featuring S and M3 and the overall effect test and heterogeneity analysis. The pooled mean ES estimates of S vs. M3 on multi-joint exercise data comprised of 34 treatment groups from eight studies (Kramer et al., 1997; Hass et al., 2000; Schlumberger et al., 2001; Rhea et al., 2002a; Paulsen et al., 2003; Humburg et al., 2007; Baker et al., 2013; Radaelli et al., 2014). The random-effects model exposed a considerable amount of variability between studies. Q heterogeneity test was: $Chi^2 = 69.07$, d.f. $= 7$, $P < 0.00001$. The heterogeneity statistic I^2 (%) $= 90$ (interpreted as high, Higgins et al., 2003), and the tau^2 test (between-trials variance) $= 0.86$. A moderate effect was observed for multi-joint exercise and M3 (ES 0.83; 95% CI 0.14–1.51). Pre- to post-intervention strength change was greater when M3 was compared to S (ES difference 0.22) with statistical significance ($P = 0.02$). The mean for S was 0.61 (95% CI 0.34–0.88). The mean ES for M3 was 0.83 (95% CI 0.53–1.13).

Trained Subjects' Effects of 1- vs. 3-Sets on Multi-Joint Only Exercise

Separate subgroup examination on the effects of pre- vs. post-training strength (trained subjects only) categorized as either S or M3 from five studies (Kramer et al., 1997; Hass et al., 2000; Schlumberger et al., 2001; Rhea et al., 2002a; Baker et al., 2013). The random-effects model exposed a low degree of variability between studies. Q heterogeneity test was: $Chi^2 = 7.73$, d.f. $= 4$, $P = 0.10$. The heterogeneity statistic I^2 (%) $= 48$ (interpreted as low-moderate, Higgins et al., 2003), and the tau^2 test (between-trials variance) $= 0.07$. A moderate effect was observed on trained only subjects for multi-joint exercises combined (ES 0.52; 95% CI 0.10–0.94). Pre- to post-intervention strength change was greater when M3 was compared to S (ES difference 0.25) with statistical significance ($P = 0.02$). The mean for S was 0.67 (95% CI 0.30 to 1.04). The mean ES for M3 was 0.92 (95% CI 0.56–1.28). Subgroup analysis of S vs. M3 pre-to post-intervention strength differences on untrained subjects was not feasible due to inadequate study data.

Effects of 1- vs. 3-Sets on Multi-Joint Upper Body Exercise

Subgroup analysis on the effects of pre- vs. post-training strength multi-joint upper body exercises (trained and untrained subjects) categorized as either S or M3 from seven studies (Hass et al., 2000; Schlumberger et al., 2001; Rhea et al., 2002a; Paulsen et al., 2003; Humburg et al., 2007; Baker et al., 2013; Radaelli et al., 2014). The random-effects model exposed a significant amount of variability

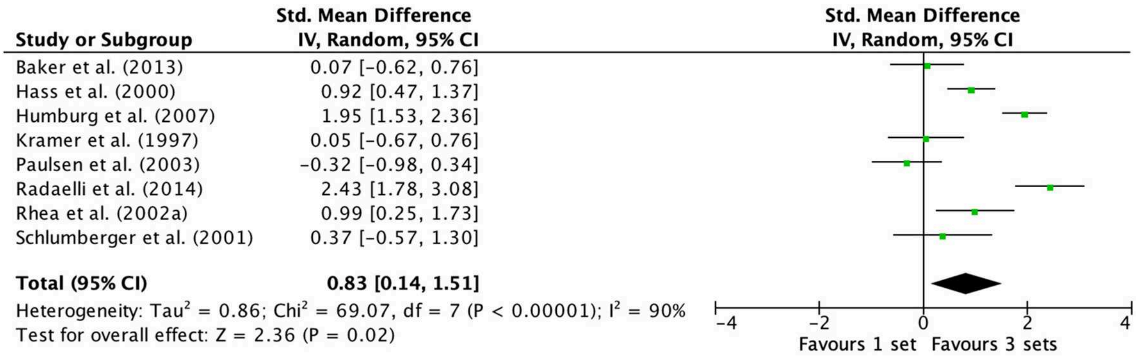

FIGURE 5 | Forest plot of 1 vs. 3-sets (trained and untrained [multi-joint exercise] combined).

between studies. Q heterogeneity test was: $Chi^2 = 70.88$, d.f. = 6, $P < 0.00001$. The heterogeneity statistic I^2 (%) = 92 [interpreted as high, (Higgins et al., 2003)] and the tau^2 test (between-trials variance) = 1.57. A large effect was observed (ES 1.15; 95% CI 0.17–2.12). Pre- to post-intervention strength change was greater when M3 was compared to S (ES difference 0.24) with statistical significance between RT set volumes ($P = 0.02$). The mean for S was 0.55 (95% CI 0.23–0.86). The mean ES for M3 was 0.79 (95% CI 0.44–1.14).

Trained Subjects' Effects of 1– vs. 3-Sets on Multi-Joint Upper Body Exercise

Subgroup examination of S vs. M3 pre- vs. post-training strength differences on trained subjects multi-joint upper body exercises comprised of four studies (Hass et al., 2000; Schlumberger et al., 2001; Rhea et al., 2002a; Baker et al., 2013). The random-effects model exposed a low to moderate amount of variability between studies. Q heterogeneity test was: $Chi^2 = 4.56$, d.f. = 3, $P = 0.21$. The heterogeneity statistic I^2 (%) = 34 (interpreted as low-moderate, Higgins et al., 2003), and the tau^2 test (between-trials variance) = 0.07. A moderate effect was observed (ES 0.52; 95% CI 0.08–0.96). Pre- to post-intervention strength gain was greater when M3 was compared to S (ES difference 0.32) with statistical significance ($P = 0.02$). The mean for S was 0.59 (95% CI 0.09–1.08). The mean ES for M3 was 0.91 (95% CI 0.49–1.32). Subgroup examination of S vs. M3 pre- to post-intervention strength differences on untrained subjects was not feasible due to limited study data.

Effects of 1- vs. 3-Sets on Multi-Joint Lower Body Exercise

Analysis of S vs. M3 pre- to post-intervention strength differences on subject's multi-joint lower body exercises comprised of five studies (Kramer et al., 1997; Rhea et al., 2002a; Paulsen et al., 2003; Humburg et al., 2007; Radaelli et al., 2014). The random-effects model showed a significant amount of variability between studies. Removal of (Humburg et al., 2007) data resulted in no heterogeneity (Q heterogeneity test was: $Chi^2 = 0.13$, d.f. = 3, $P = 0.99$). The heterogeneity statistic I^2 (%) = 0 (interpreted as none, Higgins et al., 2003), and the tau^2 test (between-trials variance) = 0.00 and trivial effect observed (ES 0.09; 95% CI −0.32 to 0.51). Pre- to post-intervention strength change was greater with M3 compared with S (ES difference 0.17) with no statistical significance ($P = 0.66$). The mean ES for S was 0.81 (95% CI 0.41–1.21). The mean ES for M3 was 0.98 (95% CI 0.45–1.51). Subgroup examination of S vs. M3 pre- to post-intervention strength differences on trained only and untrained only subjects was not feasible due to inadequate study data.

Effects of 1- vs. 3-Sets on Single-Joint Exercise

Outcomes for 1-vs.-3 sets categorized as S or M3 for single-joint resistance exercises are displayed in the forest plot (**Figure 6**). The pooled mean ES estimates of single-joint resistance exercises comprised of 36 treatment groups from nine studies (Reid et al., 1987; Hass et al., 2000; Schlumberger et al., 2001; Paulsen et al., 2003; Humburg et al., 2007; Kelly et al., 2007; Bottaro et al., 2009; Baker et al., 2013; Sooneste et al., 2013). The random-effects model exposed a low to moderate amount of variability between studies. Q heterogeneity test was: $Chi^2 = 10.61$, d.f. = 8, $P = 0.22$. The heterogeneity statistic I^2 (%) = 25 (interpreted as low-moderate, Higgins et al., 2003), and the tau^2 test (between-trials variance) = 0.03 and a small effect was observed (ES 0.49; 95% CI 0.26–0.72). Pre- to post-intervention strength change was marginally greater with M3 compared with S (ES difference 0.19) with statistical significance ($P < 0.0001$). The mean ES for S was 0.57 (95% CI 0.26–0.87). The mean ES for M3 was 0.76 (95% CI 0.54–0.98).

Trained Subjects' Effects of 1- vs. 3-Sets on Single-Joint Exercise

Subgroup examination on the effects of pre- vs. post-training strength (trained subjects only) categorized as either S or M3 from four studies (Hass et al., 2000; Schlumberger et al., 2001; Kelly et al., 2007; Baker et al., 2013). Q heterogeneity test was: $Chi^2 = 3.91$, d.f. = 3, $P = 0.27$. The random-effects model exposed a low amount of variability between studies. The heterogeneity statistic I^2 (%) = 23 (interpreted as low, Higgins et al., 2003), and the tau^2 test (between-trials variance) = 0.04. When a random effect analysis was implemented, a small effect was detected on trained only subjects for single-joint resistance exercises (ES 0.37; 95% CI −0.01 to 0.75). Pre- to

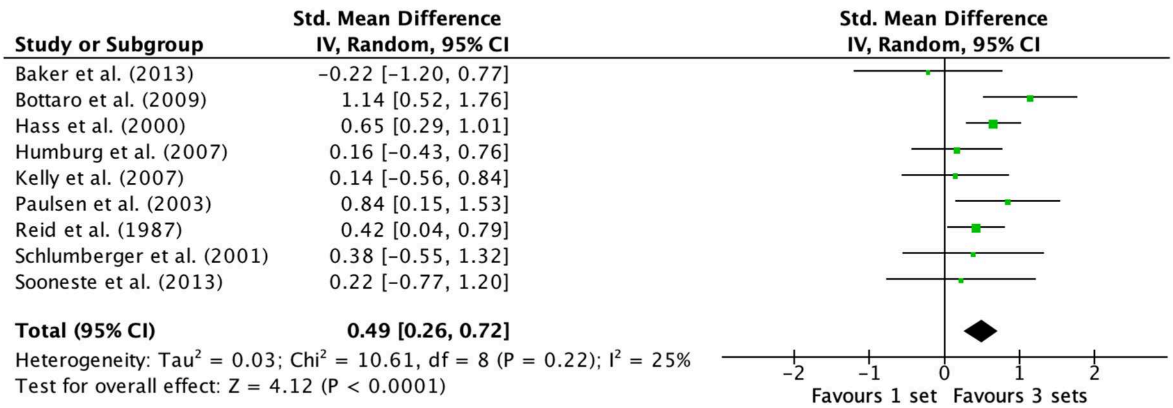

FIGURE 6 | Forest plot of 1 vs. 3-sets (trained and untrained [single-joint exercises] combined).

post-intervention strength change was greater when M3 was compared to S (ES difference 0.09) with no statistical significance (P-value = 0.06). The mean for S was 0.75 (95% CI 0.12–1.28). The mean ES for M3 was 0.84 (95% CI 0.39–1.28).

Untrained Subjects' Effects of 1- vs. 3-Sets on Single-Joint Exercise

Examination of the effects of pre- vs. post-training strength (untrained subjects only) categorized as either S or M3 from five studies (Reid et al., 1987; Paulsen et al., 2003; Humburg et al., 2007; Bottaro et al., 2009; Sooneste et al., 2013). The random-effects model showed a low to moderate amount of variability between studies. Q heterogeneity test was: $Chi^2 = 6.76$, d.f. = 4, $P = 0.15$. The heterogeneity statistic I^2 (%) = 41 (interpreted as low-moderate, Higgins et al., 2003), and the tau^2 test (between-trials variance) = 0.06, and a moderate effect was observed on untrained only subjects for single-joint exercises (ES 0.56; 95% CI 0.21–0.91). Pre- to post-intervention strength change was marginally greater when M3 was compared to S (ES difference 0.23) with statistical significance ($P = 0.002$). The mean for S was 0.51 (95% CI 0.24–0.77). The mean ES for M3 was 0.74 (95% CI 0.47–1.02).

Effects of 1- vs. 3-Sets on Upper Body Single-Joint Exercise

Subgroup examination of upper body single-joint exercises are presented in the forest plot. The pooled mean ES estimates comprised of six studies (Reid et al., 1987; Hass et al., 2000; Humburg et al., 2007; Bottaro et al., 2009; Baker et al., 2013; Sooneste et al., 2013). The random-effects model exposed a low to moderate amount of variability between studies. Q heterogeneity test was: $Chi^2 = 2.74$, d.f. = 5, $P = 0.74$. The heterogeneity statistic I^2 (%) = 0 (interpreted as no heterogeneity, Higgins et al., 2003), and the tau^2 test (between-trials variance) = 0.00, and a trivial effect was detected (ES 0.20; 95% CI −0.07 to 0.47). Pre- to post-intervention strength change was comparable when M3 was compared with S (ES difference 0.07) with no statistically significance ($P = 0.16$). The mean ES for S was 0.69 (95% CI 0.28–1.11). The mean ES for M3 was 0.76 (95% CI 0.42–1.09). Subgroup examination of S vs. M3 pre- to post-intervention strength differences on trained only and untrained only subjects was not possible due to inadequate study data.

Effects of One –vs. Three-Sets on Lower Body Single-Joint Exercise

Examination on lower body single-joint exercises comprised of six studies (Reid et al., 1987; Hass et al., 2000; Schlumberger et al., 2001; Paulsen et al., 2003; Kelly et al., 2007; Bottaro et al., 2009). The random-effects model exposed a moderate amount of variability between studies ($I^2 = 63\%$). Removal of Hass et al. (2000) data, resulted in no heterogeneity (Q heterogeneity test was: $Chi^2 = 2.24$, d.f. = 4, $P = 0.69$. The heterogeneity statistic I^2 (%) = 0 (interpreted as no heterogeneity, Higgins et al., 2003), and the tau^2 test (between-trials variance) = 0.00, and a small effect was observed (ES 0.41; 95% CI 0.08–0.74). Pre- to post-intervention strength change was greater when M3 was compared with S (ES difference 0.32) with statistical significance ($P = 0.02$). The mean ES for S was 0.40 (95% CI 0.17–0.63). The mean ES for M3 was 0.72 (95% CI 0.51–0.93). Subgroup examination of S vs. M3 pre- to post-intervention strength differences on trained only and untrained only subjects was not viable due to inadequate study data.

DISCUSSION

This paper is the first meta-analytical review that compares terrestrial RT set-volume evidence and provides recommendations for pre-spaceflight preparation. This meta-analysis sought to determine whether M3 is associated with more significant strength gains than S per resistance exercise in RT programmes (**Table 9**). Additionally, results from this meta-analysis indicate the future need for research that explores appropriate physical RT implemented during spaceflight preparation. When trained and untrained subjects were combined, M3 was associated with greater ES in both combined multi-joint and single-joint exercises compared to S (**Table 9**). However, significant heterogeneity existed when combining different population groups (trained and untrained) and exercise type (multi-joint and single-joint). When body segmentation was analyzed (upper and lower body) M3 reported greater ES compared to S. Subgroup analysis on upper body only (trained and untrained combined and untrained studies only) reported marginally greater gains in strength when M3 was compared to S but were not significant. Trained subjects only reported statistically significant pre-post-strength changes ($P < 0.0001$) in upper body RT exercise. The data for lower body exercise reported that M3 was associated with greater ES in both combined population group ($P = 0.02$) and untrained subjects only ($P = 0.02$), but not trained subjects ($P = 0.39$).

Analysis of combined population groups on pooled multi-joint exercise and upper body multi-joint exercise reported greater strength gains with M3 compared to S. However, multi-joint lower body exercise reported marginally greater gains in strength with M3 compared to S, but these were not statistically significant. Subgroup analysis on untrained subjects only reported greater ESs on single-joint only exercises with M3 compared to S, with moderate heterogeneity detected between studies. When subgroup analysis was performed on trained only subjects on combined multi-joint exercises, upper body multi-joint only, and lower body multi-joint only the ES for M3 was statistically greater compared to S for strength gains. However, analysis of single-joint only exercise on trained subjects cannot fully support the contention that M3 produced greater ESs than S, as findings were not statistically significant. The results of this analysis provide support for the use of additional sets (up to three-sets) per exercise for increasing muscle strength. However, both S and M3 demonstrated significant pre-post-strength differences in multi-joint and single-joint exercises.

Ground-Based Meta-Analytical Recommendations for Untrained Individuals

The scientific literature on daily set-volume has been heavily contested with some suggesting that S produce similar adaptations to MS (Silvester et al., 1982; Messier and Dill, 1985; Reid et al., 1987; Pollock et al., 1993; Starkey et al., 1996; Hass et al., 2000). However, others indicate that MS produces greater strength, hypertrophy, and power adaptations (Kraemer, 1997; Hass et al., 2000; Borst et al., 2001; Marx et al., 2001; McBride et al., 2003; Paulsen et al., 2003). In the context of pre-flight conditioning, the initial physical training status of each crew member must be fully considered. Specifically, as the inclusion of smaller doses of daily RT (e.g., S per exercise) may be appropriate to develop muscular strength in less conditioned (untrained) crew members, whereas more substantial doses of RT (e.g., ≥M3 per exercise) may be essential to attain further strength.

Currently, the prescription of RT for pre-flight conditioning is recommended from ground-based models and experience gained during previous missions. Present recommendations for ST consist of one-to-three-sets per exercises for untrained individuals and MS used with variations in RT volume and intensity over a period for trained individuals [American College of Sports Medicine Position Stand (ACSM), 2009]. These recommendations on terrestrial RT set-volume have been subject to strong criticism due to reported methodological constraints within the included meta-analyses (Smith and Bruce-Low, 2004; Winett, 2004; Otto and Carpinelli, 2006; Carpinelli, 2012; Fisher, 2012). For example, the meta-analysis by Rhea et al. (2003) presented data that may have nullified the mean ES and spuriously affected the results. This is due to increasing the heterogeneity of the meta-analysis, therefore, erroneously favoring MS programming. Rhea and colleagues reported that untrained subjects should perform four-sets for strength increases (ES = 2.28 ± 1.96 SD), compared with S (ES = 1.16 ± 1.59 SD), two-sets (ES = 1.75 ± 3.23 SD), and M3 (ES = 1.94 ± 3.23 SD). However, the ES standard deviation for M3 was significantly larger in comparison to the other treatment groups, with no explanation provided. Otto and Carpinelli (2006) stated that several critical errors could invalidate the results including bias in the selection process of studies, incorrect classification of subjects training status, and variances of RT loading.

A meta-analysis by Wolfe et al. (2004) suggested that untrained subjects in the initial stages of training (6–15 weeks) perform with an S programme. Wolfe et al. (2004) also reported that untrained subjects had comparable pre-post-strength gains as those of trained individuals when performing MS. When subjects performed, RT exercises to physical failure vs. subjects' perceived end, multiple-set programmes generated more substantial increases in strength compared to S ($P \leq 0.002$). A meta-analysis by Krieger (2009) examined the effects of S vs. multiple-sets of exercises on strength and suggested that two-to-three-sets were associated with a more significant ES than S. Krieger (2009) concluded that two-to-three-sets per resistance exercise were associated with 46% greater strength gains than S in both trained and untrained subjects. Finally, a meta-analysis by Fröhlich et al. (2010) of 72 studies found S training regimes to be the equivalent of multiple-set training for short intervention phases but multi-set training to be superior overextended RT intervention periods.

This current meta-analysis provides evidence that supports the contention that M3 RT leads to greater strength gains than S programming for untrained individuals or those astronauts that may be on the early phase of pre-flight conditioning. However, this analysis examined the differences in pre-post-strength gain between body segments and joint types rather than only pooling RT exercises together to generate ES. For upper body exercise, untrained subjects demonstrated a larger pooled mean ES estimate for M3 0.82 (95% CI 0.52–1.11) compared with S (0.60; 95% CI 0.34–0.85), however these results were not statistically significant ($P = 0.42$). Also, a significant degree of heterogeneity was present when exercises were "pooled" together. This intriguingly may explain why other previous meta-analyses reported varying results with regards to specific set-volume and encountered criticism from others as the included studies combined RT exercises to aggregate ES. Subgroup examination on untrained subjects was only feasible for upper and lower body and single-joint only exercises due to limited available data for multi-joint exercise. Untrained subjects pre- to post-strength gains on upper body exercise was greater when

TABLE 9 | Summary of main effects of 1 vs. 3-sets and strength change.

Main effects	ES mean	95% CI	I^2(%)	ES difference S vs. M3	*P*-value
COMBINED MULTI-JOINT AND SINGLE-JOINT EXERCISE					
Trained and untrained combined	0.93	0.41–1.45	92	0.25	0.0005[a]
Untrained subjects only	1.20	0.39–2.01	94	0.22	0.004[a]
Trained subjects only	0.63	0.05–1.22	83	0.28	0.03[a]
UPPER BODY EXERCISE (MULTI-JOINT AND SINGLE-JOINT COMBINED)					
Trained and untrained combined	0.37	0.09–0.82	68	0.19	0.11
Untrained subjects only	0.35	−0.49–1.19	74	0.23	0.42
Trained subjects only	0.63	0.34–0.92	3	0.33	<0.0001[a]
LOWER BODY EXERCISE (MULTI-JOINT AND SINGLE-JOINT COMBINED)					
Trained and untrained combined	0.35	0.10–0.60	0	0.27	0.006[a]
Untrained subjects only	0.49	0.14–0.83	0	0.28	0.005[a]
Trained subjects only	0.18	−0.23–0.58	0	0.32	0.39
MULTI–JOINT ONLY EXERCISE					
Trained and untrained combined	0.83	0.14–1.51	90	0.22	0.02[a]
Trained subjects only	0.52	0.10–0.94	48	0.31	0.02[a]
MULTI-JOINT UPPER BODY					
Trained and untrained combined	1.15	0.17–2.12	92	0.24	0.02[a]
Trained subjects only	0.52	0.08–0.96	34	0.32	0.02[a]
MULTI-JOINT LOWER BODY					
Trained and untrained combined	0.09	−0.32–0.51	0	0.17	0.66
SINGLE-JOINT EXERCISE					
Trained and untrained combined	0.49	0.26–0.72	25	0.19	<0.0001[a]
Untrained subjects only	0.56	0.21–0.91	41	0.23	0.002[a]
Trained subjects only	0.37	−0.01–0.75	23	0.09	0.06
UPPER BODY SINGLE-JOINT EXERCISE					
Trained and untrained combined	0.20	−0.07–0.47	0	0.07	0.16
LOWER BODY SINGLE-JOINT EXERCISE					
Trained and untrained combined	0.41	0.08–0.74	0	0.32	0.02[a]

ES, effect size; 95% CI, 95% confidence level; I^2, I-squared index test; S, one-set; M3, multiple-sets; [a] = statistically different between treatments.

M3 was compared with S (ES difference 0.23) but was not statistically significant ($P = 0.42$). In contrast, lower body exercises reported significantly greater strength changes ($P = 0.005$) with M3 compared with S (ES difference 0.28). Strength gains on single-joint exercises exposed a larger pooled mean ES estimate for M3 (0.74; 95% CI 0.47–1.02) compared with S (0.51; 95% CI 0.24–0.77). When S was used as a control group and M3 used as the experimental set-volume, a moderate ES of 0.56 (95% CI 0.21–0.91; $P = 0.002$) suggested that M3 was effective in generating larger strength increases.

Even though evidence from this analysis supports increase set-volume for strength gain, caution is warranted concerning the interpretation of the findings as exercises performed in the included studies may not transfer toward improved operational task functioning. Furthermore, even though superior increases in strength may be produced with M3, the necessary time and physical effort required to attain such strength developments may not be essential for preparation toward spaceflight. The time to perform this additional conditioning may be better served in completing other necessary operational tasks.

Ground-Based Meta-Analytical Recommendations for Trained Individuals

Current recommendations from NASA for pre-flight conditioning suggest that trained astronauts who are in the final stages of pre-spaceflight preparation perform MS with variations in RT volume and intensity (American College of Sports Medicine Position Stand (ACSM), 2009; Garber et al., 2011). Several ground-based meta-analyses (Rhea et al., 2003; Peterson et al., 2004; Wolfe et al., 2004; Krieger, 2009; Fröhlich et al., 2010) that are included within the American College of Sports Medicine Position Stand (ACSM) (2009) recommendations have reported superior results when performing MS for trained subjects. Rhea et al. (2003) reported strength increases in the bench press of 20% for S, compared with a 33% increase with M3. Pre- to post leg strength increased by 25.4% for S compared with an increase of 52.1% with M3. However, the inclusion of the Rhea et al. (2002a) study may have generated errors or bias when comparing the means of the one-set and three-set groups (bench press ES = 2.3 and leg press ES 6.5). Also, the post-training standard deviation bench press findings were two-to-three times greater to the pre-training standard deviation in both groups, and the authors did not provide confidence intervals for ES. The meta-analysis by Peterson et al. (2004) stated that experienced athletes should complete eight-sets per muscle group to increase muscular strength. However, due to the low number of ES in the eight-set group, these conclusions may be unreliable when evaluating the specific percentage of 1RM training. An additional meta-analysis performed by Wolfe et al. (2004) reported that MS generated more significant increases in strength ($P \leq 0.001$) for trained subjects.

This current meta-analysis cautiously provides evidence concerning increased sets and strength gain with support toward the use of additional sets (up to M3) compared to S for trained astronauts pre-flight conditioning programme. In this analysis, we reveal that multi-joint only exercises on trained subjects demonstrated a larger pooled mean ES estimate for M3 (0.99; 95% CI 0.60–1.38) compared with S (0.68; 95% CI 0.27–1.10) suggesting that M3 was more effective in producing larger strength gains. Further examination of upper body multi-joint only exercises further supports the use of M3. The pooled mean ES estimate for S was 0.59 (95% CI 0.09–1.08) compared with M3 (0.91; 95% CI 0.49–1.32) suggesting that M3 was more effective in producing strength gains. For single-joint exercises on trained subjects, there was a larger pooled mean ES estimate for M3 (0.84; 95% CI 0.39–1.28) compared with S (0.75; 95% CI 0.12–1.28). However, this was not statistically significant in producing more substantial strength gains.

