POST-EXERCISE HYPOTENSION: CLINICAL APPLICATIONS AND POTENTIAL MECHANISMS

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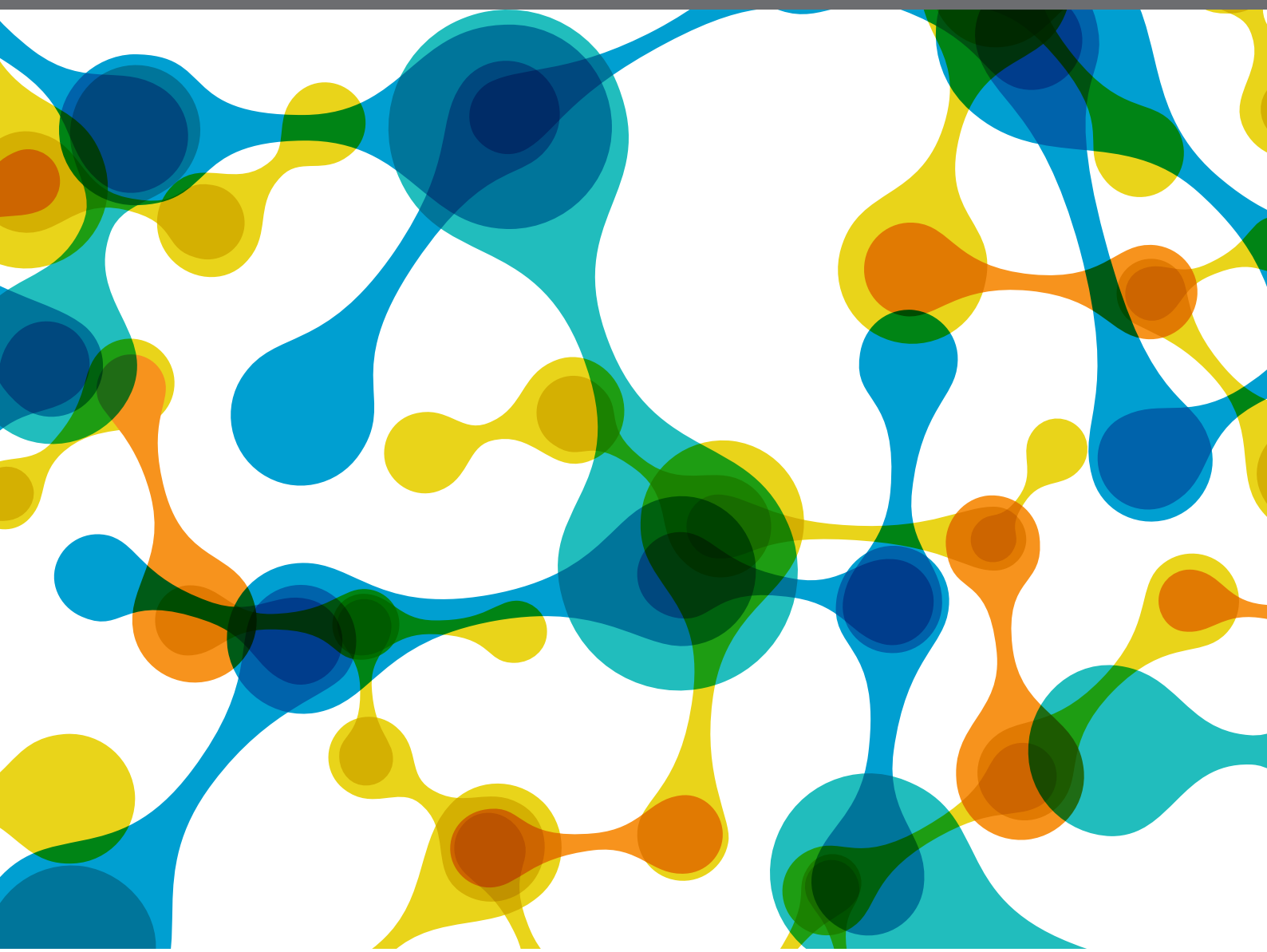

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POST-EXERCISE HYPOTENSION: CLINICAL APPLICATIONS AND POTENTIAL MECHANISMS

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EDITORIAL
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Editorial: Post-Exercise Hypotension: Clinical Applications and Potential Mechanisms

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Keywords: exercise training, exercise physiology, hypertension, physical activity, health