Exercise prescription currently implemented by space agencies include the prescription of greater RT set-volume, but crew members do not perform the volume in a linear manner. It could be hypothesized, therefore, that by increasing set-volume prior to the commencement of spaceflight may develop astronaut's pre-flight levels of upper and lower body strength. Similarly, Krieger (2010) found that this range of sets and reps was superior in producing muscular hypertrophy. This suggests that the atrophy effects of long duration spaceflight could be mitigated, but not prevented, by a more rigorous deployment of multi-set RT methods. Astronauts that are appropriately conditioned and have progressed in their individualized RT toward a trained state should perform MS per exercise to maximize muscular strength, as it could safeguard against decreases in strength. However, caution should be given with the prescription of daily RT set-volume as exposing astronaut's to chronically high training volume may expose crew members to overtraining syndrome before spaceflight. Also, the inclusion of increased set-volume may also come at the determinant of the application toward training intensity and loading (e.g., 85% 1RM) and may feasibly inhibit strength development (Stone et al., 2006). Collectively, when accounting for other programme variables (RT loading and training frequency), M3 appears to a certain degree to be more advantageous for strength development in individuals that are trained. However, careful consideration must be given toward the astronauts initial pre-training status because of variance between individuals. Furthermore, comprehensive monitoring should be considered to prevent the potential of excess fatigue and to overtrain (Day et al., 2004; Halson, 2014).

Future Considerations Toward Pre-spaceflight Muscle Conditioning

Historically, exercise has been prescribed as a method to counteract the undesired physiological effects of long duration exposure to weightlessness and to safeguard astronaut's health (both acute and chronic). Space agencies have recently acknowledged that the pre-flight physical fitness of astronauts must be higher than age centered normative measurements before spaceflight. The preparation of crew members has advanced from methods that traditionally only improved physiological tolerance toward spaceflight to practices that prepare individuals to live and work in space (Garshnek, 1989). These physical training protocols are employed as a method of countering detrimental physiological adaptations that result from μG. The physical conditioning and preparation of astronauts for spaceflight are essential; however, space agencies approach mission preparation differently. It is evident that most agencies foster a graded dose-response continuum with the initial phase of training emphasizing lower set-volume progressing to MS at the concluding stages of flight preparation.

Based on evidence generated from this analysis, it would be appropriate to suggest that astronauts perform RT via a graded dose-response continuum in preparation for in space transit. However, published research in this area is limited with evidence centered on ground-based studies from older adult populations and bed rest studies that may not fully replicate the physiological pre-spaceflight muscle conditioning status of astronauts. More evidence is required concerning the effects of RT bouts and the dose-response relationship on the training status, age and sex differences for protecting the muscular systems. A greater understanding of the mechanisms for physiological conditioning would, therefore, help to develop appropriate individual centered countermeasures that mitigate deconditioning and must be an essential area of focus for future space physiology research. Ensuring each astronaut's pre-spaceflight strength is at the desired level may help to counteract in-flight and post-flight physiological stress which is paramount for the development of a viable human space exploration programme that goes beyond Earth's orbit.

Strengths and Limitations

There are numerous strengths of this meta-analysis that separate it from previous investigations that compare S vs. M3 configurations. Considerations toward evidence derived from previous critical reviews that identify limitations regarding the quality and selection of included studies that may bias outcomes have been applied [in part]. These review articles debated the findings from previous meta-analytical studies, identifying confounding factors and imprecisions that may have influenced outcome reliability. Previous review articles in this area, have reported issues concerning robustness and rigor that control confounding variables when comparing strength outcomes. Subsequently, this meta-analysis has been founded on critical consensus, current studies, and previous evidence gathered from meta-analyses presenting a re-examination of the evidence. Greater emphasis was placed on strict inclusion and exclusion criteria, specifying why each study was excluded to allow for greater transparency. The identification and the inclusion criteria of studies were restricted to reduce heterogeneity between studies making it easier to apply the results to specific population groups (trained and untrained). This enabled direct assessments to be drawn from studies that compared S and M3 while endeavoring to control for other variables that influence strength outcomes.

This meta-analysis endeavored to limit where possible publication bias which is the most significant source of type I error (the increase of false positive results). Graphical representation via funnel plots evaluated the presence of publication bias which was not present in other meta-analytical studies (Rhea et al., 2002b, 2003; Peterson et al., 2004; Wolfe et al., 2004; Krieger, 2010). Where no publication bias was present, the ES of each included study is distributed symmetrically around the underlying true ES, with a more random variation of this value in smaller studies. Asymmetry in the plot is suggestive of bias, most often due to smaller studies which are non-significant or have an effect in the opposite direction from that assumed (Greco et al., 2013). Within our design, we were conscious of potential heterogeneity and implemented a multi-level model as a method for assessing heterogeneity across studies. Also, visual inspection of forests plots further verified this and indicated the need for further subgroupings of studies which reduced the degree of heterogeneity.

Moreover, subgroup analysis was performed to allow for the assessment of training status (trained and untrained) separately and also the analysis of multi-joint and single-joint exercises. This helped to reduce heterogeneity between groups and allowed for more consistent comparisons to be made. Lastly, efforts were made to restrict the subject pool to population groups (trained and untrained) that were physically active and within a comparable age range that mirrored that of an astronaut's pre-flight fitness status. This is due to the disparity existing with astronaut's fundamental physiological characteristics, with physical fitness levels ranging from sedentary individuals who performed little or no physical activity to athletic standard.

Limitations of this meta-analysis include the use of small sections of the published information that is often derived from an insufficient range of methodological designs that has been determined by the inadequacy of available primary data. As with all meta-analyses, limitations and restrictions exist that include the assessment of aggregate outcomes that inevitably do not assess the same construct (i.e., "comparing apples and oranges"). This is the process of search and retrieval of available journal articles, and the potential effect of publication bias (Rosenthal, 1991). Cooper and Hedges (1994) stated that "retrieval bias" may exist even when robust inclusion criteria for gathering journals articles is applied. For example, in this analysis, retrieval bias may have occurred due to the selection and retrieval of journal articles published only in English. Although we strived to include journal articles from high-quality sources, the number of relevant studies was restricted, and there remained variances in experimental design and control among included studies. For example, four of the 12 included journal articles used RCTs. The other eight used a RAN that did not include a control group; instead, a repeated measures design was used with a baseline measure implemented as the control. However, baseline measures were not uniformly applied across those studies.

In this meta-analysis, the strength increases may be due to other physiological factors that have been acknowledged to affect strength changes including sex, age, physical activity levels, prior training history, genetics and endocrine status. This analysis was unable to subcategories subjects into either male or female population groups; instead, it combined population groups. Several studies have reported that sex influences muscle morphology and functioning (Chorney and Bourgeois, 1999; Sale, 1999). Häkkinen et al. (1996) reported that males have greater muscle strength and size than women due to higher levels of anabolic hormones and greater body mass. Also, it has been inferred that due to lower blood androgen levels in women that the response to RT would induce less muscle hypertrophy compared to men. Equally, some studies have reported no differences between sexes with similar improvements in strength adaptations (Colliander and Tesch, 1991; O'Hagan et al., 1995; Roth et al., 2001).

For this analysis, every effort was made to assess strength outcomes of comparable training designs and methodological construct. However, attempting to include studies that had a standardized RT programme was problematic. Even when attempting to control for variance within studies, confounding issues that may have influenced strength development were present. The RT loading had various ranges (63–93% 1RM) that could not be controlled for which could affect strength gains. As training loading is one of the most critical parameters of ST and the volume of RT training makes it challenging to provide a clear dose-response relationship that supports M3 compared to S programming for strength gain. The previous analyses found that loading of 60% of subjects 1RM (Rhea et al., 2003; Peterson et al., 2004) was sufficient to increase strength for untrained subjects, with trained subjects recommended to perform between 80 and 85% of their 1RM [American College of Sports Medicine Position Stand (ACSM), 2009]. The disparity in the training programme type and the order of resistance exercise between groups were not comparable in all included studies which feasibly could impact upon the set number and muscular strength. Scientific literature is currently equivocal regarding the implementation of heavy or light RT loads for muscular adaptations (Fisher et al., 2017). It must be acknowledged that the different repetition ranges included within this meta-analysis may also be a possible limitation. Several studies have reported comparable strength gains when training at different repetition ranges (Morton et al., 2011; Fisher et al., 2017) whereas others have shown improved strength when individuals trained with higher RT load and a low number of repetitions (Campos et al., 2002). This could be explained by the specificity of the strength test, as training with a low number of repetitions is closer to the 1RM test (Buckner et al., 2017; Gentil et al., 2017).

Finally, strength adaptations may have resulted from the performance of repeated 1RM testing as the resistance exercise loading specificity of the 1RM-tested exercises may have indirectly affected the subject's strength. For example, a subject's pre-to-post leg extension results may have increased, due to the performance of the leg press but not to the same amount as a leg press itself. This is supported by Dankel et al. (2016) who performed 1RM and maximum voluntary contraction testing on elbow flexion. The results intimated that the increase in the 1RM result might not be solely correlated to set-volume, but due to the "learning effect" of the specific resistance exercise. This could explain the variation in untrained subjects' strength due to the principle of training specificity, as neurological learning effects could, therefore, explain the broad range of heterogeneity between the inexperienced group.

CONCLUSION

The prescription for increasing maximal strength is a multifaceted process that involves careful manipulation of RT programme variables. A known association between sets (training volume) and strength improvement would be valuable to researchers, clinicians and astronauts whether they are pre-or in-flight. Recommendations on the appropriate number of sets per session per RE that elicit strength improvements is a contentious issue. The current academic literature does little to resolve this debate with the sets to strength gain correlation remaining unquantified. It is difficult to fully draw accurate conclusions from previous meta-analyses because of confounding training variables including programme duration, training frequency, muscle groups trained and measured, strength testing procedures, repetition velocity, and training status of the subjects. Independent of training status, M3 protocols should be included when maximal strength development is the primary objective of the training routine. However, single-set programmes also produce considerable increases in muscular strength, albeit not to the same degree as that of M3, and are advocated when training time is restricted or at the start of pre-flight conditioning programme.

For astronauts at the end of pre-flight conditioning and considered to be trained individuals, the use of M3 may be at the minimum necessary if not mandatory for trained individuals to further produce strength gains. These physically trained individuals may benefit from additional time and training volume to develop minor increases in performance customarily observed at this level of training progression. However, attention should be given with these advanced trainees due to the interaction of additional RT volume and time with the other fitness and mission orientated goals. However, it is essential to clarify that these modestly greater strength improvements occur at the expense of additional training effort. Ultimately, M3 entails 200–400% greater training volume than S training modes. For astronauts lacking in time, a reduced number of sets (S) per exercise may be what is needed to achieve their desired training goals. It is essential to consider this issue as a lack of time can be a barrier to exercise adherence, and one should be cautious before recommending M3 per exercise to deconditioned astronauts as it can hinder training progression. Also, astronauts in spaceflight preparation are subject to tight scheduling and most often experience time constraints. In such phases of limited time-availability, S can still provide some (yet less) training benefit and should be favored as an alternative exercise mode rather than nothing at all. More research is necessary to define the dose-response relationship for terrestrial RT. However, due to the unique environmental conditions experienced during spaceflight, it may be difficult to fully translate evidence generated from conventional terrestrial RT intervention studies to μG.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Conflict of Interest Statement: PJ is employed by KBR.

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.

frontiers in Physiology

MINI REVIEW
published: 13 August 2019
doi: 10.3389/fphys.2019.01031

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Neuromuscular Electrical Stimulation as a Potential Countermeasure for Skeletal Muscle Atrophy and Weakness During Human Spaceflight

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OPEN ACCESS

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Specialty section:
This article was submitted to Striated Muscle Physiology, a section of the journal Frontiers in Physiology

Received: *14 April 2019*
Accepted: *26 July 2019*
Published: *13 August 2019*

Citation:
Maffiuletti NA, Green DA, Vaz MA and Dirks ML (2019) Neuromuscular Electrical Stimulation as a Potential Countermeasure for Skeletal Muscle Atrophy and Weakness During Human Spaceflight. Front. Physiol. 10:1031. doi: 10.3389/fphys.2019.01031

Human spaceflight is associated with a substantial loss of skeletal muscle mass and muscle strength. Neuromuscular electrical stimulation (NMES) evokes involuntary muscle contractions, which have the potential to preserve or restore skeletal muscle mass and neuromuscular function during and/or post spaceflight. This assumption is largely based on evidence from terrestrial disuse/immobilization studies without the use of large exercise equipment that may not be available in spaceflight beyond the International Space Station. In this mini-review we provide an overview of the rationale and evidence for NMES based on the terrestrial state-of-the-art knowledge, compare this to that used in orbit, and in ground-based analogs in order to provide practical recommendations for implementation of NMES in future space missions. Emphasis will be placed on knee extensor and plantar flexor muscles known to be particularly susceptible to deconditioning in space missions.

Keywords: muscle atrophy, spaceflight analog, countermeasure, muscle weakness, electrical stimulation

INTRODUCTION

Prolonged exposure to microgravity is associated with multi-system deconditioning including the cardiovascular (Hargens and Richardson, 2009) and musculoskeletal systems (Narici and de Boer, 2011). For instance, spaceflight-induced decrements in bone mineral density (Vico and Hargens, 2018) and skeletal muscle mass (Fitts et al., 2010) are common, particularly in lower-limb muscles (LeBlanc et al., 1995). Despite the considerable subject variability in the extent of muscle atrophy and functional loss, one of the most affected muscles seems to be the triceps surae, for which muscle fiber atrophy of 20% has been observed after 6 months of spaceflight (Fitts et al., 2000; Fitts et al., 2010). Long-term spaceflight is also known to impair functionality (Mulavara et al., 2018), neuromuscular control (Cohen et al., 2012) and skeletal muscle strength (Tesch et al., 2005; Shiba et al., 2015), with the strength decline primarily reflecting the loss of muscle mass (Fitts et al., 2010). Since the Skylab missions, it has been known that spaceflight induces more weakness in thigh than arm muscles, particularly the knee extensors, for which ∼20% of strength loss was reported after 1- and 2-month missions (Fitts et al., 2000). Recent studies suggest that in some individuals there are persistent neuromuscular control issues - compounded by and/or related to neurovestibular dysfunction (e.g., Van Ombergen et al., 2017) - resulting in extended periods of physical rehabilitation upon return to Earth (Lambrecht et al., 2017; Petersen et al., 2017).

Besides muscle atrophy, spaceflight-related muscle weakness appears also to reflect a number of neuromuscular alterations, including a selective transformation of slow muscle fibers (type I) to faster phenotypes (type II) (Trappe et al., 2009). In fact, there is evidence that slow muscle fibers are predominantly affected by spaceflight (Fitts et al., 2000; Yamakuchi et al., 2000; Sandona et al., 2012; Wang and Pessin, 2013). Recent pilot data from the SARCOLAB study also suggest that reduced plantar flexor muscle volume may be associated with altered muscle architecture, contractile protein composition, and impaired muscle fiber contractility (Rittweger et al., 2018).

Exercise Training as a Countermeasure

In order to address microgravity-induced deconditioning, exercise countermeasure training is performed daily on the International Space Station (ISS) (Hackney et al., 2015). Despite the medical standard agreements between the ISS international partners, each partner utilizes different training regimes that are to some extent individually tailored for each crewmember. For example, exercise countermeasures in the United States operating segment (NASA, ESA, JAXA, and CSA) consist of an integrated resistance and aerobic training schedule employing the advanced resistive exercise device (ARED), the second generation treadmill (T2), and a cycle ergometer with vibration isolation and stabilization (CEVIS) (Petersen et al., 2016). In contrast, the Russian operating segment employs the БД-2 treadmill, the ВБ-3 cycle ergometer, and the force loader (НС)-1 installed on the ВБ-3 ergometer (Yarmanova et al., 2015). These tools are complemented by a set of resistance bands, compression thigh cuffs, lower body negative pressure trousers, suits for lower body compression and postural (axial) loading and also an electrical stimulator.

Despite the significant investment in both resources and crew time, astronauts typically require a period of rehabilitation upon return to Earth (Lambrecht et al., 2017; Petersen et al., 2017), indicative that deconditioning is not entirely prevented (English et al., 2015; Sibonga et al., 2015). In fact, there appears to be significant variability in the relative effectiveness of ISS countermeasures across various physiological systems (Williams et al., 2009), but also between individuals (Rittweger et al., 2018). The current countermeasure regimes appear unable to fully counteract muscle atrophy and weakness during long-duration ISS missions. For example, even high-volume aerobic training (∼500 km of running) complemented with high-intensity resistance training (∼5000 high-intensity heel raises) were insufficient to prevent plantar flexor weakness and atrophy during a 6-month ISS mission (Rittweger et al., 2018). Furthermore, the current countermeasures require significant time and effort (both for exercise itself and for setup/stowage) in addition to potentially interfering with other crewmember tasks, including experimentation. This explains the increasing attention devoted to consider low-volume, simple and complementary exercise modalities, for use throughout, or potentially for only a short period prior to re-exposure to a gravitational vector, be it Earth, or the hypogravity of the Moon. One of those easily applicable and potentially powerful countermeasures – neuromuscular electrical stimulation (NMES) – is the focus of this article.

Rationale for NMES

Neuromuscular electrical stimulation involves delivering pre-programmed trains of stimuli to superficial muscles via self-adhesive skin electrodes connected to small portable current generators. Such electrical stimuli can be used to evoke relatively strong (albeit sub-maximal) muscle contractions, whose activation pattern is substantially different from that of voluntary contractions. NMES recruits motor units in a non-selective, spatially fixed, and temporally synchronous pattern (Gregory and Bickel, 2005), with the advantage of activating fast muscle fibers at relatively low force levels, but produces greater muscle fatigue when compared with voluntary actions. If provided repeatedly, NMES improves muscle strength, power and endurance in healthy individuals (Gondin et al., 2011b; Veldman et al., 2016), even though these effects are not superior to those induced by voluntary training (Bax et al., 2005). More importantly, NMES has been shown to preserve/restore muscle mass and aspects of neuromuscular function during/following a period of reduced activity due to illness, injury or surgery (Dirks et al., 2014; Jones et al., 2016; Spector et al., 2016; Maffiuletti et al., 2018), with greater effectiveness compared to other rehabilitation modalities (Bax et al., 2005). As such, NMES is widely used as a rehabilitation strategy for patients with a range of diseases (Jones et al., 2016; Spector et al., 2016), both during and following prolonged physical inactivity. NMES also provides beneficial effects in healthy subjects undergoing short periods of ground-based models of microgravity-induced deconditioning, e.g., bed rest or limb immobilization (Dirks et al., 2014). The majority of terrestrial NMES research has involved stimulation of knee extensor and/or plantar flexor muscles, whose atrophy and weakness can significantly impair locomotion. Although traditional countermeasures have the potential to partially attenuate spaceflight-induced muscle alterations (Fitts et al., 2010), no direct comparison of the effectiveness of these countermeasures versus NMES currently exists.

As such, this mini-review is focused on the use of NMES as a potentially-complementary countermeasure against skeletal muscle atrophy and weakness induced by human spaceflight. We provide an overview of the rationale and evidence for NMES-based terrestrial state-of-the-art knowledge, compare this to that employed in orbit and in ground-based analogs, and provide practical recommendations for possible NMES implementation in future space (or analog) missions.

NMES IN ORBIT: SUB-OPTIMAL USE AND EVIDENCE

Roscosmos have employed different NMES devices (see top of **Table 1**) in orbit and in ground-based analogs (Kozlovskaya, 2008). The Tonus-3 unit (Yarmanova et al., 2015) possesses four programs designed to stimulate: calf and quadriceps;

TABLE 1 | In orbit and ground-based analog NMES devices/studies and recommendations for NMES use in spaceflight.

[Device]/(Study)	Disuse model	Duration (days)	NMES Muscle	NMES Duration	NMES freq (Hz)	NMES on:off (s)	NMES Intensity	*Positive effect on muscle mass?*	*Positive effect on muscle strength?*
[Tonus-3]	Russian Space Station		Multiple muscles		10,000(60)	1.5:1.5 10:50			
[Stimul-01 HF Set]	Russian Space Station		Multiple muscles		2,500(50)				
[Stimul-01 LF Set]	Russian Space Station		Multiple muscles		25	1:2			
Mayr et al., 1999	Space Station (proposal)	/	Lower limbs	6 h/day	25–50	1:2	20–30% max tetanic force	/	/
Shiba et al., 2015	ISS (*n* = 1; ? years)	30 (188-d stay)	Upper arm	47 min/week (3×/week)	?	2:2	80% max comfortable intensity	YES	NO
Gould et al., 1982	Long-leg cast (*n* = 10; 20 years)	14	Lower limbs	16 h/day	37	5:150	Tolerance	YES	∼
Gibson et al., 1988	Long-leg cast (*n* = 7; 26 years)	40	Quad	60 min/day	30	2:9	Visible contraction (5% MVC)	YES	/
Duvoisin et al., 1989	Bed rest (*n* = 3; 36 years)	30	Lower limbs	40 min/day (2×/day)	60	4:16	Tolerance (torque recording)	YES	YES
Dirks et al., 2014	Full-leg cast (*n* = 12; 23 yrs)	5	Quad	80 min/day (2×/day)	100	5:10	Visible palpable full contraction	YES	NO
Reidy et al., 2017	Bed rest (*n* = 10; 70 years)	5 (with proteins)	Quad	120 min/day (3×/day)	75	4:10	Max tolerated intensity	YES	NO
Zange et al., 2017	Unloading device (*n* = 7; 26 years)	60 (with proteins)	Calf	40 min/day (2×/day)	30	5:5	Max tolerated intensity	YES	∼
Recommendations			**Quad Calf**	**60 min/day (2x/day)**	**30**	**5:10**	**5 min to reach max tolerated intensity, then increased whenever possible to ≥20% MVC**		

In gray, in orbit devices/studies (the others are analogs). In bold, recommendations for future implementation of NMES in space. ISS, International Space Station; MVC, maximal voluntary contraction. ∼ = Inconsistent; ? = Unknown.

calf and hamstring; calf, abdominal and back muscles; and shoulder muscles. Pulses have a duration of 1 ms and maximum current amplitude is ~300 mA. Stimulation frequency is 10 kHz modulated at 60 Hz. Stimulation (ON) time is 0.5/1.5 s with a non-stimulation (OFF) period of 1.5 s, or alternatively an ON time of 10 ± 1 s with an OFF time of 50 ± 5 s. Another Russian stimulator, the Stimul-01 HF Set, generates high-frequency alternating sinusoidal electrical stimuli at 2.5 kHz with rectangular pulses modulated at 50 Hz. This device is intended for 40-min stimulation periods of lower limb, back, neck, shoulder and arm muscles, although few details have been published (Kozlovskaya et al., 2009). The Stimul-01 LF Set, a wearable NMES system, was uploaded to the ISS in 2006 (Yarmanova et al., 2015) based on data suggesting that low-frequency stimulation is an effective countermeasure against the effects of ground-based (dry immersion) gravitational unloading (Kozlovskaya et al., 2009). The Stimul-01 LF Set provides NMES for 1 s followed by 2 s intervals. The symmetrical bipolar rectangular pulses have a duration of 1 ms and are delivered at 25 Hz, a stimulation pattern considered compatible with work-day activities without being unduly uncomfortable.

Mayr et al. (1999) described an EMG-NMES system (MYOSTIM-FES) embedded into a fabric garment for delivering NMES to the main lower-limb muscle groups (**Table 1**). The astronaut using this system was reported to be "in a much better condition during flight and after landing" (Freilinger and Mayr, 2002), although no supporting data were published. In another ISS study, NMES was delivered in the final 30 days of a 188-day mission. A 12% increase in triceps brachii muscle volume within a single astronaut was demonstrated, while muscle volume of the non-stimulated triceps was essentially unchanged (Shiba et al., 2015). Whilst limited, these data suggest that NMES application during spaceflight is feasible and potentially able to (at least partially) prevent muscle atrophy. However, currently there is a paucity of data on both NMES effectiveness in orbit, and an evidence-based rationale for its optimal use.

NMES IN GROUND-BASED ANALOGS

The major underlying cause of muscle atrophy in microgravity is a net negative muscle protein balance (Phillips et al., 2009; Wall and van Loon, 2013). Given the challenge of experimentation and countermeasures testing in space, ground-based models of microgravity such as tilted head-down bed rest, lower-limb immobilization or axial unloading are generally used. Such models have demonstrated a substantial decrease in postabsorptive and postprandial muscle protein synthesis (Gibson et al., 1987; Ferrando et al., 1996; Biolo et al., 2004; Glover et al., 2008; Wall et al., 2013; Wall et al., 2016), which is suggested to be accompanied by an increase in muscle protein breakdown in the early phase of disuse (Urso et al., 2006; Abadi et al., 2009; Wall et al., 2016). Even if the impact of spaceflight on muscle protein turnover has yet to be investigated, a similar decrease in whole-body protein synthesis was observed following long-term (>3 months) spaceflight (Stein et al., 1999). Although it remains to be established whether the same holds true for muscle (rather than whole-body) protein turnover, countermeasures which stimulate muscle protein synthesis, while simultaneously suppressing muscle protein breakdown, are likely to be effective in partially preventing muscle atrophy during prolonged spaceflight.