Editorial on the Research Topic

Post-Exercise Hypotension: Clinical Applications and Potential Mechanisms

Professional organizations worldwide recommend exercise training as an essential lifestyle strategy to prevent, treat, and manage elevated blood pressure (BP) (Physical Activity Guidelines Advisory Committee, 2018). Overall, BP reductions of 5–8 mmHg result from exercise training (Day et al.). Additionally, there is evidence that single bouts of exercise can reduce BP compared to control values. This physiological response is termed *postexercise hypotension* (PEH). The known clinical implications of PEH include:

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1) PEH occurs immediately in individuals across all levels of physical fitness (Brito et al., 2018);
2) PEH directly correlates with exercise intensity and probably volume (Eicher et al., 2010; Cunha et al., 2016; Fonseca et al., 2018; GjØvaag et al., 2020);
3) Those with the highest BP will experience the largest BP reductions (Pescatello et al., 2019);
4) PEH can persist for up to 24 h, particularly in individuals with elevated BP reducing the need for antihypertensive pharmacotherapy (Pescatello et al., 2019; Day et al.);
5) PEH correlates with the magnitude of BP reductions resulting from exercise training (Hecksteden et al., 2013; Kleinnibbelink et al., 2020) suggesting chronic BP reductions are largely due to PEH. Moreover, PEH may be an easy-to-use predictor for those who respond to exercise training as antihypertensive lifestyle therapy (Wegmann et al., 2018);
6) PEH can be used as a self-monitoring strategy to increase exercise adherence (Zaleski et al., 2019).

The purpose of this Research Topic is to expand upon the growing list of PEH benefits and to provide new evidence on the clinical applications and mechanisms underlying PEH, including the effects of different exercise modalities in different populations; mechanisms of PEH in individuals with normal/high BP; and factors optimizing the PEH response. Nine articles addressing those questions are included, four of them reviews and five original trials. We summarize their major contributions according to the subject categories.

- Methodological Quality of PEH studies

A potential source of bias in PEH studies is the inter-individual variability of the BP responses. Fecchio et al. addressed this question by investigating the inter-individual variation of BP after

acute dynamic resistance exercise. PEH showed considerable inter-individual variation and multivariate analyses revealed a greater importance of exercise volume than intensity to optimise the BP reductions.

Day et al. developed an evaluation checklist for PEH studies (PEH√list) based upon contemporary methodological quality standards. The PEH√list contains 38 items divided by sample, study, and intervention characteristics. The authors then conducted a systematic review of aerobic exercise PEH studies and applied the PEH√list. Overall, the items were not well satisfied; especially those with potential confounding effects on PEH. The instrument provides methodological guidance for researchers in future PEH studies.

- PEH response in different populations and associated mechanisms

Barros et al. investigated the effects of moderate intensity acute cycling on BP, arterial function, and heart rate variability in men living with HIV (MLHIV) under antiretroviral therapy. Acute exercise induced PEH in healthy controls, but not in MLHIV. The authors attributed the attenuated PEH in MLHIV to a vascular dysfunction limiting vasodilation.

Iellamo et al. investigated PEH along with hemodynamic and arterial baroreflex mechanisms in patients with coronary artery disease and normal BP. Exercise sessions were 30-min bouts of stationary cycling and calisthenics. Systolic BP was reduced for 12 h *vs*. the non-exercise day, concomitant with a decrease in total peripheral resistance as associated mechanism.

Jarret et al. and coworkers investigated whether obesity modulated PEH after cycling in men with obesity and hypertension. They found the onset of PEH was delayed by an hour or so, however, the magnitude of PEH from 2–4 h postexercise was similar to reports in men without obesity but with hypertension.

The mini-review by Pellinger and Emhoff presented an interesting theoretical approach linking PEH with glucose metabolism. According to the authors, the glucose regulation after exercise might benefit from the sustained postexercise vasodilation often observed in PEH, due to increased macrovascular and microvascular perfusion. This possibility highlights PEH as a desirable effect of regular exercise, particularly in patients with hypertension, diabetes, or metabolic syndrome.

- Effects of different exercise modalities on the PEH

Carpes et al. evaluated the effects of power training *vs*. a non-exercise control session on PEH, BP variability, and endothelial function among older adults with hypertension. BP reductions occurred in the first 60 min postexercise, particularly in men (−15/−7 mmHg *vs*. women), but not during the ambulatory assessment. There were no differences between sexes in BP-variability and endothelial function so the mechanism for these sex differences remain unclear.

Trindade et al. performed a meta-analysis comparing the BP changes after a session of water-based exercise *vs*. control conditions (land exercise or rest) in individuals with hypertension. PEH was most pronounced after aquatic exercise over the nighttime hours.

Marçal et al. performed a meta-analysis comparing the effects of high-intensity interval training (HIIT) and moderate-intensity continuous exercise (MICE) on PEH in individuals with normal and elevated BP. Both exercise protocols were effective in lowering office BP (1–2 mmHg; 30–60 min postexercise). PEH was greater after HIIT than MICE in the ambulatory monitoring over the daytime hours by 5.3/1.6 mmHg.

Overall, those studies reinforce the importance of the subject, expand upon current evidence, and indicate directions for future research:

1) The quality of PEH studies remains a major concern. The standardization of procedures, the inclusion of control comparisons, and the disclosure of baseline BP levels and methods of BP assessment will allow findings to be more trustworthy;
2) Various exercise modalities/protocols elicit PEH. However, confirmation trials investigating these and other modalities/protocols among a variety of populations (obesity, diabetes, heart disease, children, elderly, and paraplegic, etc.) are warranted;
3) The transient effect of acute exercise on BP reinforces that it should be preferably performed daily, but an optimal combination of volume/intensity to induce PEH remains to be determined;
4) A reduction in peripheral resistance seems to be a major determinant of PEH. However, research is needed to determine the relative role of central and peripheral mechanisms, and to clarify the interrelationships between hemodynamic and metabolic responses to acute exercise.

AUTHOR CONTRIBUTIONS

PF and LP drafted the Editorial. AC, RT, and AF critically revised the text and made substantial contributions to the final version.

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SYSTEMATIC REVIEW
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Post-exercise Hypotension Following a Single Bout of High Intensity Interval Exercise vs. a Single Bout of Moderate Intensity Continuous Exercise in Adults With or Without Hypertension: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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Background: Post-exercise hypotension (PEH) is an important tool in the daily management of patients with hypertension. Varying the exercise parameters is likely to change the blood pressure (BP) response following a bout of exercise. In recent years, high-intensity interval exercise (HIIE) has gained significant popularity in exercise-based prevention and rehabilitation of clinical populations. Yet, to date, it is not known whether a single session of HIIE maximizes PEH more than a bout of moderate-intensity continuous exercise (MICE).

Objective: To compare the effect of HIIE vs. MICE on PEH by means of a systematic review and meta-analysis.

Methods: A systematic search in the electronic databases MEDLINE, Embase, and SPORTDiscus was conducted from the earliest date available until February 24, 2020. Randomized clinical trials comparing the transient effect of a single bout of HIIE to MICE on office and/or ambulatory BP in humans (≥18 years) were included. Data were pooled using random effects models with summary data reported as weighted means and 95% confidence interval (CIs).

Results: Data from 14 trials were included, involving 18 comparisons between HIIE and MICE and 276 (193 males) participants. The immediate effects, measured as office BP at 30- and 60-min post-exercise, was similar for a bout of HIIE and MICE ($p > 0.05$ for systolic and diastolic BP). However, HIIE elicited a more pronounced BP reduction than MICE [(−5.3 mmHg (−7.3 to −3.3)/ −1.63 mmHg (−3.00 to −0.26)] during the

subsequent hours of ambulatory daytime monitoring. No differences were observed for ambulatory nighttime BP ($p > 0.05$).

Conclusion: HIIE promoted a larger PEH than MICE on ambulatory daytime BP. However, the number of studies was low, patients were mostly young to middle-aged individuals, and only a few studies included patients with hypertension. Therefore, there is a need for studies that involve older individuals with hypertension and use ambulatory BP monitoring to confirm HIIE's superiority as a safe BP lowering intervention in today's clinical practice.

Systematic Review Registration: PROSPERO (registration number: CRD42020171640).

Keywords: post-exercice, hypotension, high intensity interval exercise, systematic review & meta-analysis, office blood pressure, ambulatory blood pressure, moderate intensity aerobic exercise

INTRODUCTION

Hypertension remains the most important modifiable risk factor for cardiovascular morbidity and mortality (Forouzanfar et al., 2016). In international studies, the rate of elevated systolic blood pressure (BP) (≥110–115 and ≥140 mm Hg) increased substantially between 1990 and 2015, and disability-adjusted life years and deaths associated with elevated BP also increased (Forouzanfar et al., 2017). With the aging of the population, a further increase of 15–20% is expected worldwide (Williams et al., 2018).