Long-duration bed rest induces significant muscle weakness and atrophy (Mulavara et al., 2018). Dry immersion has been shown to elicit rapid and profound losses of lower limb-muscle contractile properties e.g., triceps surae (Kozlovskaya et al., 1984; Koryak, 1998, 1999), similar to those observed in-flight (Koryak, 2001), with signs of muscle denervation appearing after only 3 days (Demangel et al., 2017). The effects of daily low- and high-frequency NMES upon lower-limb muscles were evaluated during 7 days of dry immersion and 105 days of isolation (Koryak et al., 2008; Kozlovskaya, 2008; Koryak, 2018). Low-frequency stimulation was effective in counteracting triceps surae force-velocity property decrements, particularly with high stimulation intensities.

Various NMES protocols have been employed in a range of ground-based analog studies in an attempt to attenuate muscle atrophy and weakness in healthy subjects (**Table 1**). Despite the diversity in NMES parameters and protocols between studies (ranges for duration: 40 min to 16 h per day; frequency: 30 to 100 Hz; intensity: visible contraction to maximum tolerated current), a common finding is that daily NMES is an effective countermeasure to prevent the loss of lower-limb muscle mass associated to short-term disuse (from 5 to 60 days) as a result of casting (Gould et al., 1982; Gibson et al., 1988; Dirks et al., 2014), bed rest (Duvoisin et al., 1989; Reidy et al., 2017) and axial unloading (Zange et al., 2017). Mechanistically, this is probably due to an increase/maintenance of muscle protein synthesis (Gibson et al., 1988; Wall et al., 2012), but may also be accompanied by a suppression of muscle protein breakdown (Dirks et al., 2014). NMES might also affect other intramuscular processes including (but not limited to) emission of reactive oxygen species, insulin signaling and substrate utilization, but this is outside the scope of this mini-review (Min et al., 2011; Zuo et al., 2011). Whilst NMES preserved muscle strength in one of the analog studies (Duvoisin et al., 1989), the effects have been inconsistent (**Table 1**). As such, despite the clear potential of NMES to maintain muscle mass during unloading [particularly when complemented with protein supplementation (Dirks et al., 2017)], careful definition of NMES implementation is vital to ensure optimal muscle functional outcomes.

STATE-OF-KNOWLEDGE ON TERRESTRIAL NMES

Much work has been conducted to identify the optimal evidence-based NMES parameters/protocols for neuromuscular training/rehabilitation (Maffiuletti, 2010; Maffiuletti et al., 2018). One of the main conclusions is that the externally-controllable parameters (e.g., current and electrode characteristics) have a minor impact on NMES effectiveness (Lieber and Kelly, 1991). In fact, NMES utilization has varied substantially between in orbit, ground-based analog and terrestrial studies (see **Table 1**), despite calls for standardization as long as 30 years ago (Singer et al., 1987).

There is, however, increasing evidence that NMES effectiveness is proportional to the amount of evoked force/tension (Gondin et al., 2011a). This is generally expressed as a percentage of the maximal voluntary strength, and is referred to as "NMES training intensity." For example, in Lai et al. (1988) two groups of healthy volunteers had their quadriceps stimulated for 3 weeks at low vs. high NMES training intensities. NMES effectiveness, defined as an improvement in maximal strength mediated by NMES, was linearly related to NMES training intensity (+24 and +48% in respective groups). Therefore, NMES training intensity, not current intensity/subjective current level or any other stimulation parameter, should be (1) considered as the main determinant of NMES effectiveness, (2) quantified whenever possible on an individual basis, and (3) maximized whenever possible by means of multiple subterfuges (see e.g., Maffiuletti, 2010). Methodologically, at least four simple strategies are able to amplify the muscle response to NMES while minimizing the current-induced discomfort (i.e., the main limitation of NMES): (1) localizing the muscle motor point (i.e., the skin area above the stimulated muscle where the motor threshold is the lowest for a given electrical pulse) (Gobbo et al., 2014); (2) implementing a familiarization period of a few days; (3) providing control of the stimulation unit directly to the participant; (4) allowing the participant to contract the stimulated muscle voluntarily to divert attention from pain/discomfort induced by NMES (Maffiuletti, 2010).

FUTURE NMES RECOMMENDATIONS FOR SPACEFLIGHT

Based on terrestrial best practice we recommend the following approach for possible NMES utilization in future space missions, including long-term exploration (see also bottom of **Table 1**). NMES should be seen as a complement to, rather than a substitute for pre-existing exercise countermeasures. This implies careful planning of daily exercise training by considering that NMES is performed in static conditions – so that other non-physical tasks can be executed concomitantly – and separately from the other exercise modalities (i.e., NMES is not superimposed to running, cycling or rowing).

General Settings

Simultaneous bilateral stimulation of quadriceps femoris and triceps surae muscles should be performed using two large rectangular/elliptical electrodes per muscle (one distal and one proximal) using a space-compatible portable 4-channel stimulator. Astronauts should be in a seated position, with knee and ankle joints restrained at 90°. This knee angle is known to reduce the involvement of the biarticular gastrocnemii, which are less susceptible to muscle atrophy than the soleus (Fitts et al., 2010). In this static position, reasonable levels of muscle tension can be generated even in the absence of gravity (tension will be much lower if limb movement is permitted), which is an important prerequisite for maintaining/increasing the force generating capacity of a muscle (Lieber and Kelly, 1993).

Current-Related Settings

Biphasic sinusoidal/rectangular pulses with a duration of at least 400–600 μs should be used, with an OFF time at least twice the ON time (e.g., 5 s ON:10 s OFF). Stimulation frequency should be close to 30 Hz to ensure full tetanic contractions while minimizing fatigability (Spector et al., 2016).

Before Spaceflight

Prior to flight, muscle motor points should be localized and marked on the skin according to the methodology proposed by Gobbo and co-workers (Gobbo et al., 2014). A familiarization period of ~1 week (3–5 short sessions) should be performed to improve tolerance and thus adherence, whilst also minimizing any risk of muscle damage. Critically, the individual current intensity-evoked force relationship should be determined for each stimulated muscle group of each crewmember, which would require the use of a dynamometer (such as the MARES).

During Spaceflight

Neuromuscular electrical stimulation should ideally be performed twice daily, with stimulation periods of ~30 min. Current intensity should be progressively increased to the maximally tolerated level during the first 5 min of each session, to ensure strong muscle contractions. Current intensity should thereafter be increased throughout the entire session, ideally whenever possible. At the end of each session, average current intensity (per channel/muscle), discomfort (0–10 scale) and maximal evoked force (if available) should be recorded. NMES should preferably be combined with protein ingestion to augment its effect on muscle mass (Dirks et al., 2017).

REMAINING NMES SPACE CHALLENGES

Whilst NMES-based resistance training has potential as an inflight countermeasure, it has some limitations such as the inability to activate the entire muscle (Maffiuletti, 2010), issues with dose and tolerance (discomfort) but no long-term safety concerns (Maffiuletti et al., 2018), and unclear effects upon other physiological systems known to decondition in space (e.g., skeletal or cardiovascular systems). Nevertheless, knowledge of the methodological and physiological specificities of NMES would allow end-users to optimally apply NMES as a complement to other countermeasures for preserving lower-limb functionality (Maffiuletti, 2010).

This mini-review has focused upon muscles acting around the knee and ankle joints. Nevertheless, other muscle groups such as back extensors (Chang et al., 2016) have been shown to decondition in space, leading to functional and operational consequences (Green and Scott, 2017). Whilst NMES has recently been used upon other muscle groups and multiple body segments simultaneously (Kemmler et al., 2010), as well as with agonist-antagonist co-contraction (Shiba et al., 2015), these modalities appear unsuitable at this stage because of practical considerations and lack of convincing evidence.

CONCLUSION

Due to the significant discrepancies between the terrestrial (clinical and experimental) NMES state-of-the-art, and that currently performed in orbit and in analog studies, it is crucial to use optimal NMES knowledge on Earth to revisit and further develop NMES as a feasible strategy for human spaceflight exploration.

AUTHOR CONTRIBUTIONS

All authors conceived the manuscript, wrote, reviewed, and approved the final version of the manuscript.

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Conflict of Interest Statement: DG was employed by Wyle Laboratories GmbH but the work and its recommendations were unaffected by any commercial or financial interests.

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.

frontiers in Physiology

SYSTEMATIC REVIEW
published: 16 August 2019
doi: 10.3389/fphys.2019.01046

Effect of Time on Human Muscle Outcomes During Simulated Microgravity Exposure Without Countermeasures—Systematic Review

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OPEN ACCESS

Edited by:
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Reviewed by:
Carlo Rinaldi, University of Oxford, United Kingdom
Alan R. Hargens, University of California, San Diego, United States

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Specialty section:
This article was submitted to Environmental, Aviation and Space Physiology, a section of the journal Frontiers in Physiology

Received: *26 October 2018*
Accepted: *30 July 2019*
Published: *16 August 2019*

Citation:
Winnard A, Scott J, Waters N, Vance M and Caplan N (2019) Effect of Time on Human Muscle Outcomes During Simulated Microgravity Exposure Without Countermeasures—Systematic Review. Front. Physiol. 10:1046. doi: 10.3389/fphys.2019.01046

Background: Space Agencies are planning human missions beyond Low Earth Orbit. Consideration of how physiological system adaptation with microgravity (μG) will be managed during these mission scenarios is required. Exercise countermeasures (CM) could be used more sparingly to decrease limited resource costs, including periods of no exercise. This study provides a complete overview of the current evidence, making recommendations on the length of time humans exposed to simulated μG might safely perform no exercise considering muscles only.

Methods: Electronic databases were searched for astronaut or space simulation bed rest studies, as the most valid terrestrial simulation, from start of records to July 2017. Studies were assessed with the Quality in Prognostic Studies and bed rest analog studies assessed for transferability to astronauts using the Aerospace Medicine Systematic Review Group Tool for Assessing Bed Rest Methods. Effect sizes, based on no CM groups, were used to assess muscle outcomes over time. Outcomes included were contractile work capacity, muscle cross sectional area, muscle activity, muscle thickness, muscle volume, maximal voluntary contraction force during one repetition maximum, peak power, performance based outcomes, power, and torque/strength.

Results: Seventy-five bed rest μG simulation studies were included, many with high risk of confounding factors and participation bias. Most muscle outcomes deteriorated over time with no countermeasures. Moderate effects were apparent by 7–15 days and large by 28–56 days. Moderate effects (>0.6) became apparent in the following order, power and MVC during one repetition maximum (7 days), followed by volume, cross sectional area, torques and strengths, contractile work capacity, thickness and endurance (14 days), then muscle activity (15 days). Large effects (>1.2) became apparent in the following order, volume, cross sectional area (28 days) torques and strengths, thickness (35 days) and peak power (56 days).

Conclusions: Moderate effects on a range of muscle parameters may occur within 7–14 days of unloading, with large effects within 35 days. Combined with muscle performance requirements for mission tasks, these data, may support the design of CM programmes to maximize efficiency without compromising crew safety and mission success when incorporated with data from additional physiological systems that also need consideration.

Keywords: muscle, microgravity, spaceflight, deconditioning, astronaut

INTRODUCTION

Rationale

Space Agencies are planning to transition from International Space Station (ISS) missions to Lunar missions including a crewed base from which to test and develop hardware and procedures required for the longer term goal of human Mars missions (Foing, 2016). It is well documented that exposure to microgravity (μG) during spaceflight causes adaptation in response to gravitational unloading, especially in the musculoskeletal, cardiovascular and neuro-vestibular systems (Buckey, 2006; Baker et al., 2008). The risks to mission success due to potential injury or reduced function due to periods of unmanaged adaptation before arriving at a remote location such as Moon or Mars, where medical teams may not be present on landing, need to be addressed (Gernand, 2004). Bed rest is often used as a controlled Earth-based environment for simulating the effects of spaceflight on humans to enable more cost-effective, higher quality and safer research into effects and medical management of adaptation (Pavy-Le Traon et al., 2007). While bed rest fails to remove a Gx (chest-to-back) loading vector, such studies are considered the most valid simulation method for many physiological systems (Adams et al., 2003; Pavy-Le Traon et al., 2007), except for weight bearing, tissue fluid redistributions and skin surface areas of compression (Hargens and Vico, 2016), and when conducted rigorously are likely to generate results transferable to astronauts (Higgins and Green, 2011; Winnard and Nasser, 2017b).

Based on bed rest research and previous spaceflight experience, the ISS provides astronauts with 2.5 h per day for exercise (including setup, stowage and hygiene) using a treadmill, cycle ergometer and resistance exercise device designed and adapted for μG (Trappe et al., 2009; Loehr et al., 2011). Several years of refining ISS exercise countermeasures (CM) has led to astronauts completing 6-month missions with, on average, little to no change in bone mass or cardiovascular capacity, although the efficacy seems to vary widely between individuals (Moore et al., 2014; English et al., 2015; Sibonga et al., 2015), while muscle adaptation appears to have become progressively smaller as exercise devices and prescriptions have improved (Smith et al., 2012; Moore et al., 2014; Ploutz-Snyder et al., 2015). However, the exercise devices currently aboard ISS will almost certainly be too large and too numerous for, and the exercise prescriptions place too great a demand on the consumables and environmental management systems available on, the vehicles and habitats currently planned for future exploration missions. For this reason, space agencies have started designing smaller, low energy and low vibration exercise devices (Brusco, 2016). However, decisions will need to be made regarding choice and/or development of an effective exercise CM programme to manage physiological adaptation that will occur during exploration missions. Considerations may include reducing the frequency of exercise as currently performed on ISS and potentially having longer periods of not performing any exercise. The duration of any such no exercise periods needs to be evidence based to balance any increase physiological risks to crew against gains in spacecraft and consumables impact.

Objectives

The objectives of this review were to provide a complete summary of and synthesize the current space-related physiological evidence base and to inform decision making processes around muscle performance requirements, regarding operational CM, for exploration human space missions. Where data is lacking for any outcomes this will be highlighted as a gap or limited area of the current evidence base and used to provide a gap analysis commentary useful for future research priority setting. The aim is to aid space agencies in designing CM programmes, provide a complete summary of what muscle groups and outcomes have been assessed in the current evidence and highlight areas of minimal data or research gaps to guide future relevant research in this area. The NASA Risk Table for the Human Research Project highlights potential risks relating to spaceflight and shows the large scope of potential physiological systems that require reviewing to cover all elements of crew health and performance (National Aeronautics and Space Administration, 2019). As the scope is too large for a single review, it is suggested that the various systems be reviewed individually. Once a series of reviews has been complete a position statement summarizing across each system can provide a holistic overview. Therefore, this specific review investigated the rate at which muscle parameters change during simulated μG exposure, when no countermeasures are taken, to inform operational decisions regarding the possibility of using exercise CM programmes more sparingly for exploration missions, including the implementation of exercise "holidays" (i.e., a period of time within the mission when no exercise CM are employed). Conclusions of this review alone must be treated in a muscle context and need considering alongside other relevant health and performance components.

Research Question

At what time point do people exposed to simulated μG while not performing CM reach a moderate or large effect on muscle health outcomes?

METHODS

Study Design

The Cochrane Collaboration Guidebook (Higgins and Green, 2011) and preferred reporting items for systematic reviews and meta-analyses (PRISMA) were adhered to Moher et al. (2009). No external funding or research grants were received for this work.

Participants

The following inclusion criteria were employed. The target population was astronauts, however, as astronauts have taken part in space agency recommended exercise programmes to date, there was no inactive data available from this population. Therefore, healthy terrestrial adults, with no gender restrictions, taking part in μG analog bed rest studies, were included. Bed rest studies were the only terrestrial model included as they are considered the most valid ground based model for simulating human spaceflight for periods beyond a few minutes (Adams et al., 2003; Pavy-Le Traon et al., 2007). Therefore, to maintain the greatest level of transferability to astronauts and in keeping with our other systematic reviews only bed rest studies that stated they were simulating human spaceflight were considered. No clinical bed rest situations such as critical care were included as they would likely have confounding co-morbities and not transfer well to astronauts. All participants in the included bed rest studies were healthy at baseline, however, no exclusion was made relating to baseline level of physical condition beyond being healthy. Only control group data were relevant, therefore no inclusion criteria were based on interventions. Control groups had to be inactive and not undergo any type of intervention. Included studies had to report outcomes relating to muscles. For completeness of reporting the current state of the evidence base and avoid introducing selection bias, no exclusion was made based on type of outcome or amount of data. The evidence based led outcomes were determined from pre-scoping and the main review searches and were grouped for analysis as cross-sectional area, volume, shape, size, activity, power, performance and joint torque and forces at either a regional or global level. Included studies had to be randomized controlled trials (RCT), controlled clinical trials (CT), longitudinal, interrupted time series or before and after studies.

Systematic Review Protocol

Search Strategy, Data Sources, Studies Sections, and Data Extraction

A range of relevant terms grouped by main search terms were constructed using Boolean logic (astronaut*, spaceflight, space flight, space*, weightless*, microgravity, micro gravity, bed-rest, bed rest, bed rest, dry immersion, muscle*, strength*) to search the following databases up to July 2017: Pubmed, CINAHL, Web of Science, NASA Technical Reports Server and The Cochrane Collaboration Library. No restrictions on type of bed rest or publication dates were applied, and due to the inability to use "Boolean logic" on the NASA Technical Reports Server, the strategy was adapted to keyword searches. The full search strategy is available in **Table 1**.

TABLE 1 | Search strategy for database literature search.

Search number	Term	Keywords in Boolean logic format
1	Microgravity	"astronaut" OR "spaceflight OR "space flight OR "space*" OR "weightless*" OR "microgravity" OR "micro gravity"
2	Bed rest	"bed-rest" OR "bedrest" OR "bed rest" OR "dry immersion"
3	Muscle	"musc*" OR "strength*"
4	Combined	1 AND 2 AND 3

Initial screening was performed using abstracts and titles by two authors (MV and AW), blinded to each other's decisions, using Rayyan (https://rayyan.qcri.org/) (Ouzzani et al., 2016). Rayyan also automatically detects duplicate studies and data and all flagged potential duplication was assessed by agreement of three blinded authors. Where there was any disagreement whether the study met the inclusion criteria from initial screening the full text was obtained. A third author (NC) was used to resolve disagreements of included/excluded studies. An adapted version of the Aerospace Medicine Systematic Review Group (AMSRG) "Data extraction form," version 2, July 2017 (AMSRG, 2018) was used by two authors (MV and NW) to extract data from each paper, and disagreements were discussed by three authors (AW, NW and MV) to reach consensus.

Data Analysis

Quality Assessment

The Quality in Prognostic Studies (QUIPS) tool was used to assess risk of bias of all the included studies, with "H," "M," and "L" showing high, moderate and low risk, respectively, using pre-defined published definitions for each level (Hayden et al., 2013). Risk of bias results were used to comment on the current quality and completeness of the evidence base and do not change how studies were treated during analysis. As per published recommendations, only studies that were rated low risk of bias in all QUIPS domains were deemed as low risk overall (Hayden et al., 2013). The AMSRG "Tool for Assessing Bed Rest Methods" (Winnard and Nasser, 2017a,b) was used to assess the bed rest methodological quality, and transferability to astronaut populations, of all included studies, with "y" indicating the point was met, "n" not met, and "?" unclear. This is a relatively new tool, yet to be validated, that has been used in several other reviews (Richter et al., 2017; Winnard et al., 2017) and the development of the tool is explained in Winnard et al. (2017).

Main Analysis

Effect sizes (Hedges' g) were calculated between pre and post-bed rest values for each outcome individually without an overall pooled effect. Hedges' g was used to bias correct for the typically small sample sizes, as only control group data from μG simulation studies were eventually included. The reported data set that was as close to immediate pre and the end of bed rest was used for the analysis. No exclusion or analysis variation was made based on the individual study analysis methods. The pooled standard deviation for Hedges' g was calculated using the root mean square of the pre and post-group standard deviations. This version does not specifically include the sample size (n), preventing any complications that could arise from inflating n when both group means are from the same sample. Results were first sub-grouped by outcome measure type and then by muscle group before being listed in order of ascending days spent in simulated μG. Individual effects sizes were calculated and plotted in figures for each outcome at every time point where data were available. To enable a brief overview of the large data set to also be provided, an unweighted mean effect at each common time point within each muscle group was used to provide a summary result. This was only done when more than one study assessed the same outcome at the same time point. These statistics were chosen due to data being from the same sample rather than a separate intervention and control group, thus making a traditional weighted effects meta-analysis pooling inappropriate. Traditional meta-analysis assumes two different sets of individuals in each group (Higgins and Green, 2011) meaning a violation of underlying assumptions would have occurred if applied to this review. The summary unweighted mean, while being a less robust statistic, enabled an overarching overview to be reported in addition to each individual effect size, and overlaid on the figures, without violating statistical assumptions. Ninety-five percent confidence intervals were calculated for individual and unweighted group means. Readers should note that due to varying effect sizes across the various muscles and groupings, the effect size axis scale varies accordingly throughout the figures.

The point at which effects consistently reached a magnitude of 0.6 (moderate) or 1.2 (large) was highlighted as a time point when a worthwhile mechanistic change had occurred (Hopkins et al., 2009). Plots of all individual effects and 95% confidence interval tails, in order of ascending days in simulated μG, were overlaid with the mean effect and polynomial trend line of the mean effects. A polynomial trend allowed for the trend line to curve in case of progressively worsening, or plateauing patterns. In cases where data were lacking and varied (spanning more than one effect size cut off between data points), the trend line was highlighted as likely unreliable in the results section, meaning more data should be collected before a reliable trend can be established. The limited data sets are however still included for completeness of reporting the current state of the evidence base and highlight both minimal data areas and research gaps. The mean effect summary and trend line were only used to visually highlight the time point at which the mean effects passed the 0.6 and 1.2 magnitude point. A funnel plot of all the mean effects plotted against study size was used to show potential publication bias.

Sub Group Analysis

Ten sub groups were created based on the measurement methods units used for each for analysis as follows (with original units measured in): (1) contractile work capacity (J), (2) cross sectional area (mm^2, cm^2), (3) muscle activity (μV, mV, normalized), (4) muscle thickness (mm, cm), (5) muscle volume (cm^3), (6) maximal voluntary contraction force during one repetition maximum (kg, N, Nm) (7), peak power (W), (8) performance based outcomes (including endurance time, jump power, force, velocity height and acceleration, sit to stand time, center of mass variation, and sprint time) (s, mm, cm, m, W/kg), (9) power ($rad \cdot s^{-1}$, $m \cdot s^{-1}$), and (10) torques and strength (Nm, ft-lb). Within each subgroup data were further sub-grouped for analysis by major muscle groups. For completeness of reporting, any measures that did not fit within major muscle groupings were grouped for analysis and reported as either "other lower limb," "other trunk," or "other upper limb" outcomes, to enable every outcome measure extracted from included studies to be reported in the results. The outcomes included in the "other" groupings are listed in the text.

RESULTS

Study Selection, Characteristics, and Risk of Bias

In total, 112 studies were included after duplicates removed, all of which were screened for inclusion into the analysis. There were 37 not included in the analysis due the reasons provided in the PRISMA flow diagram (**Figure 1**). Therefore, 75 studies (**Table 2**) were included, producing 922 individual effect sizes across all sub groups and outcomes. All studies were bed rest μG simulations as no astronaut studies to date included an inactive control group exposed to μG due to space agency recommended exercise programmes. There is no comparison descriptor column in **Table 2** as we only considered control groups who had no intervention, treated as before and after simulated μG exposure comparisons. The most common bed rest duration was 60 days, with shortest and longest durations being seven and 120 days, respectively. The most common study design was RCT. Most of the studies scored four on the bed rest quality score, with the highest score being six, and the lowest score was two. Only three studies were assessed to have a low risk of bias. As only intervention studies' control group data were included and no actual prognostic studies were found and included, question three on the QUIPS about prognostic factors was rated as n/a for all the included studies. A rating for question 3 would have been provided had any actual prognostic studies been found and included. However, for this review, time in μG can be considered the prognostic factor and the quality of the μG simulation was critiqued in detail within the bed rest quality scores. There is some asymmetry in the funnel plot in **Figure 2**, suggesting potential publication bias toward studies reporting decreases in muscles, however there are studies, including smaller ones, that do report an increase. Fourty five studies specified a time period ahead of the bed rest period in which baseline measures were recorded ranging from 1 to 21 days. Of these, 11 (Greenleaf et al., 1983, 1989, 1994b; Dudley et al., 1989; Ellis et al., 1993; Ferrando et al., 1995; Portero et al., 1996; Muir et al., 2011; Lee et al., 2014; English et al., 2016; Schneider et al., 2016) stated utilizing a pre-bed rest ambulatory control period in their methods section. However, it was not clear in any of the studies what the control period involved or if there was any pre-bed rest deconditioning that was measured or adjusted for. One study, Mulder et al. (2008) measured baseline outcomes on day 4 of bed rest and

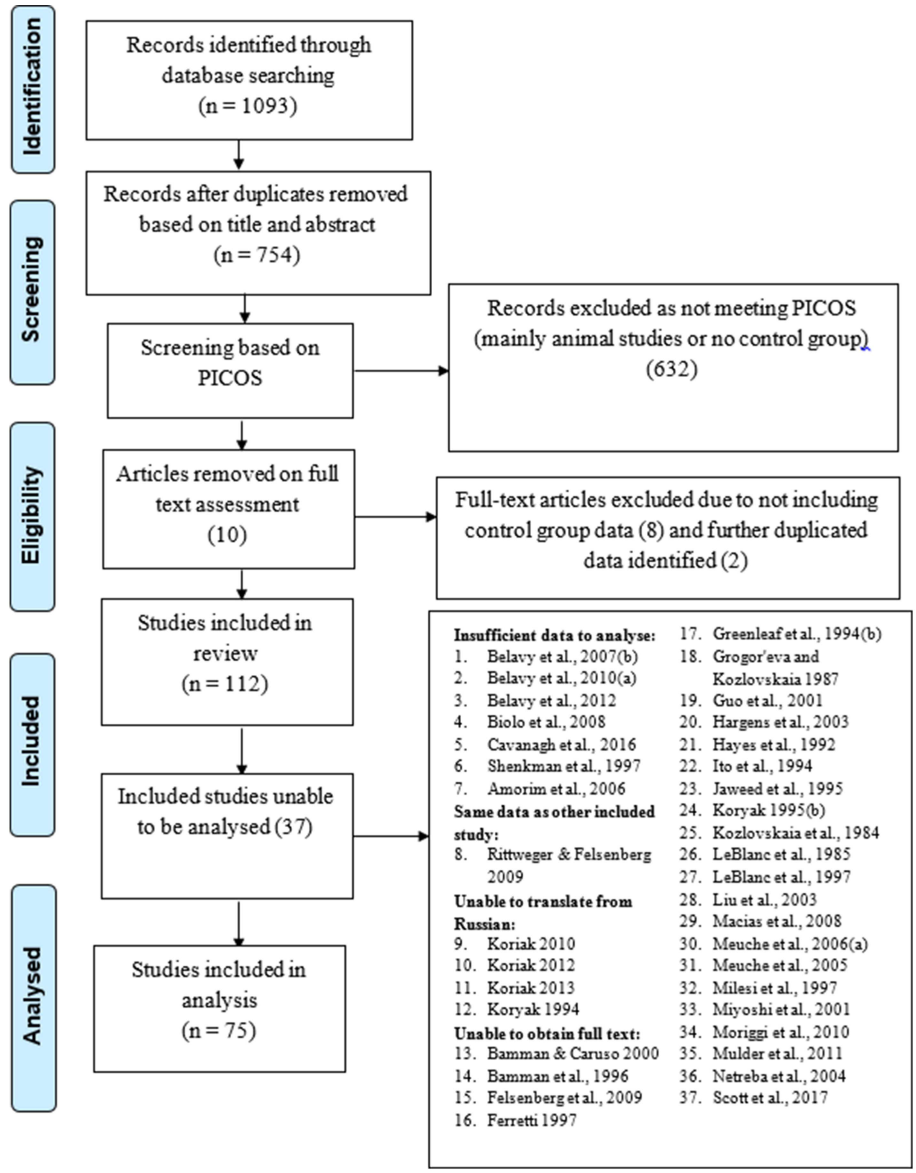

FIGURE 1 | PRISMA flow diagram of inclusion/exclusion process.

acknowledges this could have led to underestimating the effect of bed rest, especially for time sensitive outcomes such as those associated with muscle. Full data tables for results per muscle are available in supplementary data tables as indicated in each results sub-section. The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any interested parties.

Synthesized Findings

Muscle Volume

All muscle volumes decreased over time. Moderate effects were becoming apparent by 14 days and large by 28 days. Very little data were available for Hip Flexor, Gluteal, Multifidus, and Erector Spinae muscles, where a moderate or greater effect was never reached for Hip Flexors and Erector Spinae muscles and only a moderate effect was apparent by 27 and 90 days for Gluteal and Multifidus muscles, respectively. Other lower limb muscles that included Gracilis, Sartorius, Piriformis, Obturators, and Pectineus muscles, reached a moderate effect by 14 days. Other trunk muscles that included Levator Scapulae, Longus Colli, Sternocleidomastoid, and Scalene muscles never reached a moderate effect. The breakdown of individual volume effects per muscle is available in **Supplementary Table 1** and associated summary plots in **Figure 3**.

Muscle Cross Sectional Area

All muscle cross sectional areas decreased over time. Moderate effects were apparent by 14 days and large by 28 days. The same

TABLE 2 | Characteristics of analyzed studies.

Study (analysis cross reference no.)	Design	*n*	Outcomes	Bed rest quality tool								TOT	QUIPS risk of bias tool						
				Days	1	2	3	4	5	6	7		1	2	3	4	5	6	Overall
Akima et al. (2000)[1]	RCT	4	Cross-sectional area, torque, volume	20	y	?	?	y	y	?	y	4	M	L	n/a	L	H	L	H
Akima et al. (2003)[2]	RCT	6	Cross-sectional area, torque	20	y	?	?	y	y	?	y	4	M	L	n/a	L	M	L	H
Akima et al. (2005)[3]	RCT	5	Activity (EMG), volume, MVC	20	y	y	?	y	y	?	y	5	M	L	n/a	L	M	L	H
Akima et al. (2007)[4]	RCT	6	Muscle volume	20	y	?	?	y	y	?	y	4	M	L	n/a	L	M	L	H
Alkner and Tesch (2004)[5]	RCT	9	Volume, MVC, force, power, torque, activity (EMG)	90	y	?	?	y	y	?	y	4	M	L	n/a	L	M	L	H
Alkner et al. (2016)[6]	RCT	9	Activity (EMG), force	90	y	?	?	y	y	?	y	4	M	L	n/a	L	M	L	H
Arbeille et al. (2009)[7]	RCT	8	Volume	60	y	y	?	y	y	?	y	5	L	L	n/a	L	M	L	H
Bamman et al. (1997)[8]	RCT	8	MVC, activity (EMG), torque, power, work	14	y	y	?	y	y	?	y	5	L	L	n/a	L	M	L	H
Belavy et al. (2007a)[9]	RCT	10		56	n	y	?	y	?	?	y	3	L	L	n/a	L	H	L	H
Belavy et al. (2008)[10]	RCT	10	Cross-sectional area	56	?	y	?	y	?	?	y	3	L	L	n/a	L	H	L	H
Belavy et al. (2009a)[11]	RCT	10	Volume	56	?	y	?	y	?	?	y	3	L	L	n/a	L	H	L	H
Belavy et al. (2009b)[12]	RCT	10	Volume	56	?	y	?	y	?	?	y	3	L	L	n/a	L	H	L	H
Belavy et al. (2010b)[13]	RCT	9	Cross-sectional area	60	y	y	y	y	y	?	y	6	H	L	n/a	L	H	L	H
Belavy et al. (2011a)[14]	RCT	9	Cross-sectional area	60	y	y	y	y	y	?	y	6	M	L	n/a	L	M	L	H
Belavy et al. (2011b)[15]	RCT	9	Volume	90	y	y	?	y	?	?	y	4	L	L	n/a	L	H	L	H
Belavy et al. (2011c)[16]	CO	7	Cross-sectional area, muscle signal intensity	21	y	?	?	y	?	?	y	3	M	L	n/a	L	H	L	H
Belavy et al. (2013)[17]	RCT	9	Volume	60	y	y	y	y	y	?	y	6	H	L	n/a	L	H	L	H
Belavy et al. (2017)[18]	RCT	8	Muscle atrophy	56	?	y	?	y	?	?	y	3	L	L	n/a	L	H	L	H
Berg et al. (1997)[19]	RCT	7	Torque, activity (EMG), angular velocity, fiber types/size, cross-sectional area	42	y	?	?	y	y	?	y	4	M	L	n/a	L	H	L	H
Berg et al. (2007)[20]	RCT	5	MVC, cross-sectional area	35	n	?	?	y	y	?	y	3	H	L	n/a	L	H	L	H
Berry et al. (1993)[21]	CO	6	Cross-sectional area	30	y	?	?	y	?	?	y	3	H	L	n/a	L	H	L	H
Buehring et al. (2011)[22]	RCT	10	MVC, activity, jump power, jump height	56	n	y	?	y	?	?	y	3	L	L	n/a	L	H	L	H
Caiozzo et al. (2009)[23]	RCT	7	Torque, cross-sectional area	21	y	?	?	y	?	?	y	3	H	L	n/a	L	H	L	H
Cescon and Gazzoni (2010)[24]	RCT	4	Single and global motor unit conduction velocity	14	y	y	?	y	y	?	y	5	L	L	n/a	L	M	L	H
Convertino et al. (1989)[25]	B&A	8	cross-sectional area	30	y	?	?	?	?	?	y	2	H	L	n/a	L	H	L	H
de Boer et al. (2008)[26]	B&A	10	Thickness	35	n	?	?	y	y	?	y	3	M	L	n/a	L	H	L	H
Dudley et al. (1989)[27]	B&A	7	Torque	30	y	?	?	?	?	?	y	2	H	L	n/a	L	H	L	H
Duvoisin et al. (1989)[28]	TS	3	Torque velocity	30	y	?	?	?	?	?	y	2	H	L	n/a	L	H	L	H
Ellis et al. (1993)[29]	CS	5	Thickness	30	y	y	y	y	y	?	y	6	M	L	n/a	L	M	L	H
English et al. (2011)[30]	B&A	8	Torque	60	n	y	y	y	y	?	y	5	L	L	n/a	L	M	H	H
English et al. (2016)[31]	RCT	9	Torque and work	14	?	y	?	y	y	?	y	4	L	L	n/a	L	M	L	H
Ferrando et al. (1995)[32]	B&A	6	Volume	7	?	y	?	y	y	?	y	4	H	L	n/a	L	H	L	H
Ferretti et al. (2001)[33]	TS	7	Cross-sectional area, jump power	42	y	?	?	y	y	?	y	4	M	L	n/a	L	M	L	H
Fu et al. (2016)[34]	TS	8	Activity (EMG), force	45	y	y	?	y	y	?	y	5	M	L	n/a	L	M	L	H
Funato et al. (1997)[35]	TS	10	Strength, velocity	20	?	?	?	y	?	?	y	2	M	L	n/a	L	H	L	H
Gast et al. (2012)[36]	RCT	9	Jump height and power, sit-to-stand tests, sprint time, leg press (1RM)	60	y	y	y	y	y	?	y	6	L	M	n/a	L	M	L	H
Germain et al. (1995)[37]	RCT	6	Torque	28	y	?	?	y	y	?	y	4	M	L	n/a	L	H	L	H
Greenleaf et al. (1983)[38]	RCO	7	Hand grip endurance	14	?	y	?	?	?	?	y	2	H	L	n/a	L	H	L	H
Greenleaf et al. (1989)[39]	RCT	5	Work, torque	30	y	y	?	y	y	?	y	5	M	L	n/a	L	M	L	H
Greenleaf et al. (1994a)[40]	RCT	5	Volume	30	y	y	?	y	y	?	?	4	M	L	n/a	M	H	L	H

(Continued)

TABLE 2 | Continued

Study (analysis cross reference no.)	Design	*n*	Outcomes	Bed rest quality tool								TOT	QUIPS risk of bias tool						
				Days	1	2	3	4	5	6	7		1	2	3	4	5	6	Overall
Holguin et al. (2007)[41]	RCT	11	Volume	90	Y	Y	?	Y	Y	?	Y	5	H	L	n/a	L	M	L	H
Holt et al. (2016)[42]	RCT	8	Cross-sectional area	60	y	y	y	y	y	?	y	6	L	L	n/a	L	L	L	L
Kawashima et al. (2004)[43]	B&A	10	Cross-sectional area	20	n	y	?	y	y	?	y	4	H	L	n/a	L	H	L	H
Koryak (1995a)[44]	B&A	6	MVC, force, time to peak tension, total contraction time	120	y	?	?	y	y	?	y	4	L	L	n/a	L	M	L	H
Koryak (1996)[45]	B&A	6	MVC, twitch tension, time to peak tension, total contraction time, surface action potentials	7	n	?	?	y	?	?	y	2	H	L	n/a	L	H	L	H
Koryak (1998a)[46]	B&A	6	Maximal twitch response force, strength, MVC, time-to peak tension, total contraction time	120	y	?	?	y	?	?	y	3	M	L	n/a	L	H	L	H
Koryak (1998b)[47]	RCT	4	MVC, evoked tetanic tension, maximal twitch tension, twitch time-to-peak tension, total contraction time	120	y	?	?	y	y	?	y	4	M	L	n/a	L	H	L	H
Koryak (1999)[48]	B&A	10	MVC, tension of maximal twitch, evoked tetanic tension, time to peak tension, total contraction time	120	y	?	?	y	y	?	y	4	M	L	n/a	L	M	L	H
Koryak (2002)[49]	B&A	6	Tension of maximal twitch, evoked tetanic tension, time to peak tension, total contraction time, surface action potential	7	n	?	?	y	y	?	y	3	M	L	n/a	L	M	L	H
Koryak (2010)[50]	RCT	6	MVC, twitch tension, time to peak tension, total contraction time	60	y	y	?	y	y	?	y	5	M	L	n/a	L	M	L	H
Koryak (2014)[51]	RCT	6	Volume, electromyogram	20	y	?	?	y	y	?	y	4	M	L	n/a	L	M	L	H
Kouzaki et al. (2007)[52]	RCT	6	Volume, electromyogram	20	y	?	?	y	y	?	y	4	M	L	n/a	L	M	L	H
Krainski et al. (2014)[53]	RCT	9	Volume, torque	35	y	y	y	y	y	?	y	6	L	L	n/a	L	L	L	L
LeBlanc et al. (1988)[54]	B&A	9	Cross-sectional area	35	n	y	?	y	y	?	y	4	H	L	n/a	L	H	L	H
Lee et al. (2014)[55]	RCT	24	Torque, 1RM, lean mass	60	y	y	y	y	y	?	y	6	L	L	n/a	L	L	L	L
Macias et al. (2007)[56]	RCT	15	Strength, torque	28	y	?	?	y	y	?	y	4	M	L	n/a	L	H	L	H
Miokovic et al. (2011)[57]	RCT	9	Volume	60	y	y	y	y	y	?	y	6	M	L	n/a	L	M	L	H
Miokovic et al. (2012)[58]	RCT	9	Volume	60	y	y	y	y	y	?	y	6	H	L	n/a	L	H	L	H
Miokovic et al. (2014)[59]	RCT	8	Volume	60	y	y	y	y	y	?	y	6	H	L	n/a	L	H	L	H
Muir et al. (2011)[60]	RCT	13	Strength, postural stability	90	y	?	y	y	y	?	y	5	M	H	n/a	L	M	L	H
Mulder et al. (2006)[61]	RCT	10	Cross-sectional area	56	n	y	?	y	?	?	y	3	L	L	n/a	L	H	L	H
Mulder et al. (2007)[62]	RCT	10	Torque	56	?	y	?	y	y	?	y	4	L	L	n/a	L	M	L	H
Mulder et al. (2008)[63]	RCT	8	Time to peak tension	56	?	y	?	y	y	?	y	4	L	L	n/a	L	M	L	H
Mulder et al. (2009a)[64]	RCT	9	Cross-sectional area, activity (EMG)	60	y	y	y	y	y	?	y	6	H	L	n/a	L	H	L	H
Mulder et al. (2009b)[65]	RCT	10	Knee extensor MVC	56	N	y	?	y	y	?	y	4	L	L	n/a	L	M	L	H
Narici et al. (1997)[66]	CS	8	Cross-sectional area, force	17	y	?	?	?	?	?	y	2	H	L	n/a	M	H	L	H
Pisot et al. (2008)[67]	B&A	10	Contraction time, muscle maximal displacement	35	n	y	?	y	y	?	y	4	H	L	n/a	L	H	L	H
Portero et al. (1996)[68]	B&A	12	MVC	30	y	?	?	y	?	?	y	3	H	L	n/a	L	H	L	H
Reeves et al. (2002)[69]	RCT	6	Force, resting fascicle length, fascicle length at MVC	90	y	y	?	y	y	?	y	5	M	L	n/a	L	M	L	H
Rittweger et al. (2005)[70]	RCT	9	Cross-sectional area	90	y	y	?	y	?	?	y	4	L	L	n/a	L	H	L	H
Rittweger et al. (2013)[71]	RCT	9	Cross-sectional area	90	y	y	?	y	?	?	y	4	M	L	n/a	L	M	L	H
Schneider et al. (2016)[72]	RCT	8	Torque, work, lean mass	30	y	y	?	y	y	?	y	5	H	L	n/a	L	L	L	H

(Continued)

TABLE 2 | Continued

Study (analysis cross reference no.)	Design	*n*	Outcomes	Bed rest quality tool								TOT	QUIPS risk of bias tool						
				Days	1	2	3	4	5	6	7		1	2	3	4	5	6	Overall
Shinohara et al. (2003)[73]	RCT	6	MVC, activity EMG	20	y	y	?	y	y	?	y	5	H	L	n/a	L	H	L	H
Trappe et al. (2001)[74]	CS	8	Torque	17	y	y	?	?	?	?	y	3	H	H	n/a	L	H	L	H
Trappe et al. (2007)[75]	RCT	8	Volume force	60	y	y	?	y	y	y	y	6	L	L	n/a	L	M	L	H

Bed rest quality scores: (1) 6 degrees head down tilt, (2) controlled diet, (3) fixed daily routine, (4) standardized bed rest phases, (5) uninterrupted bed rest, (6) restricted sunlight exposure, (7) same outcome measures for all. Quips risk of bias tool: (1) participation, (2) attrition, (3) prognostic factor measurement, (4) confounding factors, (5) statistical analysis and reporting. RCT, randomized controlled trial. CO, cross over; B&A, before and after; TS, time series; CS, cross sectional; RCO, randomized cross over.

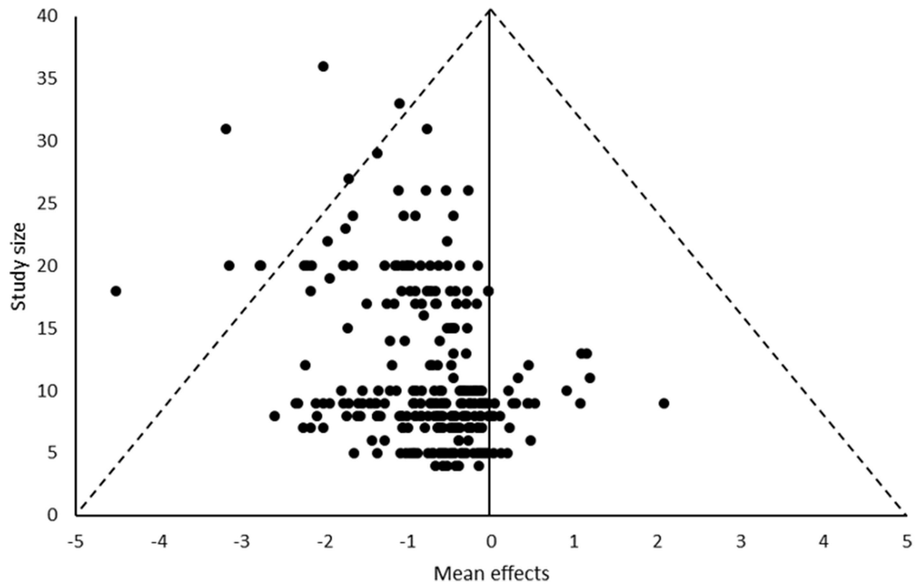

FIGURE 2 | Funnel plot of all effects.

effect time points were found for other lower limb muscles that included Gracilis and Sartorius muscles and total thigh and calf cross sectional area. Very little data were available for Hip Flexor, Gluteal, Hamstring and Hip Adductor muscles where a moderate or greater effect was never reached. Multifidus and other trunk muscles, including Quadratus Lumborum and combined Multifidus and Erector Spinae cross sectional area, only reached a large effect by 60 days. Upper limb muscle outcomes consisted of forearm muscle cross sectional area which only reached a large effect after 89 days. The breakdown of individual cross sectional area effects per muscle are available in **Supplementary Table 2** and associated summary plots in **Figure 4**. The polynomial trend for Dorsi Flexor muscles appeared to be unreliable.

Torques and Strength

Torques and strengths decreased over time. Moderate effects became apparent by 14 days for Quadriceps muscles only. Additional moderate effects became apparently by 30 days and large effects by 35 days. Dorsi Flexor, Hamstring, Hip Extensor, Hip Flexor, other trunk, and other upper limb muscles never reached a large effect. Other trunk muscles included trunk flexors and extensors tested in combination within functional movements. Upper limb muscles included elbow flexor and extensor muscles and shoulder abductor and adductor muscles. The breakdown of individual torques and strength effects per muscle is available in **Supplementary Table 3** and associated summary plots in **Figure 5**. The polynomial trend for Dorsi Flexor muscles appeared to be unreliable after 60 days.

Contractile Work Capacity

Although there are very little available data for contractile work capacity it appears to decrease over time. Moderate effects became apparent by 14 days in Plantar Flexor and Quadriceps muscles. However, this is based on only one study for each muscle at 14 days. The breakdown of individual contractile work capacity effects per muscle is available in **Supplementary Table 4** and associated summary plots in **Figure 6**. Data were limited for all muscles.

Muscle Thickness

Muscle thickness decreased over time. Moderate and large effects became apparent by 14 days. There were very little

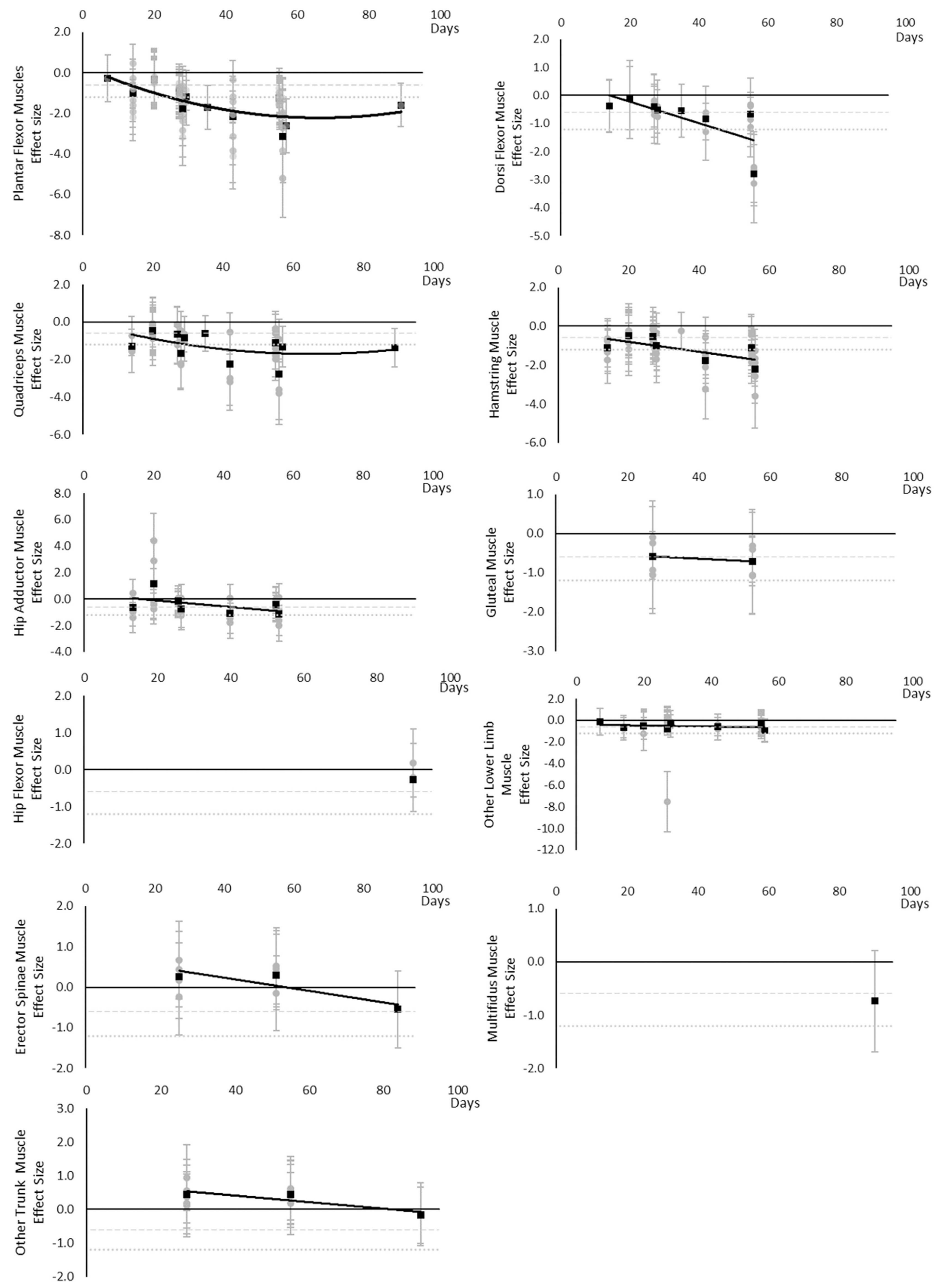

FIGURE 3 | Effect size plots for muscle volume over time from individual (gray) and average (black) effect sizes at each time point, with 0.6 (dotted line) and 1.2 (dashed line) effect magnitudes and average effect trend line overlaid.

data for Plantar Flexor, Dorsi Flexor and Quadriceps muscles, showing Dorsi Flexor muscles reached a moderate effect by 35 days and only Plantar Flexor and Quadriceps muscles reached a large effect by 35 days. Internal Oblique muscle reached a moderate effect at 14 days. Erector Spinae muscle was similar to Internal Oblique muscle, but only reached a

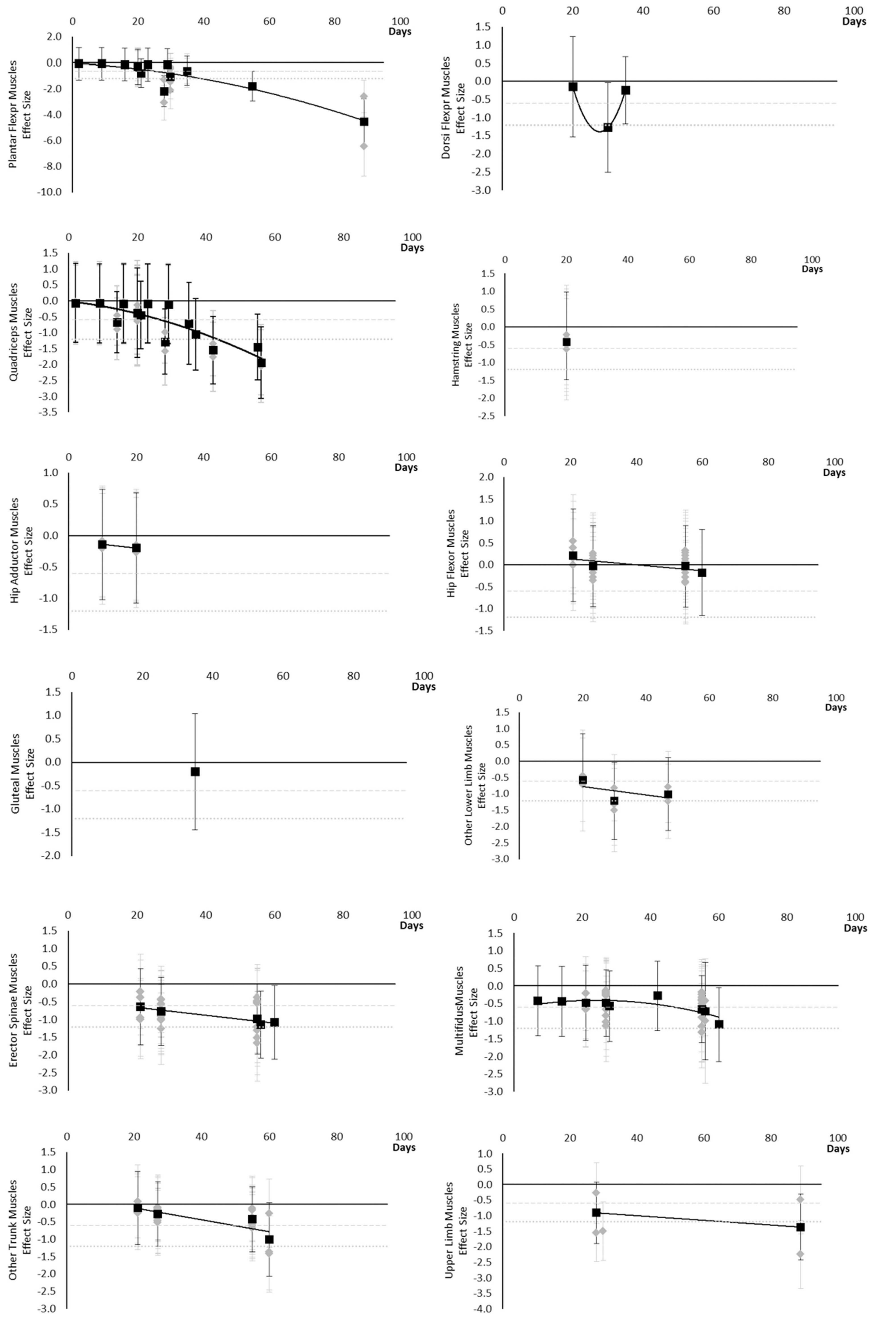

FIGURE 4 | Effect size plots for muscle cross sectional area over time from individual (gray) and average (black) effect sizes at each time point, with 0.6 (dotted line) and 1.2 (dashed line) effect magnitudes and average effect trend line overlaid.

borderline moderate effect within the available data. Upper limb muscles data only included Biceps Brachii muscle thickness, reaching a moderate effect by 35 days. The breakdown of individual muscle thickness effects per muscle is available in **Supplementary Table 5** and associated summary plots in **Figure 7**.