To reduce the burden associated with hypertension, more emphasis on lifestyle changes is needed. Nowadays, all guidelines on BP management unequivocally recommend exercise as an important non-pharmacological therapy in the prevention, treatment, and control of high BP (Whelton et al., 2018; Williams et al., 2018; Hanssen et al., 2021). Preferably, exercise is performed on a daily basis, as it was previously shown that BP is significantly reduced following a single bout of exercise (Pescatello et al., 2004). If sustained and lasting long enough, this phenomenon-which is called post-exercise hypotension (PEH)-can play an important role in the daily management of hypertensive patients by transiently lowering their BP toward (more) normal values for a significant part of the day (MacDonald, 2002).

In line with pharmacokinetics of drug therapy, it might be expected that the occurrence and magnitude of PEH following a single bout or dose of exercise will depend on the exercise characteristics: i.e., type of exercise, volume, duration, or intensity of the session. Though, results on, for instance, the role of aerobic exercise intensity remains inconclusive. Pescatello and colleagues found PEH to be more pronounced in the first 5 h after a 40-min bout at moderate (60% of VO2max) vs. light intensity (40% of VO2max), though this difference disappeared when BP was measured over the full course of 9 h (Pescatello et al., 2004). In contrast, others found PEH to be larger after higher vs. lower intensity exercise bouts when PEH was evaluated by means of 24 h ambulatory BP monitoring (Quinn, 2000; Eicher et al., 2010). In recent years, growing evidence has shown that high-intensity interval training provokes superior health benefits compared to moderate-intensity continuous training in both healthy individuals and patients with established cardiovascular disease (Pattyn et al., 2014; Ito, 2019; Liu et al., 2019; Williams et al., 2019).

Contrary to these overall superior results, studies investigating the effect of high intensity interval training on BP have been less conclusive. A recent meta-analysis pooling data from seven trials (164 participants) found comparable reductions in office BP in adults with pre- to established hypertension following chronic high intensity interval training and moderate intensity continuous training (Costa et al., 2018). In line with this, similar changes in 24 h ambulatory BP (three studies, 93 participants) and measures of central arterial stiffness (13 studies, 395 participants) following 4–16 weeks of high intensity interval training or moderate intensity continuous training was found in another meta-analysis (Way et al., 2019). On the other hand, larger reductions in office diastolic BP, but not systolic BP, were reported after high intensity interval training in a meta-analysis of 15 studies including only patients with hypertension (Leal et al., 2020). However, whether a single bout of high intensity interval exercise (HIIE) affects PEH more than a bout of moderate intensity continuous exercise (MICE) remains to be determined as individual studies have been small and reported contradictory results (Tordi et al., 2010; Pimenta et al., 2019).

Therefore, the aim of this systematic review and meta-analysis was to assess the effect of a bout of HIIE vs. a bout of moderate intensity continuous exercise (MICE) on PEH in individuals with normal BP, pre-hypertension or hypertension.

METHODS

This systematic review was conducted and reported according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009). The study protocol was prospectively registered with PROSPERO (registration number: CRD42020171640).

Search Strategy

A systematic search was performed in three electronic databases (MEDLINE [OvidSP], Embase [OvidSP], and SPORTDiscus [EBSCOhost]) from their inception to February 24, 2020. The

search strategy included a combination of free text terms for the key concepts "blood pressure," "high intensity interval exercise," and "moderate intensity continuous exercise." The full search strategy for each database search is shown in **Supplementary File 1** in Supplementary Material. No language restrictions were imposed on the search.

Study Eligibility Criteria

Studies were included if they applied a randomized clinical trial design and were performed in humans (≥18 years) with an optimal BP, normal BP, high normal BP, or hypertension, and with no other concomitant disease. Trials should compare the effect of one single session of land-based HIIE vs. one single session of land-based MICE and report on office and/or ambulatory BP measured at least 30 min following the exercise bouts. Only data from full-text peer-reviewed publications were considered for inclusion. Exclusion criteria included any study not meeting all the criteria above.