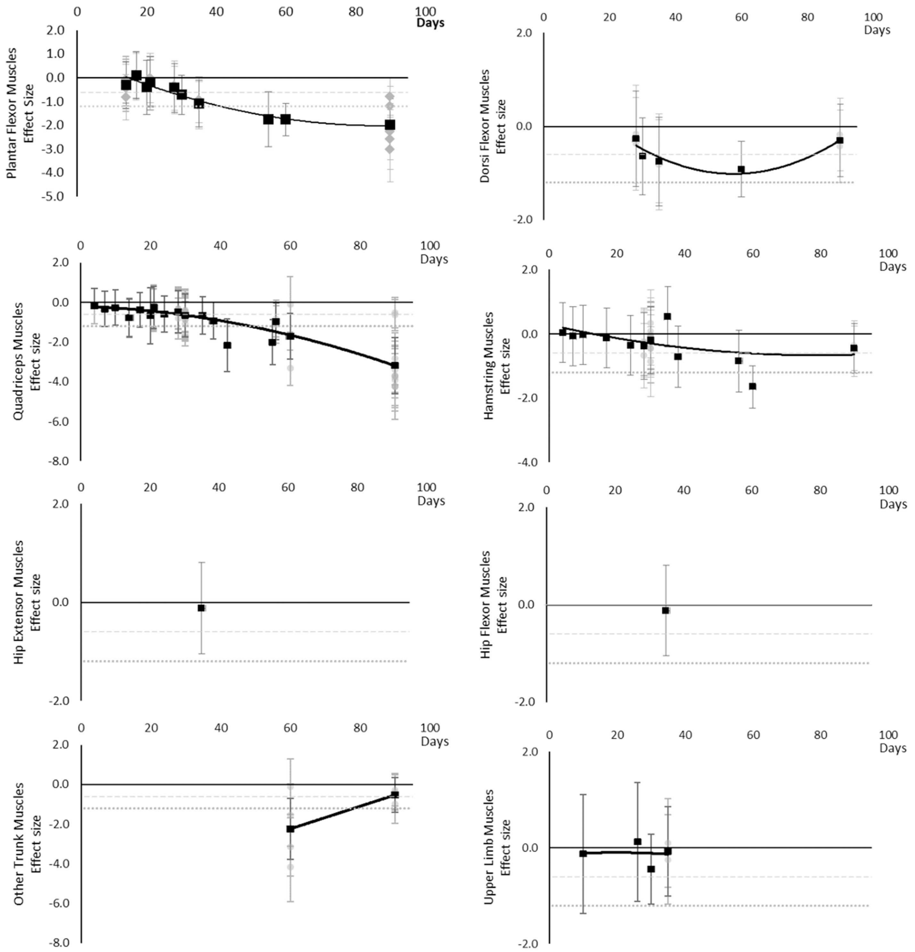

FIGURE 5 | Effect size plots for torques and strength over time from individual (gray) and average (black) effect sizes at each time point, with 0.6 (dotted line) and 1.2 (dashed line) effect magnitudes and average effect trend line overlaid.

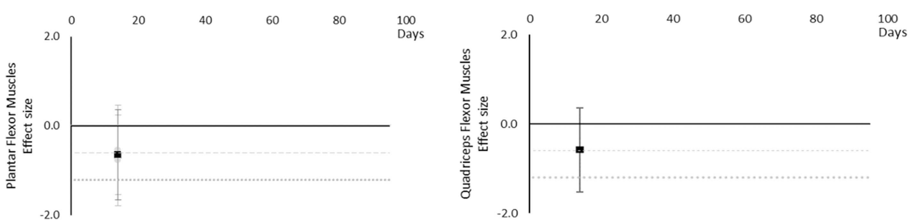

FIGURE 6 | Effect size plots for contractile work capacity over time from individual (gray) and average (black) effect sizes at each time point, with 0.6 (dotted line) and 1.2 (dashed line) effect magnitudes and average effect trend line overlaid.

Peak Power

Peak power decreased over time. Large effects became apparent by 56 days for jump power and 62 days for Plantar Flexor and Quadriceps muscles. There was insufficient data to determine a time point for when any moderate effects were reached. The breakdown of individual peak power effects per outcome is available in **Supplementary Table 6** and associated summary plots in **Figure 8**.

Muscle Activity

Muscle activity (via electromyography) generally decreased over time, however a transient increase was seen in Plantar Flexor, Dorsi Flexor and Quadriceps muscles and only at 20 days. In Plantar Flexor and Quadriceps muscles, muscle activity decreased again after 20 days, there were no data for Dorsi Flexor muscles beyond 20 days to establish a post 20 day trend. Moderate effects were apparent in upper limb muscle groups

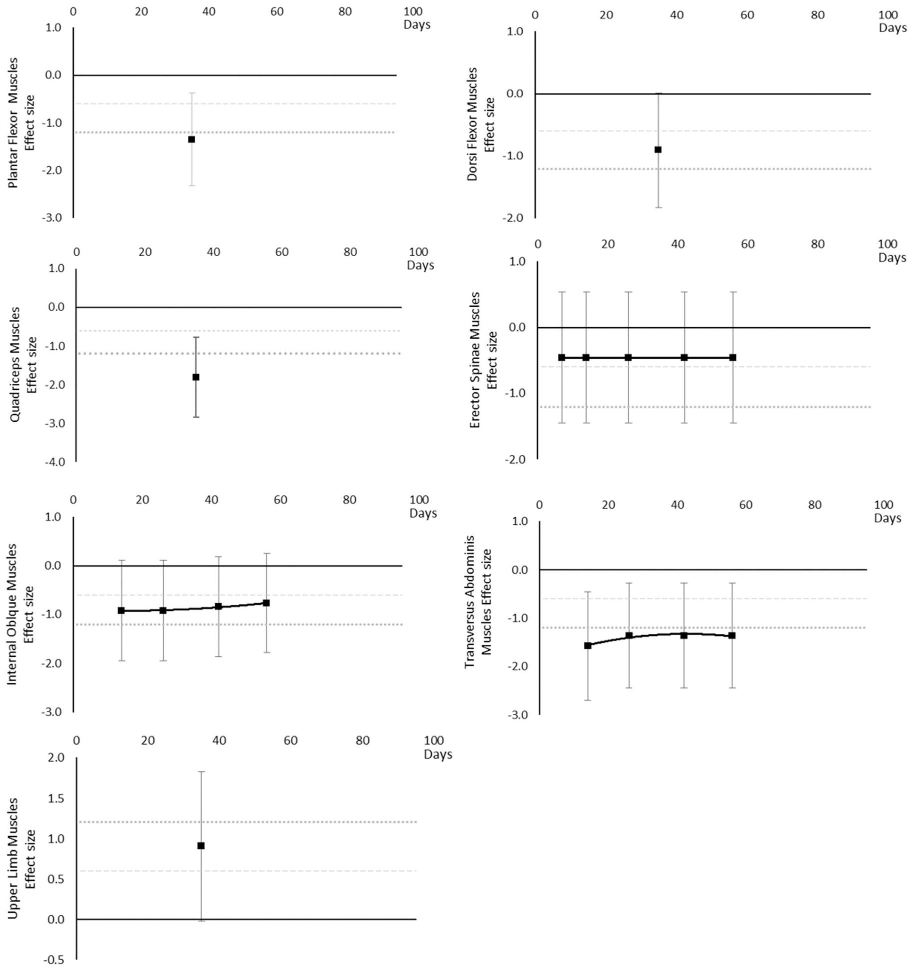

FIGURE 7 | Effect size plots for muscle thickness over time from individual (gray) and average (black) effect sizes at each time point, with 0.6 (dotted line) and 1.2 (dashed line) effect magnitudes and average effect trend line overlaid.

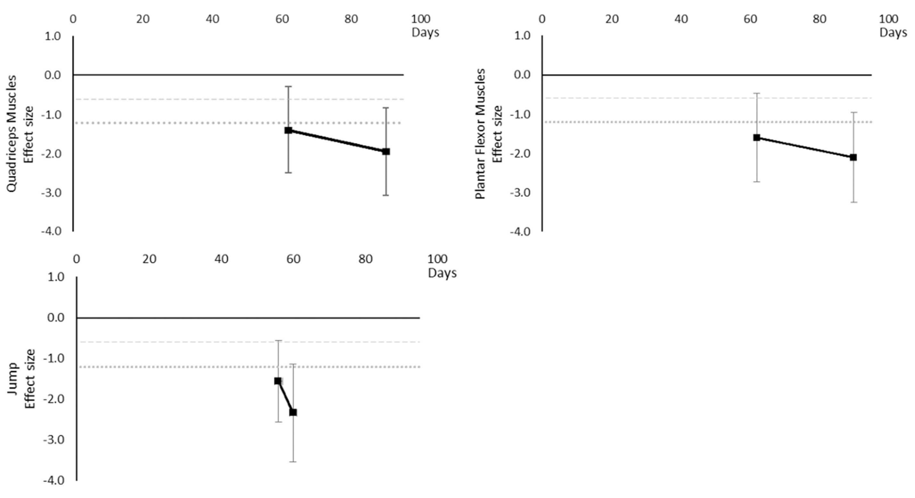

FIGURE 8 | Effect size plots for peak power over time from individual (gray) and average (black) effect sizes at each time point, with 0.6 (dotted line) and 1.2 (dashed line) effect magnitudes and average effect trend line overlaid.

by 15 days but not until 90 days for Dorsi and Plantar Flexor muscles which were the only muscles with data at the 90 day point. The breakdown of individual activity effects per muscle is available in **Supplementary Table 7** and associated summary plots in **Figure 9**.

Maximal Voluntary Contraction During One Repetition Maximum

Maximal voluntary contraction during one repetition maximum decreased over time except for other upper limb outcomes that remained mostly unchanged as far as data were available up to 45 days. Moderate effects became apparent by 7 days and large effects by 35 days. Other lower limb outcomes that included maximal isometric force during supine squat, hip extensor force and legs total work never reached a large effect, but had no data available beyond 35 days. The breakdown of individual MVC during one repetition maximum effects per muscle is available in **Supplementary Table 8** and associated summary plots in **Figure 10**. The polynomial trend for Hamstring muscles appeared to be unsafe after 20 days.

Power

Power decreased over time. Moderate effects became apparent by 7 days and large effects by 20 days, although these were only seen in the Quadriceps muscle data. Hamstring, Hip Flexor, and upper limb muscles that included elbow flexors and extensors reached moderate effects by 20 days. Plantar Flexors never reached a moderate effect but data were only available at 14 days. Other trunk muscles included trunk flexors and extensors tested in combination within functional movements. The breakdown of individual power effects per muscle is available in **Supplementary Table 9** and associated summary plots in **Figure 11**.

Performance Based

Performance based outcomes all worsened over time, as although sit to stand, balance, and sprint time outcomes all had positive effects, this was considered a worsening effect within these measures. Endurance reached a large effect by 14 days, jumping a moderate effect at 42 days and large by 44 days, sit to stand and balance reached large effects by 60 days and sprint time by 62 days. Data for most outcomes were only available for one time point and so trends over time for individual outcomes are not able to be determined. The breakdown of individual performance based effects per outcome is available in **Supplementary Table 10** and associated summary plots in **Figure 12**. It should be noted that while these outcomes are grouped as being performance based for this review, they may differ and each individual measure should be considered on its own merit.

DISCUSSION

Summary of Main Findings

The main finding of the review was that muscle cross-sectional area, volume, shape, size, activity, power, performance, torque, and force-based outcomes, at either regional or global level, all decline over time, based on the current evidence base. Moderate effects became apparent in the following order: power and MVC during one repetition maximum (7 days), followed by volume, cross sectional area, torques and strengths, contractile work capacity, thickness and endurance (14 days), then muscle activity (15 days). Large effects became apparent in the following order: volume, cross sectional area (28 days) torques and strengths, thickness (35 days), and peak power (56 days). No large effects were found for muscle activity. There were limited data for contractile work capacity and no large effects were apparent. In general, lower limb and trunk muscles appeared to decline more rapidly than upper limb muscles. Locomotion muscles such as Plantar Flexor and Quadriceps muscles also generally appeared to decline more rapidly than other muscles groups and with larger effect sizes.

Findings Within Context of Human Space Mission Profiles

Human spaceflight missions differ in duration, so results have to be placed into the context of mission profiles and operationally important considerations. Operationally, performance-related measures such as power, MVC, torques and strengths are considered most critical. In terms of mission profiles, typical ISS missions involve approximately 180 days in μG (Bryant et al., 2017). The provision of time for exercise CM is mandated for these missions and developments have led to improved efficacy over the lifetime of ISS (Trappe et al., 2009; Ploutz-Snyder, 2013; Hackney et al., 2015). Assuming that the rate of change during bed rest is reasonably transferable to that experienced in μG, the results of this systematic review suggest that large effects would be apparent within a 180 day ISS mission if no exercise CM were employed. That ISS astronauts are able to complete missions without problems from muscle deterioration and successfully return to Earth may provide some level of evidence with which to judge current countermeasures as effective. However, the focus of this review is exploration beyond Low Earth Orbit. Lunar and Martian (exploration) mission profiles were defined in the HUMEX study (Horneck et al., 2006) that modeled exploration mission durations including transit times in μG and planetary stay times in low (<1 G) gravity (**Figure 13**). HUMEX defined three scenarios, including a Lunar mission with a 180 day surface stay (Horneck et al., 2003) and two Mars missions with either a 30 or 400 day surface stay (Horneck et al., 2006). In HUMEX, inter planetary transit time in μG was 5 days for Lunar missions and 203–213 days for Mars.

Mars

It is clear from the findings of this review that changes in muscle outcomes, including performance related measures, with large effects would be observed if no CM were performed during a 200+ day transit to Mars. A risk assessment (Gernand, 2004) has highlighted that decreased muscle mass, strength, and endurance is likely to lead to inability to complete mission critical tasks such as exiting a spacecraft on landing, performing strenuous extra vehicular activity and being functional during increased Gz loading on non-Earth planetary surfaces where a landing support and rehabilitation team may not be available. Therefore, effective CM to prevent muscle deterioration are likely going to

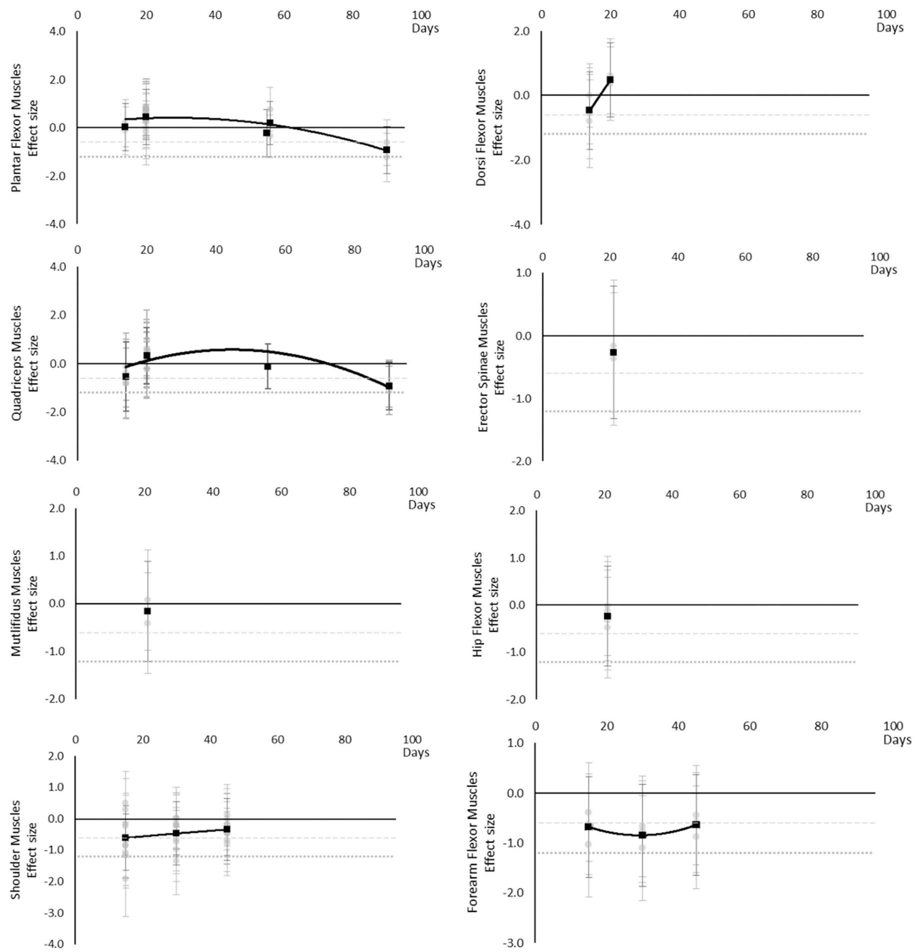

FIGURE 9 | Effect size plots for EMG muscle activity over time from individual (gray) and average (black) effect sizes at each time point, with 0.6 (dotted line) and 1.2 (dashed line) effect magnitudes and average effect trend line overlaid.

be required for Mars missions unless absolute strength mission requirements can be reduced or eliminated, to mitigate risks of crews being unable to perform mission critical tasks and continue to function safely on arrival at Mars. However, based on the occurrence of large effect sizes in the present results only after 28–35 days, exercise CM "holidays" might be considered during Mars transits/orbits to save resources if agencies were confident that moderate changes in muscle performance could be reversed using in-flight exercise equipment and prescriptions.

Moon

The results of this review suggest that exercise CM might not be required during a 5 day Lunar transit period, as moderate effects on muscle are not likely to be apparent until 7 days. The initial changes in power and MVC might not be functionally limiting enough to risk mission success, compared to muscle size, strength, and endurance effects that do not reach a moderate size until 14 days. Therefore, further investigation of any effects within the expected Earth-Lunar transit period, considered against minimal clinically worthwhile and mission critical magnitude changes, may be useful to confirm this finding.

As a Lunar landing may occur at 8 days in the HUMEX models, the pre-flight strength of crew and the absolute strength and functional requirements of Lunar landing activities would need to be considered when deciding whether or not employ exercise CM prior to attempting a landing. While not employing exercise CM might be considered for the Earth-Lunar transit period, a recent systematic review of biomechanical responses to reduced gravity (Richter et al., 2017) showed that exercise CM would likely be needed during stays on the planetary surfaces of both Moon (0.16 g) and Mars (0.38 g). As time in both μG and low gravity accumulates over the entire mission duration (196-d in total for the HUMEX model), exercise CM are also likely to be needed during the return to Earth transit. However, not using exercise CM on the return transit might be considered if key muscle outcomes could be maintained at, or restored to, pre-mission levels by the end of a Lunar surface stay. Based on the occurrence of large effect sizes in the present results, in an off-nominal situation, such as an emergency, a longer period, possibly up to around 30 days, without exercise CM might be considered if the risks of moderate-large effects can be managed in some other way, for example, knowing support and

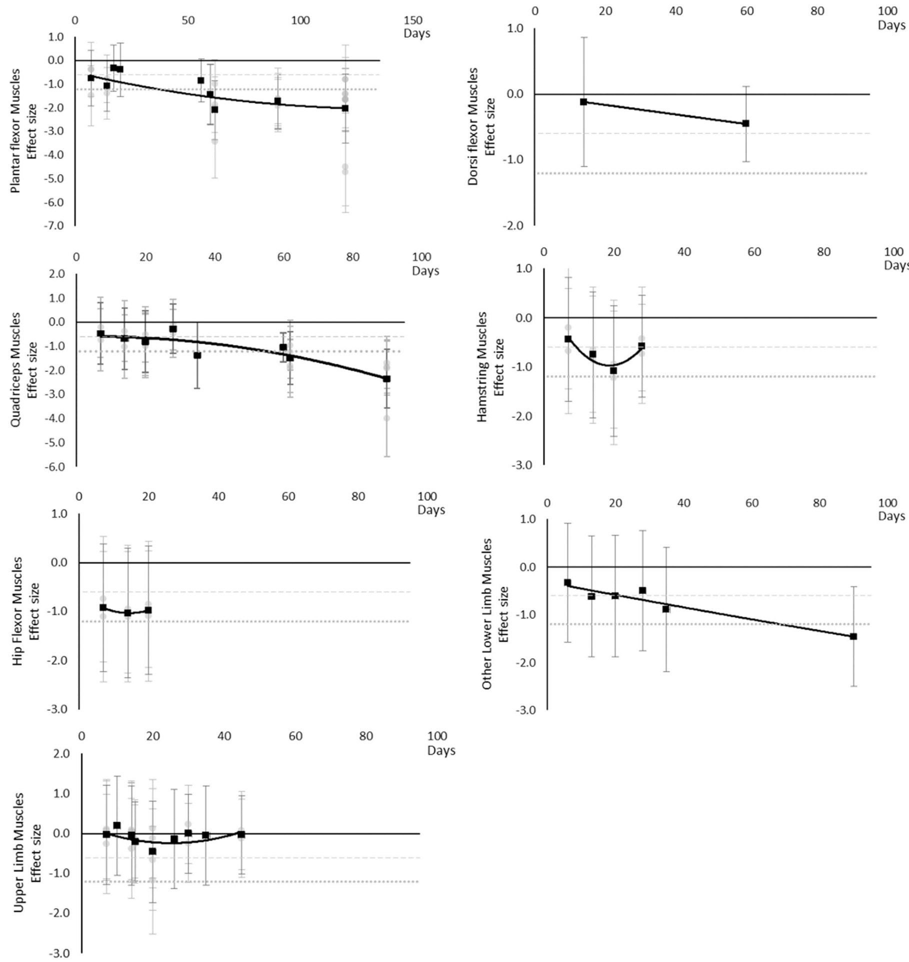

FIGURE 10 | Effect size plots for MVC during one rep max over time from individual (gray) and average (black) effect sizes at each time point, with 0.6 (dotted line) and 1.2 (dashed line) effect magnitudes and average effect trend line overlaid.

a full rehabilitation programme are available at the destination arrival site. As with Mars missions, for long Lunar orbital missions with extended periods in μG, an exercise CM "holiday" of the same duration might be considered if agencies were confident that moderate changes in muscle performance could be reversed in-flight.

Individuals More Susceptible to μG Induced Muscle Changes

An individual with a relatively lower muscle outcome measure may be more susceptible to experiencing a negative functional impact of negative changes in these outcomes compared to someone with greater initial measures. It is expected that most missions will require an absolute (minimal) level of strength to achieve mission critical tasks such as donning/doffing and standing up/moving whilst wearing a space suit in low gravity, hatch opening, and pulling/dragging a fellow crew member wearing a space suit during an emergency. The absolute level is defined as the precise required strength outcome in raw units to achieve a task, as opposed to considering relative changes with effect size or percentage changes. A relative (%) reduction in strength will make all tasks with an absolute strength requirement more challenging for all individuals, but the biggest impact will be felt by those who have a lower initial level of absolute strength. For example, a strong individual might be able to lose 30% of their pre-flight strength and still comfortably achieve a mission critical task (and also still be stronger than a weaker individual was prior to flight), whereas a weaker individual might already be close to their physical limit during this task without any deconditioning. Operationally, having an estimate of the most rapid possible rate of change in muscle outcomes may be useful in the case of a crew member with low pre-flight absolute strength, or an individual highly susceptible to μG adaptation. In the present study, the most extreme negative value within the confidence interval for each outcome provides an estimate of the most extreme worst likely true value that might be encountered with exposure to μG. Based on this estimation, the results of this analysis suggest that the change experienced by an individual astronaut might reach a large effect size in some muscles within a 7 day lunar transit period for volume, cross sectional area, contractive work capacity, thickness, power, and MVC. However, the confidence

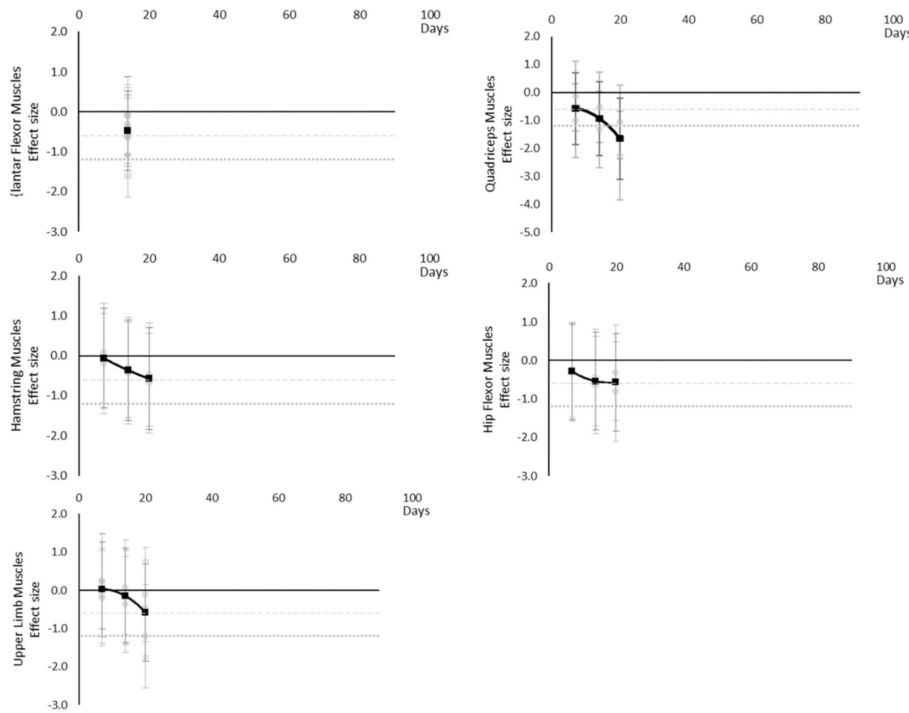

FIGURE 11 | Effect size plots for power over time from individual (gray) and average (black) effect sizes at each time point, with 0.6 (dotted line) and 1.2 (dashed line) effect magnitudes and average effect trend line overlaid.

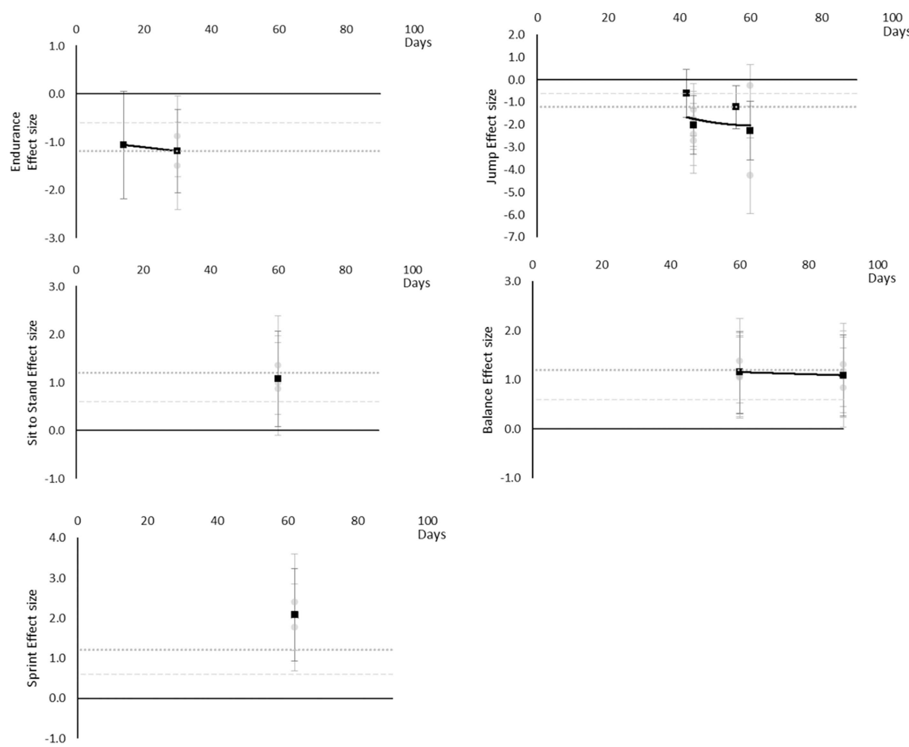

FIGURE 12 | Effect size plots for performance based over time from individual (gray) and average (black) effect sizes at each time point, with 0.6 (dotted line) and 1.2 (dashed line) effect magnitudes and average effect trend line overlaid.

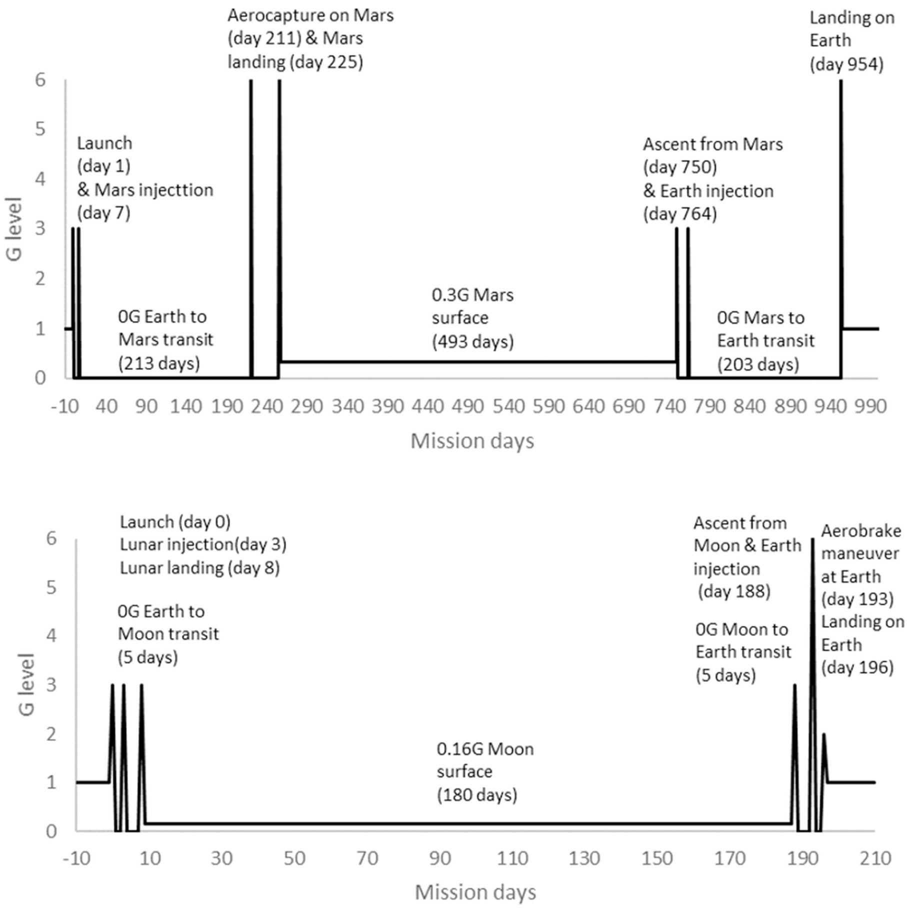

FIGURE 13 | Mission profiles for 180 day surface stay Lunar mission (Bottom) and 493 day surface stay Mars mission (Top), adapted from HUMEX (Horneck et al., 2003, 2006).

intervals are wide due to the small sample sizes across the current evidence base, so this estimate should be treated with caution as it may be exaggerated. Individual effects are difficult to determine in a transferable way to the true population from the data currently available or from individual case studies. Ideally, a population selected for their increased susceptible to unloading/μG-induced muscular adaptation should be studied in a long-duration μG analog to produce a representable average effect that could be transferred to the true population with more reasonable confidence. Until such data are available, estimating the maximum rate of decline in an individual in response to μG exposure of such a duration will remain difficult. In addition, consideration would also be needed should an individual be selected to perform some tasks in a mission that are not considered mission critical, but are essential to other mission goals. It may be that checking for susceptibility to outcomes that are linked more strongly to mission success is checked and made part of astronaut eligibility screening, it could also be any more susceptible mission critical individuals undergo more rigorous preflight and inflight training protocols or consider use of other more removed countermeasures beyond the scope of this review.

Exercise countermeasure development may want to consider focusing on those which might best address the more susceptible outcome changes in this review, volume, cross sectional area, contractive work capacity, thickness, power, and MVC while also ensuring any proposed exercises are tailored to tasks considered critical, such as donning/doffing and standing up/moving whilst wearing a space suit in low gravity, hatch opening, and pulling/dragging a fellow crew member wearing a space suit. The impact of any chosen exercise types on future spacecraft exercise hardware would also need further consideration. Future research should consider identifying exercise countermeasures that would best address the more susceptible outcomes and be feasible with any technical constraints of new space vehicles planned for use within Moon and Mars missions.

Countermeasure Requirement

As CM are likely to be needed on the return trip from both Moon and on the journeys to and from Mars, such CM will need developing. Countermeasure devices should support lower limb and trunk muscle exercise as these decline earlier than other body regions and are essential for locomotion and for spinal function on return to G loading (Bamman, 1996; Pavy-Le Traon et al., 2007; Evetts et al., 2014; Stokes et al., 2016; Winnard et al., 2017). Based on the results of the present study, if exercise CM are used during very short missions/transits (e.g., up to 7 days), devices should support exercise that maintains power and maximal force production, as moderate effects appeared early in these performance outcomes. Up to around 15 days, exercise CM might need only to prevent moderate size effects in muscle. Consideration could be made around if lower intensity exercise, or potentially a break in countermeasures would be safe. However, once μG exposure duration reaches around 30 days and above, large effects in muscle will likely need to be managed and this would likely require devices/prescriptions optimized within the constraints of the vehicle/habitat.

This pattern fits current European Space Agency (ESA) ISS Long Duration Mission (LDM) exercise prescriptions (Petersen et al., 2016) that include an initial 20-day familiarization phase to allow crew to adjust to exercise in μG and minimize injury risk, in which exercise intensity is moderate compared to pre-flight maximum capacity. However, as there is currently no systematic measurement of muscle performance in-flight, the impact of this period of lower intensity exercise on overall changes in muscle during an LDM is unknown. It is also unclear if crew members may have had better results at the end of a mission had they begun exercising more intensely earlier in the mission. Following the 20-day familiarization period, exercise prescriptions are increased in intensity to 80%+ maximal capacity. In the final 15–30 days of a long duration mission (>49 days) intensity is kept high, but focus on resistance and running exercises. In flight resistance exercise prescriptions for European astronauts also focus on lower limb muscles (squats, heel raises, deadlifts) ESA has found are most susceptible to μG induced changes from (non-systematic) measures that have been taken (Petersen et al., 2016). Similar exercise prescriptions, focusing on lower limb muscles and maintaining outcomes already highlighted in this review, might form a good basis for initial planning for any exercises required for Lunar and Mars missions. Additionally, research on preventing deconditioning of older adults might also be useful as preventing loss of power in functional lower limb muscles is important in this population and simple loading exercises have shown helpful in this context (Byrne et al., 2016). It should also be noted, however, that a systematic review of in-flight CM for maintaining spinal health in μG found that, while resistance based exercises helped prevent muscle changes, they did not help with non-muscle outcomes such as spinal morphology (Winnard et al., 2017). Moreover, a number of other physiological systems/organs also adapt to μG, including bone and aerobic capacity, but the efficacy of resistance exercise during gravitational unloading on them is unknown as systematic reviews similar to the present study have yet to be performed. Therefore, while the recommendations of this review are expected to help plan CM for *muscle* changes, additional holistic consideration of other physiological systems will likely be required. Finally, any CM development for exploration missions will also have to consider constraints of space vehicles that will be used, such as available physical space, limited number of devices that can be included in the space craft, consumables, generation of heat, carbon dioxide, and vibration, which are likely to be more restricted than the ISS (Hackney et al., 2015). Before any pause in exercise countermeasures could be taken, the results of this review would need to be validated in microgravity and ideally actual astronauts through experimental studies. No such published studies of astronauts not performing exercise to document muscle changes over the time frames considered in this review was found. Space agencies and researchers would also need to consider the ethical implications and acceptability of any such study.

Completeness and Quality of Current Evidence

There were missing and limited data across all the outcome measure subgroups, and gaps in the evidence base were clearly shown in the results tables. There was a lack of standardized time points at which measures were recorded, even across studies reporting the same outcome measures. Limited data were found repeatedly for Gluteal and Hip Flexor muscles across several outcome measure subgroups. Data were lacking for contractile work capacity, muscle thickness, and peak power outcome measures where further research is recommended to validate the trends seen over time in the current evidence base. No patient reported outcome measures have been reported across the bed rest studies, meaning it is unclear how relevant the measures are to patients (in this case astronauts) (Dawson et al., 2010; Nelson et al., 2015). In addition, only seven out of the 75 analyzed studies considered functional performance based outcomes that are more likely to be directly relevant to astronauts. While strong efforts on behalf of space agencies to standardize bed rest studies has occurred including listing required surrogate measures (Sunblad et al., 2014), patient reported outcomes such as their ability to perform a task felt of value to them, remain missing on the whole. It is recommended that the scientific and space medical operations communities agree on set times points at which outcome measures should be tested to enable easier comparisons across studies and for overall trends to be more easily identifiable. While ESA requires agency bed rest studies to be performed to set standards, it might be beneficial to consider running a specific initiative in the wider Aerospace Medicine field to establish core outcome sets relevant to space medicine operations that should then be used in all associated research. This could be based on recommending use of standard space agency developed tests such as functional and Field Test parameters developed by NASA and Russia The Core Outcome Measures in Effectiveness Trials (COMET) is an example initiative that facilitates development and application of core outcome sets and research has been published on how to reach consensus using such an approach (Prinsen et al., 2014). It is also recommended that patient reported outcome measures, and increased reporting of functional performance based outcome measures, be included in both future research and space medical operations to ensure that outcome measures are assessing phenomena that are relevant to astronauts. This recommendation echoes a recent European Space Agency topical team report that also found patient reported outcome measures not being used in space medicine research and operations (Stokes et al., 2016). The report recommended the use of such outcomes and suggested potential for development of new such outcome measures specifically for space medicine with operational space medicine input to ensure relevance across research and clinical settings. It would be of further benefit if clinically worthwhile, or concerning, changes were defined for key outcome measures, so that results can be placed into a clinically meaningful context. Reporting results based on clinically meaningful raw changes would likely be more informative to operational decisions compared to the more mechanistic null hypothesis tests, effect size or percentage change measures currently used. The high risk of bias and lack of core outcome measure sets means that the conclusions reached by this review should be treated with some caution. A bed rest study could be performed to confirm the findings of this review. If performed, the study would ideally be a randomized controlled trial comparing inactive bed rest with controls not performing bed rest but controlled for all potential confounding factors. For example, exercise and any other types of muscle interventions would need to be strictly controlled for the period of the study. The bed rest element would ideally comply with all aspects of the AMSRG bed rest quality tool to improve transferability of results to astronauts (Winnard and Nasser, 2017b). Finally, all modifiable risk of bias elements would need controlling and a risk of bias tool for randomized controlled trials, such as provided by Cochrane (Higgins et al., 2011), could be used as a guide to check what elements need to be controlled to minimize bias risks.

Most of the studies scored four on the bed rest tool, with no studies scoring a full seven points, although 13 studies scored six. The reasons for marking studies down was mostly due it being unclear if criteria had been met rather than clearly failing a point. The most common unclear criteria was related to restricted sunlight exposure followed by ensuring a fixed daily routine. The high risk of bias results were most commonly caused by not clearly showing how confounding factors were managed and providing adequate description of participation. The participation domain considers participant eligibility criteria, source of participants, baseline descriptions, description of sampling frame and recruitment, description of period and place of recruitment, and inclusion/exclusion criteria (Hayden et al., 2013). The sunlight exposure criteria has more impact on bone outcomes (Holick, 2004) due to its role in vitamin D levels within human bone homeostasis (Tarver, 2013) so might not be a large concern for the muscle outcomes presented in this review. However, it is recommended that future bed rest protocol information be clear on all the criteria assessed on the bed rest quality tool and especially on the fixed daily routine and restricted sunlight points, while also ensuring that information is provided about control of confounding factors to help reduce risk of bias and participation considerations. In addition, studies that assess time sensitive outcomes, such as muscle (in which the results of this review show effects of deconditioning can occur by 7 days), should report any potential for pre-bed rest deconditioning during familiarization and baseline measure periods and any attempts to control for this. There is potential that participants who are admitted to bed rest facilities several days in advance for control measures could decondition within this period. Some studies state including an ambulatory control period, but none report details of what this involved or if there was potential for pre-bed rest deconditioning to influence results.

There was some asymmetry in the funnel plot showing potential publication bias toward studies reporting a decrease in muscle outcomes. However, there were studies present on the increasing side of the plot, so the risk is not likely to be high. In addition, it is expected that many of the muscle outcomes would decrease during a period of inactivity such as bed rest, therefore, it not surprising most studies reported decreases. Therefore, while it appears a risk of reporting bias may exist, the presence of some studies reporting increases and the expected pattern of more decreases being reporting suggest this finding should be treated with caution and the potential risk is likely to be low.

Limitations

This review only considered muscle outcomes. Spaceflight is known to affect many more human physiological systems including bone, cardiovascular and vestibular (Pavy-Le Traon et al., 2007). These results alone, therefore, only provide a muscle based perspective. As typical meta-analysis statistics assume two independent groups (Higgins and Green, 2011), a more basic effect size analysis without these assumptions had to be used due to only considering changes over time in the control group of each study. Therefore, some caution should be taken as the mean effect sizes are not weighted and heterogeneity scores are not available. However, as most studies had small sample sizes, a weighted result is not expected to produce largely different results. Additionally, the findings of this review appear to match actual spaceflight findings and patterns, such as the European Space Agency exercise prescription for long duration missions that performs lower intensity exercises for the first 20 days. While actual measures are not taken during flight, the 20 days has so far not resulted in any mission critical functional decline (Petersen et al., 2016). The 20 day period would fit with the findings of this review that only moderate effects would be expected before 28 days and gives some partial validation, from actual astronaut data, to the findings of this review. The review is also broad and, in places, the variation around the outcomes appears large suggesting heterogeneity of data may be high, although the large intervals could also be due to the small sample sizes that were a common feature of the included bed rest studies. Due to the broad data set that summarizes the entire muscle evidence base, additional data on pre-bed rest fitness of participants was not extracted for analysis. While studies were selected that had healthy adults undergoing spaceflight simulation bed rest, individual physical condition was not considered beyond this. Therefore, there may be some limitations to the transferability of astronauts who undergo training with space agencies prior to missions. However, a broad summary of the entire current evidence base with basic effect size analysis was the best way to try to address the overarching research questions, look for high level trends, and present a summary of the current state of the complete evidence base.

Conclusions

The results of this review suggest that moderate effects on a range of muscle function parameters may occur within 7–14 days of unloading, with large effects within 35 days. Combined with identification of muscle performance requirements for future exploration mission tasks, these data, may support the design of CM programmes to optimize their efficient use without compromising crew safety and mission success. However, the data suggests CM are likely to still be needed for longer transit/orbital periods of 14–28+ days, such as a prolonged Lunar orbit, deep space exploration, or a Mars mission, as moderate effects occur between 7–14 days and large effects by 28 days for most muscle outcomes. However, if large effect sizes occur only after 28–35 days, to save resources, space agencies might consider short missions without exercise CM, or fixed periods of abstinence during longer μG exposures, if they could be confident that moderate changes in muscle performance could be reversed in-flight. Finally, several research gaps are highlighted for future bed rest studies in which standardized time points for measurements should be used and clear information provided on sunlight exposure control, fixed daily routine, and control of any confounding factors.

ANALYZED STUDY LIST

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AUTHOR CONTRIBUTIONS

AW: initial concept ideas, protocol planning and drafting, search screening, analyzing, and drafting all manuscript versions. JS: methods advice, protocol drafting, and approving final draft. NW: data extraction, analysis, and drafting final version. MV: protocol planning, search screening, data analysis, drafting text, and checking final version. NC: protocol planning, search screening, methods advice, manuscript drafting, and approving final version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2019.01046/full#supplementary-material

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Conflict of Interest Statement: 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 Physiology

HYPOTHESIS AND THEORY
published: 10 September 2019
doi: 10.3389/fphys.2019.01150

Comparisons of Resistance Training and "Cardio" Exercise Modalities as Countermeasures to Microgravity-Induced Physical Deconditioning: New Perspectives and Lessons Learned From Terrestrial Studies

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OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Environmental, Aviation and Space Physiology, a section of the journal Frontiers in Physiology

Received: 21 February 2019
Accepted: 26 August 2019
Published: 10 September 2019

Citation:
Steele J, Androulakis-Korakakis P, Perrin C, Fisher JP, Gentil P, Scott C and Rosenberger A (2019) Comparisons of Resistance Training and "Cardio" Exercise Modalities as Countermeasures to Microgravity-Induced Physical Deconditioning: New Perspectives and Lessons Learned From Terrestrial Studies. Front. Physiol. 10:1150. doi: 10.3389/fphys.2019.01150

Prolonged periods in microgravity (μG) environments result in deconditioning of numerous physiological systems, particularly muscle at molecular, single fiber, and whole muscle levels. This deconditioning leads to loss of strength and cardiorespiratory fitness. Loading muscle produces mechanical tension with resultant mechanotransduction initiating molecular signaling that stimulates adaptations in muscle. Exercise can reverse deconditioning resultant from phases of detraining, de-loading, or immobilization. On Earth, applications of loading using exercise models are common, as well as in μG settings as countermeasures to deconditioning. The primary modalities include, but are not limited to, aerobic training (or "cardio") and resistance training, and have historically been dichotomized; the former primarily thought to improve cardiorespiratory fitness, and the latter primarily improving strength and muscle size. However, recent work questions this dichotomy, suggesting adaptations to loading through exercise are affected by intensity of effort independent of modality. Furthermore, similar adaptations may occur where sufficient intensity of effort is used. Traditional countermeasures for μG-induced deconditioning have focused upon engineering-based solutions to enable application of traditional models of exercise. Yet, contemporary developments in understanding of the applications, and subsequent adaptations, to exercise induced muscular loading in terrestrial settings have advanced such in recent years that it may be appropriate to revisit the evidence to inform how exercise can used in μG. With the planned decommissioning of the International Space Station as early as 2024 and future goals of manned moon and Mars missions, efficiency of resources must be prioritized. Engineering-based solutions to apply exercise modalities inevitably present issues relating to devices mass, size, energy use, heat production, and ultimately cost. It is necessary to identify exercise countermeasures to combat deconditioning while limiting these issues. As such, this brief narrative review considers recent developments in our understanding of skeletal muscle adaptation to loading through exercise from studies conducted in terrestrial settings, and their applications in μG environments. We consider the role of intensity of effort, comparisons of exercise modalities, the need for concurrent exercise approaches, and other issues often not considered in terrestrial exercise studies but are of concern in μG environments (i.e., O_2 consumption, CO_2 production, and energy costs of exercise).

Keywords: resistance training, cardio, aerobic training, microgravity, space

INTRODUCTION

The physiological responses and adaptations to prolonged periods spent in microgravity (μG) environments have been described as a "classical" topic within the field of environmental and applied exercise physiology (Grassi, 2018). Indeed, the resultant deconditioning of numerous physiological systems and loss of strength, power, and cardiorespiratory fitness is well documented (Tesch et al., 2005; Lang et al., 2006; Trappe et al., 2009; Moore et al., 2010; Platts et al., 2014; Bloomberg et al., 2015). Exercise has long been used as the primary countermeasure for μG-induced deconditioning and the history of this has been detailed in an accompanying paper introducing this Research Topic (Scott et al., 2018). Recent reviews (Loenneke et al., 2012; Carpinelli, 2014) have also discussed the considerable attempts to solve the issue of how best to employ this countermeasure in μG environments. Many of these attempts revolve around what could be considered "engineering-based" solutions to employ the traditional exercise modalities often used on Earth as countermeasures for similar deconditioning (e.g., detraining, de-loading, disease, or immobilization). Broadly speaking, exercise is often (though not exclusively) dichotomized into two primary modalities, aerobic training (or "cardio") and resistance training, with the former primarily thought to stimulate improvements in cardiorespiratory fitness, and the latter thought primarily to stimulate improvements in strength, power, and muscle size. Approaches to solve the issue of performing these typical modalities in μG have included deployment of currently used equipment on the International Space Station (ISS). For example, the Combined Operational Load Bearing External Resistance Treadmill (COLBERT)/Treadmill 2 (T2), Cycle Ergometer with Vibration Isolation and Stabilization System (CEVIS), and Advanced Resistive Exercise Device (ARED) among others such as suits for muscle loading (Penguin-3), lower body negative pressure (Chibis), and lower body g-loading (Kentavr), in addition to electrical stimulators (Tonus-3). The different agencies involved have to date employed a range of countermeasure protocols using such devices (Loehr et al., 2015; Yarmanova et al., 2015; Petersen et al., 2016). However, with the planned decommissioning of the ISS in 2024 (the earliest point in time though it may continue past this date), and future goals of manned moon and Mars missions, "engineering-based" solutions to apply both traditional "cardio" and resistance training exercise modalities inevitably present issues. These primarily relate to the mass, size, energy use, heat production, and ultimately cost of devices. It is therefore necessary to identify exercise countermeasures to combat the losses in strength, power, muscle mass, and cardiorespiratory fitness while limiting these issues.

However, this is not a simple task. Research on astronauts actually experiencing μG, particularly over extended periods of time, presents a number of barriers including logistics such as device sizes, costs, and participant sample sizes due to both difficulty in recruiting and the considerable between participant variability in many outcome measures often of interest. As such, "analogs" for μG environments are often used, with the most common being the bed rest study. A recent issue of *Medicine and Science in Sports and Exercise* detailed the results of NASA's relatively recent 70-day bed rest study. This involved the use of concurrent resistance training and "cardio" exercise, in addition to testosterone supplementation, as countermeasures to deconditioning in a range of physiological systems (Cromwell et al., 2018; Dillon et al., 2018; Mulavara et al., 2018; Murach et al., 2018; Ploutz-Synder et al., 2018; Scott et al., 2018). The exercise interventions examined in the aforementioned bed rest study have been somewhat influenced by the recent body of literature supporting the use of high effort interval based "cardio" protocols [i.e., High Intensity Interval Training (HIIT)] as this was implemented as part of the concurrent program. The SPRINT protocol was designed to require less time and be performed at high intensities of effort including: HIIT performed using a custom-built vertical treadmill; resistance training using a custom built horizontal squat device; and both HIIT and resistance training using a flywheel device. Further, work from Russia has historically detailed the countermeasures used with cosmonauts (Kozlovskaya et al., 1995, 2015; Kozlovskaya and Grigoriev, 2004) and recently has compared the effects of either treadmill training with alternating sessions of higher and lower effort HIIT ($n = 7$), or traditional continuous endurance treadmill training ($n = 8$; Fomina et al., 2016). They examined the cosmonauts over 189 ± 12.4 days aboard the ISS and found the HIIT protocol to result in maintenance of most pre-flight outcomes compared to the losses seen in the traditional endurance training. The Canadian Space Agency (CSA), Japan Aerospace Exploration Agency (JAXA), and European Space Agency (ESA) are currently using similar protocols that have been detailed extensively (Loehr et al., 2015).

It seems that developments within terrestrial studies in exercise physiology have been incorporated into the research programs of those μG analogs. However, other recent work based upon terrestrial studies (Fisher and Steele, 2014) has also begun to question the traditional dichotomy regarding resistance training and "cardio" exercise, including the need for concurrent training approaches. Furthermore, the same authors suggest that adaptations to loading through exercise may be primarily influenced by the intensity of effort employed independent of modality, and that similar adaptations might be achieved with differing exercise modes assuming sufficient intensity of effort is reached. Indeed, this questioning is of interest to pursue since it could imply that a lower volume of overall exercise might be adequate for astronaut's physical fitness training in μG. Though astronauts value their time for exercise for wider personal wellbeing and many would likely prefer more time for such activity, from an operational perspective any approach that might help reduce time spent exercising could be considered beneficial, particularly if it can also yield similar physiological outcomes compared with greater volumes of exercise.

Contemporary developments in understanding of the applications of, and subsequent adaptations to, exercise-induced muscular loading in terrestrial settings have advanced in recent years. It may be appropriate to revisit the evidence to better understand how exercise might be applied in μG for potential investigation in future studies of μG analogs such as bed rest studies. In this brief review, we focus on the application of resistance training and "cardio" training modalities. Topics covered include: the role of intensity of effort, comparisons of exercise modalities (resistance training vs. "cardio"), and whether there is a need for concurrent exercise approaches currently used as countermeasures, as well as other issues often not considered in terrestrial exercise studies but which are of concern in μG environments such as O_2 consumption and CO_2 production in addition to energy costs of exercise. We note that resistance training and "cardio" training neither reflect the entirety of possible approaches to exercise countermeasures, nor are cardiorespiratory fitness, strength, power, and muscle size, the only outcomes that might be of interest when discussing the deconditioning that occurs in response to μG environments. Scott et al. (2019) list a number of alternative countermeasure approaches in addition to other outcomes of interest in their Introduction to this Research Topic. We encourage the reader to consider the other reviews covered in this Research Topic, which discuss many of these alternative approaches. Further, we add that the recent advances in understanding of exercise response from terrestrial studies presented here should be considered as candidates for further research within μG analogs. Their ability to be effectively implemented into true μG settings not be assumed based upon terrestrial studies.

INTENSITY OF EFFORT: A POSSIBLE EQUALIZER FOR ADAPTATION?

The intensity of effort during exercise can be defined in relation to the current ability to meet the demands of the task being attempted, and for resistance training this is often considered with respect to the proximity to momentary failure (Steele, 2014; Steele et al., 2017). The perception of that effort is thought to arise from the central motor command required to drive the musculature to perform the task being attempted (Marcora, 2009; Pageaux, 2016), and of course, this drive is influenced by the ability of that musculature to meet those demands, which can be determined by various fatigue processes and afferent feedback from the muscles (Steele and Fisher, 2018). Thus, it is thought that effort, both that required and perceived, is likely intrinsically linked to motor command and motor unit recruitment (de Morree et al., 2012; Guo et al., 2017; Potvin and Fuglevand, 2017).

As noted, it has recently been speculated that, assuming effort is matched, adaptations to exercise are likely to be similar (Fisher and Steele, 2014). Indeed, with respect to resistance training this appears to be the case for muscular adaptations. When performed to momentary failure, recent work suggests there may be little effect of load (Schoenfeld et al., 2017), repetition duration (Schoenfeld et al., 2015; Hackett et al., 2018; Carlson et al., 2019), muscle action (Fisher et al., 2016b), or whether "advanced" techniques are employed such as pre-exhaustion (Fisher et al., 2014), breakdown sets (Fisher et al., 2016a), or blood flow restriction (Barcelos et al., 2015; Farup et al., 2015). This is not to say that it is a requirement to train to a maximal intensity of effort (i.e., to momentary failure) to produce adaptation, or that doing so is necessarily optimal; indeed, findings regarding this are conflicting (Davies et al., 2016). Recently, it has also been shown that during high effort but non-momentary failure training there are similar adaptations irrespective of load and that these may even be similar to when training to momentary failure (Nóbrega et al., 2018). It is not clear what the dose–response nature of proximity to failure and thus effort is, or whether a threshold phenomenon might exist to optimize adaptation (Steele et al., 2017). However, what does seem clear is that when effort is high and appropriately matched, various resistance training manipulations yield very similar adaptations as noted by Phillips and Winett (2010): "*…effort is internal to the person, can be created with a variety of protocols, and is not dependent upon a specific amount of external force*". As such, effort could be considered in both resistance training and "cardio" training as being determined primarily with respect to proximity to momentary failure.

The importance of high or maximal intensity of effort has become apparent and studies of concurrent exercise in μG simulations have begun to use these approaches for both "cardio" and resistance training (Cotter et al., 2015). However, it is not known whether similar effects are seen across modalities when either modality alone is performed. As an example, resistance training has been evidenced to result in improvements in cardiorespiratory fitness (Steele et al., 2012; Ozaki et al., 2013; Ashton et al., 2018), and "cardio" training to improve strength and muscle size (Konopka and Harber, 2014; Ozaki et al., 2015) though their comparative effects are less clear. Studies have attempted to compare "cardio" and resistance training modalities, some of which have appropriately controlled for effort, and duration. Others have examined what could be considered more traditional representations of the two approaches. In the following section, we will review these studies and consider whether the stimulus and adaptation resulting from exercise-induced loading is influenced by the modality used.

COMPARISONS OF TRADITIONAL "CARDIO" AND RESISTANCE TRAINING APPROACHES

Traditional approaches to "cardio" are often performed using locomotive or ergometer tasks (e.g., walking, jogging, running, cycling, rowing, etc.) in a continuous fashion with respect to duration at submaximal intensities of effort commonly determined relative to either maximal heart rate, heart rate reserve, VO_2max, or sometimes using ratings of perceived effort scales. Sometimes they are performed using "high intensity interval approaches" though many studies that compare modalities still use submaximal intensities of effort and are unmatched compared to the resistance training approaches examined. Contrastingly, resistance training is often performed with external resistance of varying degrees relative to maximal strength provided by either free weights, machines, bodyweight, or some other implements (e.g., resistance bands), either with single or multiple sets of repetitions which may or may not be performed to momentary failure (but are often performed to a relatively high effort). Most people would recognize these approaches as being "ecologically valid" implementations of either "cardio" or resistance training (i.e., reflective or their implementation in "real-life" settings) and numerous studies have compared these forms.

When comparing resistance training and "cardio" approaches, though some studies suggest no significant differences for changes in cardiorespiratory fitness (Messier and Dill, 1985; Hepple et al., 1997; Sawczyn et al., 2015), the majority suggest that "cardio" type approaches favor cardiorespiratory fitness increases (Goldberg et al., 1994; Poehlman et al., 2000; Ferrara et al., 2006; Sillanpaa et al., 2008; Wilkinson et al., 2008; Ahtiainen et al., 2009). Similarly, for strength changes, though there are exceptions (Messier and Dill, 1985), the majority of research suggests that resistance training produces greater increases in strength than "cardio" type training (Goldberg et al., 1994; Poehlman et al., 2000; Ferrara et al., 2006; Sillanpaa et al., 2008; Wilkinson et al., 2008; Ahtiainen et al., 2009). Furthermore, a recent meta-analysis has also shown that resistance training produces more favorable changes in muscle hypertrophy compared to "cardio" type approaches (Grgic et al., 2018).

This body of research suggests a specificity of training response with respect to "cardio" and resistance training, with the former favoring cardiorespiratory fitness and the latter favoring strength and hypertrophy. However, these results apply to broad comparisons of these two ecologically valid approaches to training. Yet the results of the aforementioned comparative studies do not necessarily imply that the modality, and thus mechanical resistance (e.g., the load on a resistance exercise, or the power output on a cycle ergometer) itself independent of the manner in which exercise is performed with it, is influential with respect to adaptations. Many of the studies cited have often tested their outcomes in manners that might favor particular interventions. For example, cardiorespiratory fitness being tested on the modality for which the "cardio" intervention was trained, and conversely strength being tested as a one repetition maximum in the exercise for which the resistance training intervention was specifically trained. Further, as noted, in none of the aforementioned comparative studies were attempts made to control for the effort and duration of the two interventions. However, in recent years, there have been attempts to conduct research comparing across exercise modalities while controlling for effort and duration examining both the acute physiological responses in addition to the chronic physiological adaptations.

EFFORT AND DURATION MATCHED MODALITY COMPARISONS

A number of studies have examined the influence of modality upon acute responses, typically focusing upon measures, which may be speculated to have a potential role in mediating chronic adaptations. Vilaça-Alves et al. (2016) compared both upper and lower body "cardio" (upper- and lower-body cycle ergometry) and resistance exercise (smith machine bench press and smith machine half squat) modalities during low intensity of effort with physiologically matched tasks (demands eliciting 4 mmol.L^{-1} of blood lactate). They examined the oxygen uptake responses between the two modalities finding no differences and concluded that the manner of exercise performance, and not the modality, was likely the primary determinant of this physiological response. More recently, Steele et al. (2018) compared the acute response of lower body "cardio" (recumbent cycle ergometry) to resistance exercise (leg press) during high intensity of effort tasks, matched for effort and duration (4 × 60 s sprints for "cardio" and 4 × 12 repetition maximum for resistance exercise with time matched using a 2 s concentric and 3 s eccentric repetition duration). They considered a range of physiological responses including oxygen consumption, respiratory exchange ratio, blood lactate, estimated energy expenditure, muscle swelling, and electromyography finding no differences between the modalities for any outcome. Steele et al. (2018) examined only amplitude based electromyographical variables but Noble et al. (2019) have also examined normalized (to % max) electromyographic amplitudes, which appear to be greater during typical resistance training (single leg knee extension) compared with "cardio" mode (single leg cycle ergometry) exercise performed to volitional failure. Unlike Steele et al. (2018), time to task failure in Noble et al. (2019) was unclear and thus, it is unknown if it was similar between conditions. Amplitude-based analyses may not reflect the entirety of motor units recruited where task durations differ, particularly if differing recruitment patterns are occurring (i.e., sequential recruitment of low to high threshold during low force tasks, and simultaneous recruitment of both low and high threshold motor units during high force tasks; Enoka and Duchateau, 2015; Fisher et al., 2017; Potvin and Fuglevand, 2017; Vigotsky et al., 2017). However, Kuznetsov et al. (2011) examined resistance training (knee extension) and "cardio" exercise (cycling) modalities performed to momentary failure (thus controlling for effort) using frequency based electromyographic analyses and reported that similar recruitment of motor units may occur during both modalities. These findings might be expected considering the possible link between effort and central motor drive as noted above. For example, motor unit recruitment for active muscles might be relative to task demands independent of the exercise modality, which might also be true for other physiological responses such as oxygen consumption, blood lactate production, muscle edema, etc.

Similarity in acute responses between modalities when effort and duration are matched has led to the hypothesis that the accompanying chronic physiological adaptations may therefore be similar as well (Fisher and Steele, 2014). However, to date, research examining this is limited. Only two studies have been published to our knowledge (Álvarez et al., 2017; Androulakis-Korakakis et al., 2018); though, our lab and others have been conducting research in this area, the initial findings of three further studies are also presented below.

Androulakis-Korakakis et al. (2018) examined an 8 week intervention of additional (i.e., alongside their normal training) "high intensity interval training" performed using either a "cardio" exercise modality (cycle ergometry) or a resistance training modality (squats and deadlifts) in powerlifting and strongman athletes. Both were performed 2x/week for 7 sets of either 30 s on the cycle ergometer or sets of ~16–30 s alternating with squats and deadlifts at a rating of perceived effort of 8–9 (on a 0–10 scale) and with 90 s rest between sets. Predicted VO_2max using the step test and predicted 1 repetition maximum on the knee extension were selected as outcomes to avoid issues of specificity (as discussed above) of training modality affecting test outcomes. Both outcomes improved, yet there were no statistically significant differences between groups[1] for change in predicted VO_2max [Δ = 4.6 ml.kg.min^{-1} (95%CIs = 3.0 to 6.3) vs. Δ = 3.4 ml.kg.min^{-1} (95%CIs = 1.7 to 5.1) for "cardio" and resistance training, respectively; $p = 0.259$] or for change in predicted knee extension 1 repetition maximum [Δ = 7.1 kg (95%CIs = 4.4 to 9.7) vs. Δ = 6.9 kg (95%CIs = 4.2 to 9.5) for "cardio" and resistance training, respectively; $p = 0.895$]. It is surprising to see improvements in an already well-trained population such as this, and thus, it might be expected that results may translate to untrained populations as well.

Álvarez et al. (2017) recently compared 12 weeks of effort and duration matched "cardio" (cycle ergometer "high intensity interval training") and resistance training (full body resistance training including biceps curls, knee extension, shoulder press, and upright rows) 3x/week in insulin resistant women. Each was performed with the same work:rest intervals (60 s:120 s) for 12 sets at a rating of perceived effort of 8–10 (on a 0–10 scale). Their outcomes included body composition/anthropometry, cardiovascular outcomes, plasmatic concentrations, strength, and endurance. For most of these, they found improvements but no statistically significant differences between groups. However, for strength there were greater changes in the resistance training group, though strength was tested using 1RM on the same exercises used in training (measured as 1RM in biceps curl, knee extension, shoulder press, and upright row). To the contrary, endurance performance was tested as 2 km walking test which improved in both groups with no statistically significant differences between them (both improving by ~2 min; $p = 0.284$).

More recently, Gil-Sotomayor et al. (2018) presented results from a study comparing 12 weeks of "high intensity interval training" combined with a low carbohydrate high fat diet using either "cardio" (cycle and/or treadmill ergometer) or resistance training (pull-down, leg press, bench press, dumbbell row, sumo squat, and push-ups) 3x/week. Both were effort and duration matched and performed with the same work:rest ratio (60 s:60 s) for 10 sets each with a target rating of perceived effort of 16–18 (on a 6–20 scale). They reported that VO_2 peak, body mass, fat mass, and visceral fat were all significantly improved in both groups. For VO_2 peak, Hedge's g for changes were 0.57 and 0.53 for "cardio" and resistance training, respectively. Of note, lean body mass did decrease slightly for the "cardio" modality ($g = -0.07$) and did not change for resistance training ($g = 0.00$).

Finally, our labs are currently completing a training intervention study using a similar approach to the aforementioned acute responses study by Steele et al. (2018) using a within-participant design, in addition to having recently completed a further between-group training intervention study. In this within-participant study, Armes et al. (unpublished) have begun examining lower body "cardio" (unilateral recumbent cycle ergometry) with lower body resistance exercise (unilateral leg press) matched for effort and duration (4 × 30 s sprints and 4 × ~5–7 repetitions to momentary failure at 2 s:3 s repetition duration for "cardio" and resistance exercise, respectively). A within-participant design, whereby participants limbs were randomized to conditions in a counterbalanced fashion based upon dominant limb, has been used to increase power and precision for estimates by reducing between-condition variation from independent samples (MacInnis et al., 2017). The training consists of two sessions per week for 8 weeks with both conditions performed in each session with the order alternated in order to avoid any specific order effects of performing one condition prior to the other. Outcomes being examined include unilateral VO_2 peak and time to exhaustion during an incremental exercise test on an upright cycle ergometer, unilateral isometric knee extension strength, and ultrasound measured quadriceps muscle thickness. Based on precision (i.e., desired width of confidence intervals set at 0.5 population standard deviation), target N was calculated at 21, though here we present preliminary data for $N = 8$ participants[2] (**Figure 1**). Despite the within-participant design, there is evidently considerable variation or noise in the data. However, at this stage, descriptively it seems that VO_2 peak improves slightly on average with only a small difference between conditions for this change and the same seems to be the case for strength. Time to exhaustion, however, though improving for both conditions has clearly increased to a greater degree in the "cardio" condition. Although training was performed with a recumbent cycle ergometer and testing was on an upright cycle ergometer, there was sufficient transfer with respect to the specificity of motor tasks that improved time to exhaustion independently of VO_2 peak. Lastly, and likely reflective of the inherent noise in the measures, or individual variation in response, quadriceps muscle thickness did not clearly change for either condition and the average changes seen so far fall within the technical error of measurement for our lab (0.14 cm).

[1]Note, data has been reanalyzed using JASP (version 0.9.1, University of Amsterdam, Netherlands) for this study with ANCOVA for the change in outcome (post-minus pre-scores) using pre-scores as covariates.

[2]Note, one participant did not complete post testing for VO_2 peak and time to exhaustion due to illness and so $N = 7$ for these outcomes.

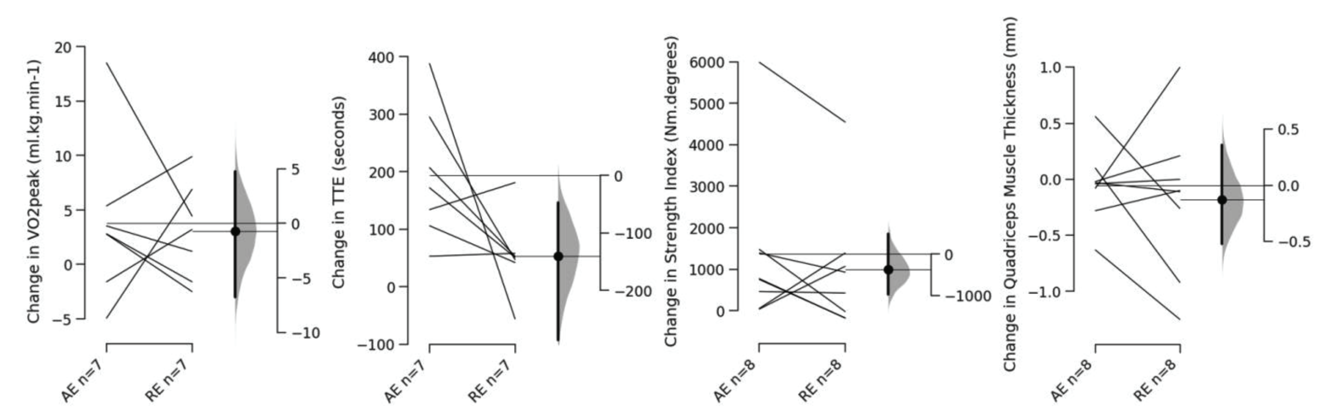

FIGURE 1 | From left to right, individual responses and paired comparisons (floating axis showing mean difference with 95% confidence intervals) for change in VO_2 peak, time to exhaustion during progressive ramp unilateral cycle test, isometric knee extension strength index (area under torque curve), and quadriceps muscle thickness; AE, Aerobic Exercise/"Cardio" Group; RE, Resistance Training Group.

A between-group training intervention study completed by Silva et al. (2019) was conducted in trained males (with a minimum of 6 months prior resistance training experience) and using either resistance training on a leg press (4 × ~10–12 repetitions to momentary failure at concentric to eccentric 1 s:2 s repetition duration ratio) or "cardio" training on an upright cycle ergometer (4 × 30 s sprints). Outcomes included strength measured using knee extension 10RM, VO_2peak measured using a maximal incremental treadmill protocol, and body composition measures of the legs using dual X-ray densitometry (DXA). Analysis using ANCOVA with baseline values as covariates revealed no statistically significant between group differences ($F_{(1,22)} = 0.261$, $p = 0.614$) for change in strength with improvements in both the leg press group [estimated marginal mean (95% CIs) Δ = 10.1 kg (6.9 to 13.3)] and cycle ergometer group [estimated marginal mean (95% CIs) Δ = 9.1 kg (6.1 to 12.2)]. There were also no statistically significant between-group differences for changes in total leg mass ($F_{(1,22)} = 1.589$, $p = 0.221$), leg lean mass ($F_{(1,22)} = 0.491$, $p = 0.491$), or leg fat mass ($F_{(1,22)} = 1.238$, $p = 0.278$) and changes within-groups were negligible. For changes in VO_2peak, however, there was a statistically significant between-group difference ($F_{(1,22)} = 5.926$, $p = 0.023$) revealing greater increase for the cycle ergometer group [estimated marginal mean (95% CIs) Δ = 5.66 ml.kg.min^{-1} (2.63 to 8.68)] compared with the leg press group [estimated marginal mean (95% CIs) Δ = 1.23 ml.kg.min^{-1} (−1.92 to 4.38)]. Considering the different training and testing modality, this change is interesting and contradicts results reported by others regarding changes in cardiorespiratory fitness measured with a range of tests and using effort matched protocols (Álvarez et al., 2017; Gil-Sotomayor et al., 2018), including those in trained populations (Androulakis-Korakakis et al., 2018). However, the study by Silva et al. (2019) there was considerable variation in maximal criteria from the incremental treadmill protocol with none of the participants reaching a respiratory exchange ratio >1.15 and also a number of participants showing differences in end of test max heart rate (>10 beats.min^{-1}) between pre- and post-tests suggesting that truly maximal efforts may not have occurred. In contrast, all participants that have been tested so far by Armes et al. (unpublished) have met maximal criteria for the incremental exercise test (RER >1.15, hear rate ± 10 beats. min^{-1} of age predicted max, Borg scale rating of 20, and blood lactate >8 mmol.L^{-1}).

Considering the pattern of findings from this emerging body of research, there does seem to be evidence supporting the hypothesis of physiological adaptations and responses being primarily determined by effort, and less influenced by modality. In fact, random effects meta-analysis[3] comparing effect sizes between "cardio" and resistance training modalities for 4 of the studies discussed above (Álvarez et al., 2017; Androulakis-Korakakis et al., 2018; Silva et al., 2019; Armes et al., unpublished) seem to support that presently there is little evidence suggesting a difference between modalities when effort is controlled for. For strength, the effect size favored resistance training with a small effect (though this was not significant with the robust estimate) though with moderate precision for the estimate (**Figure 2**) and trivially for changes in cardiorespiratory fitness measures in "cardio" training (**Figure 3**). This is an emerging area and despite the similarity of findings across studies there is clearly further work required to approach a more precise understanding of the differences, or lack thereof, in adaptations produced by different yet effort matched modalities. However, the potential implications of what we understand so far are discussed below. For now, we briefly look to other considerations often overlooked in research considering exercise countermeasures to μG-induced deconditioning.

[3]Performed using the "metafor" package in R (version 3.5.1; R Core Development Team, https://www.r-project.org/) and an alpha of 0.05 considered in all tests. Between group effect sizes using Cohen's *d* were calculated for differences between groups in change scores, and pooled change score standard deviations used as the denominator (Morris, 2007; Borenstein et al., 2009; Dankel and Loenneke, 2018). The study of Gil-Sotomayor et al. (2018) was not included due to data on variance being unavailable. Because of the 4 strength outcomes used in Álvarez et al. (2017) a multilevel mixed effects meta-analysis was performed for strength changes with cluster robust variance estimation. ES for *d* were interpreted with reference to Cohen's (1988) thresholds; trivial (<0.2) small (0.2 to <0.5), moderate (0.5 to <0.8), and large (>0.8) and positive ES values indicated higher scores of the outcome in favor of the resistance training group.

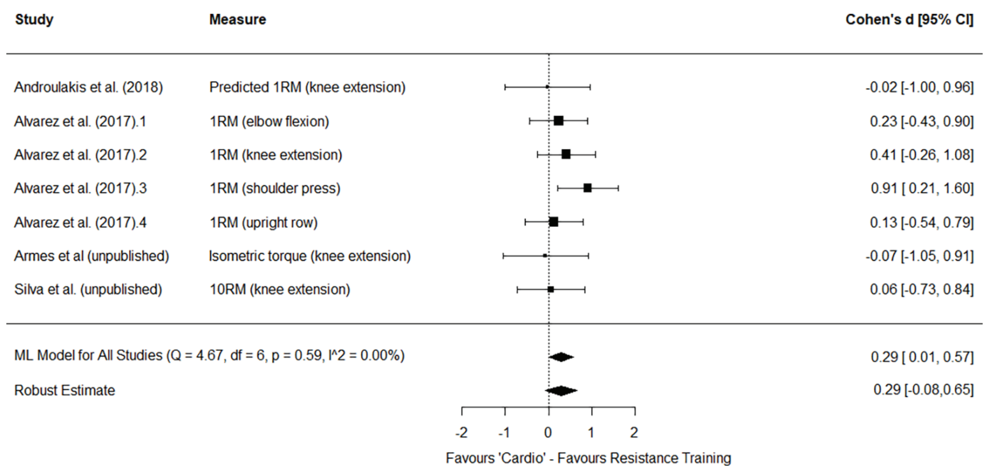

FIGURE 2 | Forest plot for multilevel (ML) mixed effects meta-analysis of strength outcomes from studies using effort matched designs to compare "cardio" and resistance training modalities.

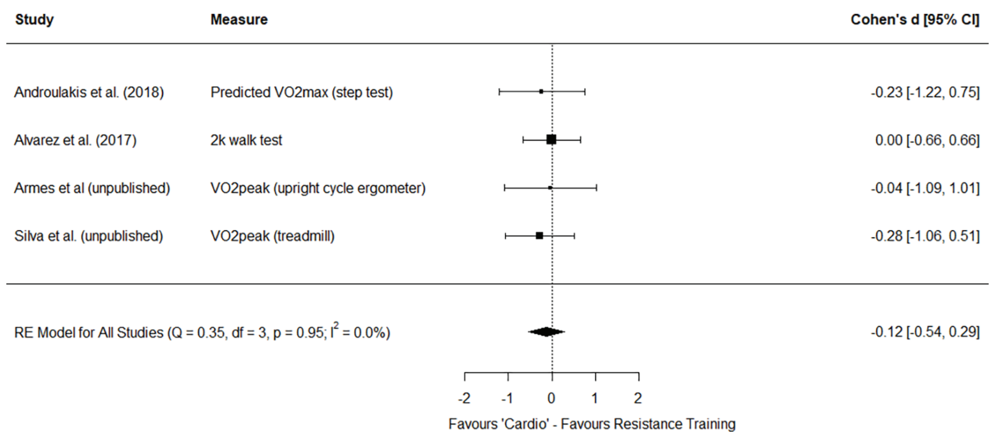

FIGURE 3 | Forest plot for random effects (RE) meta-analysis of cardiorespiratory fitness outcomes from studies using effort matched designs to compare "cardio" and resistance training modalities.

OTHER CONSIDERATIONS: O_2 CONSUMPTION, CO_2 PRODUCTION, AND ENERGY COSTS

Factors which are often underappreciated when considering exercise countermeasures for μG-induced deconditioning are that, compared to rest, exercise increases O_2 consumption, CO_2 production, and energy costs. Combined, the former two mean that more O_2 needs to be produced *via* electrolysis and additional CO_2 need to be removed. Furthermore, the additional energy expenditure from exercise requires that additional resources are necessary to replenish that energy used by the astronauts (i.e., food rations). This is particularly noteworthy since data shows an increased energy requirement (1.4 × resting metabolic rate) through elevations in basal metabolic rate in both simulated (Acheson et al., 1995), and μG environments (Stein et al., 1999). As such, it is of interest to consider the effects of "cardio" and resistance training upon O_2 consumption, CO_2 production, and energy costs. However, there is little research specifically examining this area, especially that which has controlled for effort and duration of exercise to examine the effects of modality. Work matched comparisons of different resistance training approaches (circuit style or traditional consecutive sets) show that O_2 consumption (aerobic energy expenditure during exercise and rest interval) and total energy expenditure is similar (Aniceto et al., 2013). Although, it is noteworthy that anaerobic energy expenditure estimated from production of blood lactate was higher in consecutive sets compared with circuit style of resistance training suggesting CO_2 production may be higher (Aniceto et al., 2013). Thus, other technical elements of how resistance training protocols are manipulated may be important to consider. For example, consecutive sets of resistance training when performed not to momentary failure likely results in increasing effort with each set due to residual fatigue. Though it would seem that effort may be an important factor impacting the similarity of responses and adaptations to different exercise modalities. Scott and Earnest (2011) have shown that aerobic, anaerobic, and recovery energy expenditures are all higher with resistance training performed to momentary failure even when work is matched. As noted earlier, it appears that O_2 consumption, CO_2 production, and energy costs are more a function of the intensity of effort of exercise as opposed to the modality.

DISCUSSION AND SUGGESTIONS FOR POTENTIAL RESEARCH AND SOLUTIONS

Though currently there is limited research examining the role of modality of exercise, what has been conducted is suggestive of greater similarity in the physiological responses and adaptations between "cardio" and resistance training than historical dichotomies would predict, assuming effort and duration are matched. Considering this, the prevailing use of concurrent training modalities on the ISS to counter μG-induced deconditioning of physiological systems may be unnecessary. Indeed, of interest is that similar changes can occur even in well-trained participants as reported by Androulakis-Korakakis et al. (2018) and found by Silva et al. (2019) despite the fact that the adaptive response to exercise is attenuated in trained persons. Astronauts undergo considerable physical preparation prior to entering μG environments and then subsequently experience deconditioning akin to that which might occur from a period of detraining. Periods of detraining have been shown to restore sensitivity of anabolic signaling pathways in skeletal muscle (Ogasawara et al., 2013). Thus, considering the similar responses reported in both trained (Androulakis-Korakakis et al., 2018; Silva et al., 2019) and also untrained populations (Álvarez et al., 2017; Gil-Sotomayor et al., 2018) it seems reasonable to speculate that single modality approaches to counter μG-induced deconditioning might be appropriate. This could potentially halve the time required by astronauts for engagement in training as a countermeasure and potentially have concurrent impact on reducing volume of space taken up by equipment, as well as reducing O_2 consumption, CO_2 production and energy use by the astronauts in addition to heat production and energy use from exercise devices themselves.

In this sense, it could also be argued that either "cardio" or resistance training approaches might therefore be chosen as the preferred modality, though we would argue that resistance training approaches in general include further benefits over and above "cardio" based approaches which we discuss below. As noted, the choice of a single modality may solve issues of time, volume of space, and energy use/heat production. Moreover, resistance training in contrast to "cardio" approaches can be performed in a manner that better addresses these issues. For example, isometric resistance training has been shown to require lower VO_2 consumption and energy cost compared with dynamic forms (Scott et al., 2015). It can also be performed without the need for external devices ("just" proper fixation in the spacecraft is needed in most exercises). Isometric resistance training can also be performed using contralateral limb provided resistance (i.e., using one limb to resist the movement of the other) which can elicit similar electromyographical activity as traditional free weight training (Fisher et al., 2016c). Maximal isometric co-contraction approaches have also been examined and found to be effective for upper limb (Maeo et al., 2014a,b) and trunk and hip musculature (Tayashiki et al., 2016), though may be potentially less effective for the lower limbs (Maeo and Kaneshisa, 2014). There may be some concerns with the use of isometrics for countering μG deconditioning. Haddad et al. (2006) suggested that their use did not counteract the downregulation of anabolic signaling that occurred from short term unloading, though follow up research from their lab found that, assuming sufficient volume of exercise is performed, signaling is similar independent of muscle action (Garma et al., 2007). This being said, early work has suggested that adaptations to contractile kinetics may differ between isometric and concentric resistance training (Duchateau and Hainaut, 1984) and so perhaps a combination of the two may be best. Other examinations of "no load" resistance training have been reported showing that dynamic movement coupled with maximal voluntary effort to activate the muscle involved produces high electromyographical activity independent of training status, limb dominance, movement velocity, or the use of visual feedback (Gentil et al., 2017), and such training has been shown to produce similar increases in muscle size and strength compared to traditional dynamic free weight training (Counts et al., 2016). In addition, there are more simple approaches to providing external resistance for dynamic resistance training compared to those primarily used in current μG environments. For example, partner assisted manual resistance training has been shown to be similarly effective to more traditional approaches (Dorgo et al., 2009), however, at least for missions to the ISS where crew time is critical and their schedule is often constrained, this training regimen may be less favorable. Also, a simple self-powered rope trainer has been examined for possible use in μG environments and shown to be equally effective in increasing strength as traditional free weight resistance training (Behringer et al., 2016). Further, even when performed using minimal doses (twice a week using 3 multi-joint exercises performed for two sets to a rating of perceived effort of 8 out of 10, where 10 would be the point of momentary failure), elastic resistance bands have been shown to produce similar strength changes to traditional free weight or machine-based resistance training (Souza et al., 2019).

Thus, there may be the potential to employ resistance training based approaches alone and in such a way where the equipment requirements are further reduced. However, were future research to examine and validate resistance training as an effective single modality in μG analog studies, for it to be considered appropriate as the single modality approach for space missions, other aspects need also to be taken into consideration. We have focused here upon cardiorespiratory fitness, strength, and muscle size as they have been the primary outcomes for terrestrial comparative studies. However, specific performance levels for certain tasks would likely be needed to maintain the ability to perform these specific motor patterns. Without inclusion of at least some walking/running there may be a potential injury risk due to altered gait/running patterns, and vice versa, were only a single "cardio" modality approach used there may be problems in lifting/carrying objects on the surface of Mars. Of course, it should be noted that at present, research is limited and further evidence would likely be required to conclusively suggest a single modality as being sufficient. Further, the suggested approaches mentioned specifically for application of resistance training have not been examined in direct comparison to "cardio" based modalities. There is scope for this research to be conducted and we feel should be encouraged for future μG analogs such as bed rest studies. In most of the studies cited above though, maximal or near-maximal efforts were employed and in many cases novel resistance training techniques were compared to traditional free weight based resistance training. In combination with the similar positive results between different resistance training approaches when effort is matched, along with the emerging evidence suggesting "cardio" and resistance training modalities may produce similar adaptations if effort is matched, we pose the hypothesis that adaptations to exercise-induced loading may be more influenced by the manner in which they are performed, primarily the effort put forth, as opposed to the nature of the specific modality utilized. This may result from the similar physiological stimulus experienced when effort is matched. Indeed, as noted effort may be intrinsically linked to motor unit recruitment for performance of physical tasks. However, it should be noted that some work has suggested that, at least at very low efforts (i.e., postural support from m. soleus and m. gastrocnemius during "dry immersion" involving <7% of maximal voluntary force) motor unit recruitment order may be altered with μG exposure (Shiqueva et al., 2015). Whether this would be the case under higher effort exercise conditions in μG is less clear. As such, though we feel there is considerable scope for lessons learned from traditional terrestrial exercise science studies about effort-based paradigms for exercise-induced skeletal muscle loading to be applied to μG analogs and environments, there remains the need to examine the effects of them both acutely and chronically in these settings.

We reiterate here that resistance training and "cardio" training do not reflect the entirety of possible approaches to exercise countermeasures, nor are cardiorespiratory fitness, strength, power, and muscle size the only outcomes that might be of interest when discussing the deconditioning that occurs in response to μG environments. However, this review presents emerging evidence from terrestrial setting that, where effort and duration are matched, both resistance training and "cardio" training may produce largely similar physiological responses and adaptations. These recent advances in understanding of exercise response from terrestrial studies should be considered as candidates for further research within μG analogs and for a wider range of outcome measures as a step toward their consideration for implementation into true μG settings.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

JS and PG contributed to conception and design of the review. JS performed the statistical analysis and wrote the first draft of the manuscript. PA-K, CP, JF, PG, CS, and AR wrote sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

FUNDING

PG is supported by a Research Grant from CNPq (304435/2018-0).

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Conflict of Interest Statement: 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 Physiology

OPINION
published: 02 October 2019
doi: 10.3389/fphys.2019.01266

High-Intensity Exercise With Blood Flow Restriction or in Hypoxia as Valuable Spaceflight Countermeasures?

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Keywords: BFR, altitude, vascular, perfusion, blood volume, occlusion

OPEN ACCESS

Edited by:
Tobias Weber, European Space Agency (ESA), France

Reviewed by:
Satoshi Iwase, Aichi Medical University, Japan
Jochen Zange, Helmholtz Association of German Research Centers (HZ), Germany

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Specialty section:
This article was submitted to Environmental, Aviation and Space Physiology, a section of the journal Frontiers in Physiology

Received: *20 June 2019*
Accepted: *19 September 2019*
Published: *02 October 2019*

Citation:
Willis SJ, Borrani F and Millet GP (2019) High-Intensity Exercise With Blood Flow Restriction or in Hypoxia as Valuable Spaceflight Countermeasures? Front. Physiol. 10:1266. doi: 10.3389/fphys.2019.01266

INTRODUCTION

Determining effective countermeasures to the physical issues of microgravity, radiation, and isolation (i.e., decreased aerobic capacity and cardiovascular dysfunction, along with muscle atrophy, bone and muscle loss, and hypocapnia) is crucial for human space flights (Demontis et al., 2017). Since the initial Apollo Program (1961–1972), there is still a great challenge in determining and replicating the most efficient exercise countermeasures mainly due to restricted time, habitable volume, and maintenance of the life support systems (Scott et al., 2019). Additionally, risks of pressure loss in the space habitat and thus compression sickness together with a hypoxic environment must be considered and should be combated through acclimatization and sufficient training/preparation (Lewis, 2018; Millet, in press). When considering time restrictions for spaceflight preparation, in-flight exercise time, and access for exercise, combining exercise methods for rapid adaptation appears paramount.

The hypoxic stimulus is an important consideration for spaceflight (Bodkin et al., 2006) and requires an effective pre-acclimatization. A balance is needed between the barometric conditions of the habitat and the safety threshold of oxygen concentrations due to flammability. In this context, it is applicable to incorporate hypoxic training methods for acclimation with preference of hypobaric hypoxia (decreased barometric pressure and oxygen fraction) over normobaric hypoxia due to the risks associated with excessive oxygen in the atmosphere of the space habitat (Millet, in press). It has been shown that passive hypoxic exposure leads to negligible adaptations in skeletal muscle tissue (Lundby et al., 2009), while the combination of prolonged passive exposure to hypoxia with exercise, specifically high-intensity exercise (Live High-Train Low and High, LHTLH) induces beneficial transcriptional responses, which are not present with passive exposure only (i.e., traditional "Live High-Train Low" training method) (Brocherie et al., 2018). Among the specific responses associated to LHTLH, there are increased mRNA levels in the vastus lateralis involved in oxygen signaling, oxygen carrier, mitochondrial biogenesis, and metabolism (Brocherie et al., 2018), as well as positive functional adaptations as shown by the improved oxidative capacity in type I and type II fibers, while maintaining fiber size (van der Zwaard et al., 2018). During acute hypoxic exposure, the lowered oxygen delivery induces a lower aerobic performance (Lundby et al., 2009; Slivka, 2017). Though exercise helps to protect skeletal muscle from these declines, there is an upregulation of the VEGF and glycolytic genes (amongst hundreds of others) through the HIF-1 oxygen-sensing pathway. Moreover, chronic exposure to hypoxia leads to improved mitochondrial and capillary density and enhanced oxidative capacity (Lundby et al., 2009; Slivka, 2017). Altogether, the combinations of passive hypoxic exposure as experienced during space flights and high-intensity exercise in hypoxia appear as adequate strategies for improving peak power production and maximal oxygen consumption.

HIGH-INTENSITY EXERCISE WITH SYSTEMIC HYPOXIA

The effect of combining high-intensity exercise with systemic hypoxia elicits greater muscle perfusion and oxygenation (Brocherie et al., 2017) along with enhanced muscle transcriptional responses of the vastus lateralis when compared to normoxia (Faiss et al., 2013; Brocherie et al., 2018). Specifically, these researchers identified molecular adaptations which improve oxygen signaling (HIF-1α), oxygen carrying (Mb), and pH regulation (CA3) via upregulation of genes, along with downregulation of genes involved in mitochondrial biogenesis (TFAM and PGC-1α). These alterations suggest improved anaerobic glycolytic activity of the muscle (Faiss et al., 2013) and improved fast-twitch fiber recruitment in the vastus lateralis after repeated sprint training in hypoxia (McDonough et al., 2005), particularly by compensatory vasodilation and increased rate of phosphocreatine resynthesis (Hoppeler and Vogt, 2001; Zoll et al., 2006) which are linked to performance enhancement. It is important to consider that not all muscles react in similar ways regarding growth, atrophy, and their response to hypoxic conditions, as they are highly influenced by changes in perfusion pressure (Fitzpatrick et al., 1996). As such, any decrease in perfusion pressure across a physiological range to the contracting muscles results in an increase in muscle activation to maintain a constant force output (Fitzpatrick et al., 1996). Furthermore, vascular adaptations occur after maximal intensity training in hypoxia through increased changes in blood perfusion (via changes in total hemoglobin) and contribute to the delay of fatigue in both the lower (Faiss et al., 2013) and upper body (Faiss et al., 2014) (vastus lateralis and triceps brachii, respectively). During high-intensity exercise in hypoxia, there are great stresses placed on oxygen transport and the vascular system. Due to the reduced oxygen availability in the environment, vasodilation occurs to increase blood flow to the muscle tissue and maintain oxygen delivery. Additionally, the increased changes in blood perfusion due to the combination of high-intensity and hypoxic stress may be a stimulus for altering vascular blood flow regulation due to neural, metabolic, and mechanical influences. Of interest is that short blocks (i.e., as little as 4–8 repeated sprint training sessions in hypoxia), led to improved performance for elite athletes in different sports as cycling (Faiss et al., 2013), cross-country skiing (Faiss et al., 2014), rugby (Beard et al., 2018, 2019), and tennis (Brechbuhl et al., 2018). To our knowledge, there is no data available on the effects of such exercises in astronauts and other participants during spaceflights but one may speculate that performing high-intensity exercise training in hypoxia may be a valuable and practical method for exercise countermeasure during spaceflight missions.

BLOOD FLOW RESTRICTION

Other methods exist for inducing a hypoxic stimulus to muscles: The compression of the vasculature proximal to the skeletal muscle results in inadequate oxygen supply (hypoxia) within the muscle tissue (Patterson et al., 2019). Rather than reducing the oxygen in the atmospheric environment on a systemic level, hypoxia can occur on a local level when an external pressure is applied to the limbs to create partial restriction of blood flow (blood flow restriction, BFR). In this manner, the vascular occlusion (or ischemia) diminishes blood flow by vascular resistance and venous return is substantially limited (Kaijser et al., 1990). BFR has been shown to upregulate the mRNA expression in the vastus lateralis of the vascular endothelial growth factor (VEGF and VEGFR-2) along with HIF-1α and eNOS, suggesting angiogenesis due to the increased stimuli of ischemic and shear stress during low-load resistance exercise (Scott et al., 2014; Taylor et al., 2016; Ferguson et al., 2018). The AMPK pathway is responsible for regulating energy metabolism where kinases are activated in response to stresses that deplete ATP including those of hypoxia and ischemia. This pathway activates catabolism while suppressing synthesis, leading to imbalanced energy metabolism. Further, reactive oxygen species (ROS) production is increased in these conditions due to high levels of metabolic stress and leads to an unbalanced oxidative status. Furthermore, the lower partial pressure of oxygen during BFR exercise limits the amount of ROS production at least acutely, lowering the mitochondrial H_2O_2 emission rates and electron leak to ROS (Petrick et al., 2019). The knowledge of the mechanisms and adaptations are limited during continuous exercise training with BFR. With low-intensity exercise of about 40% VO_{2max}, BFR has shown to increase strength and hypertrophy (Slysz et al., 2016; Conceicao et al., 2019), in both walking (Abe et al., 2006) and leg-cycling exercise (Abe et al., 2010; Conceicao et al., 2019) in as early as 3 weeks (Abe et al., 2006) and with greatest effectiveness after ≥6 weeks of training (Slysz et al., 2016). Furthermore, BFR training during low-intensity walking and leg-cycling has been shown to increase strength as well as aerobic capacity in young (Slysz et al., 2016), old (Abe et al., 2010), and trained participants (Park et al., 2010). Moreover, the use of BFR techniques are important to consider as a method to counteract muscle degeneration and sarcopenia over a range of passive, resistance training, and continuous exercise protocols (Patterson et al., 2019). BFR provides a potent, gravitational-like stimulus on the cardiovascular system and may counteract the orthostatic intolerance upon return to Earth (Iida et al., 2007; Nakajima et al., 2008). Research has demonstrated that BFR was similar regarding physiological and hemodynamic responses to lower body negative pressure (LBNP) eliciting blood pooling in the lower limbs, reduced venous return, and hemodynamic responses of decreased stroke volume, increased cardiac output, and increased total peripheral resistance as similar to LBNP (Stevens and Lamb, 1965; Tomaselli et al., 1987; Lathers and Charles, 1993). Researchers suggested that the use of bilateral thigh BFR likely partially simulates the hemodynamic, systemic cardiovascular, autonomic nervous, and hormonal effects of orthostasis as seen during simulated weightlessness (Nakajima et al., 2008). Additionally suggesting that BFR training may provide an appropriate countermeasure to combat the associated declines in atrophy associated with weightlessness (Nakajima et al., 2008). Further, the altered hemodynamic and chemical/metabolic signals during BFR exercise (Ferguson et al., 2018) likely effect the improvement in vascular function through remodeling of the arterial lumen, which contributes to the cardio-protective effects of exercise (Thijssen et al., 2012). Additionally, the magnitude and location (conduit, resistance, capillary vessel) of the vascular adaptations depend on the intensity, volume of exposure, and mode of training (Green et al., 2011). Indeed, when combining BFR and/or systemic hypoxia with high-intensity exercise, a robust stimulus is placed on the vascular mechanisms (Willis et al., 2018, 2019a,b). These different methods of systemic and local hypoxia along with the differing underlying mechanisms (metabolic vasodilation and vascular resistance, respectively) can provide a great stimulus alone or in combination to alter vascular conductance and blood flow regulation.

HIGH-INTENSITY EXERCISE WITH BLOOD FLOW RESTRICTION

In general, high-intensity exercise reduces tissue oxygen availability and therefore increases the oxygen extraction in order to maintain oxygen delivery (Granger and Shepherd, 1973). This is further challenged when high-intensity exercise is combined with hypoxia (Casey and Joyner, 2012). When high-intensity exercise is performed with BFR, in addition to a strong deoxygenation due to the localized hypoxia, there is a larger increase in the changes in blood perfusion in both legs and arms (vastus lateralis and biceps brachii, respectively) (Willis et al., 2018, 2019b). High-intensity exercise with BFR is able to create a potent stimulus via vascular resistance and altered vasodilatory responses, and was shown to be more robust than with systemic hypoxia in both legs and arms (Peyrard et al., 2019; Willis et al., 2019a,b). In fact, during high-intensity exercise with a certain level of BFR, an additional stimulus of systemic hypoxia is likely blunted (Willis et al., 2019a). At this moment, the mechanisms of the interaction between hypertrophic, hypoxic, and vascular adaptations remain elusive. Though studies have not yet been conducted in a microgravity environment, incorporating these methods of hypoxia and BFR during high-intensity exercise elicits responses that are likely beneficial to improve the physical capacities, since deconditioning and muscle atrophy, are present during spaceflight missions.

PRACTICAL APPLICATIONS TO SPACEFLIGHT PARTICIPANTS

Incorporating high-intensity exercise training in hypoxia with legs or arms is beneficial for improving performance and delaying fatigue by way of adaptations to improve muscle oxygenation, specifically of the vastus lateralis and triceps brachii (Faiss et al., 2013, 2014). Furthermore, acutely performing high-intensity exercise with BFR elicits greater reactivity regarding changes in blood volume and oxygenation than with systemic hypoxia alone in both the legs and arms (vastus lateralis and biceps brachii, respectively) (Willis et al., 2018, 2019b), with a greater effect in the arms (Willis et al., 2019a). Altogether, utilizing these training methods is beneficial for increasing the efficiency of blood and oxygen transport allowing increased vascular proficiency. The implementation of short training blocks can be valuable to induce a rapid and robust stimulus in a short time frame, thus providing a time-saving strategy and effective method for adaptations to occur. While the optimal stimulus depends on the population of interest, suggested training recommendations are as follows. The high-intensity exercise protocol should last ∼60 min including the warm-up and cool-down periods and be performed 2–3 times a week during blocks of training (2–5 weeks duration) as part of a periodized training program. During each session, the athlete performs a series of 3–4 sets of 4–7 maximal to supra-maximal "all-out" sprints (4–15s duration) in hypoxia (3,000–3,800 m and 14.2–12.8% FiO_2) and/or with BFR of about 45% of total occlusion pressure. It is important to achieve a specific sprint-to-rest ratio of 1:2–1:4 with inter-set recovery about 3–5 min without occlusion. This training has been successful in inducing adaptations in hypoxic conditions as shown by many researchers (Brocherie et al., 2017). This specific training should be performed in alteration with low-intensity exercise to maintain and develop basic fitness along with aerobic metabolism.

CONCLUSION

Performing high-intensity exercise with BFR or hypoxia are promising training methods for both legs and arms in order to increase physical conditions prior to, during, and after returning from spaceflight missions. This training may rapidly induce vascular adaptations and allow for combined metabolic and hypertrophic effects to counteract the decreased aerobic capacity and muscle atrophy occurring with microgravity, and allow adaptations to occur which may enhance endothelial function and lead to improved tissue oxygenation. Altogether, high-intensity exercise with BFR or in the hypoxic condition of the space vehicle should be considered as a practical, efficient, time effective, and influential countermeasure for space travelers.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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