Study Selection

Citations were imported into Rayyan, a specific electronic application for systematic review and meta-analysis (https://rayyan.qcri.org/welcome), and duplicates were identified and subsequently removed using the duplicate function. Then, two reviewers (I.R.M., K.F.G.) independently screened the titles and abstracts of all studies for eligibility. Then the full texts of all studies that met the inclusion criteria, or if there was uncertainty, were retrieved and reviewed by both reviewers. Disagreements between both reviewers were discussed with a third researcher (V.A.C) to obtain consensus. Reviewers were not blinded to the journal or authors. The rationale for excluding full-text articles was documented.

Data Extraction

A specific developed data extraction file was used by both authors (I.R.M., K.F.G.) to extract data on study source (authors, publication year, country of origin), study design, sample size, participant characteristics (mean age, sex distribution, hypertension status), exercise intervention characteristics (intensity, duration, mode), BP assessment method, BP outcomes, and outcomes related to BP regulating mechanisms. Discrepancies were resolved by consensus. Authors of 13 studies were contacted twice by e-mail over a 1-month period asking to provide missing data in cases of incomplete reporting. After 1 month, five authors provided more detailed information (Mourot et al., 2004; de Carvalho et al., 2014; Morales-palomo et al., 2017; Pimenta et al., 2019), two authors reported no access to the data (Scott et al., 2008; Lacombe et al., 2011), one author reported the lack of these data (Klein et al., 2019), and five authors did not reply.

Assessment of Study Quality

Two reviewers (I.R.M., K.F.G.) independently assessed the methodological quality by using the Cochrane Collaboration "risk of bias" tool (Review Manager 5.3). The Cochrane Risk of Bias Tool was slightly adapted to the study design and consisted of the following items: (i) random sequence generation, (ii) blinding of outcome assessment, (iii) incomplete outcome data for BP, (iv) eligibility criteria clearly described, (v) exercise intervention reproducible, (vi) point and variability measure reported for all BP measurements, and (vii) BP measured by automated device. Each criterion was rated by I.R.M. and K.F.G. as either "high risk," "low risk," or "unclear" risk of bias. In case of disagreement of rating, agreement was solved by mutual consensus. Studies were not excluded based on their quality.

Statistical Analyses

Statistical analyses were performed with Comprehensive Meta-Analysis software (CMA, version 2.2.064, Biostat, NJ, USA). The primary outcome measures were responses in office (30 and 60 min post-exercise) and ambulatory systolic and diastolic BP. Data expressed using the standard error of the mean (SEM) were first converted to standard deviation (SD) by the formula: $SD = SEM \times \sqrt{n}$. To compare the effects of single bouts of HIIE vs. MICE on office BP, we first calculated delta-score between post-exercise BP (at 30 or 60 min) and pre-exercise BP. Imputed study-level correlation coefficient for change from pre-intervention SD was set at a conservative estimate of 0.5 across all studies. For studies that compared two different HIIE study groups to a single MICE group, separate effect sizes were calculated for each comparison. To compare the effect of both exercise interventions on ambulatory BP we used the post intervention mean BP's following HIIE and MICE. Individual study results were then pooled using random-effect models with significance set at $p < 0.05$ (two-tailed). In addition, we also computed standardized mean difference (SMD), i.e., mean difference between the interventions divided by the pooled standard deviation. Descriptive data for each of the individual studies are reported as means ± standard deviations (SD); pooled effects are reported as mean weighted difference and its 95% confidence intervals (CI). I^2 statistics were calculated to provide an estimation of the degree of heterogeneity in effect among the studies. I^2 between 25 and 50% represents small amounts of inconsistency, whereas between 50 and 75% and above 75% represents medium to large amounts of inconsistency, respectively (Higgins and Thompson, 2002). Publication bias was examined by visual inspection of the different funnel plots' asymmetry. Duval and Tweedie's Trim and Fill procedure was applied to estimate the effect of publication bias on the results (Duval and Tweedie, 2000). In addition, small-study effect was investigated by regression of effect sizes and standard error of effect sizes as proposed by Egger et al. (1997). Finally, sensitivity analysis excluding selected trials which differed on a specific characteristic from the overall trials included in the analyses were performed to explore the robustness of results.

RESULTS

Study Selection

A PRISMA flow diagram of the literature search and selection is presented in **Figure 1**. The initial search identified 1994 potentially relevant studies of which 37 full text articles were assessed for eligibility. After screening of the full-text, 14 papers could be included

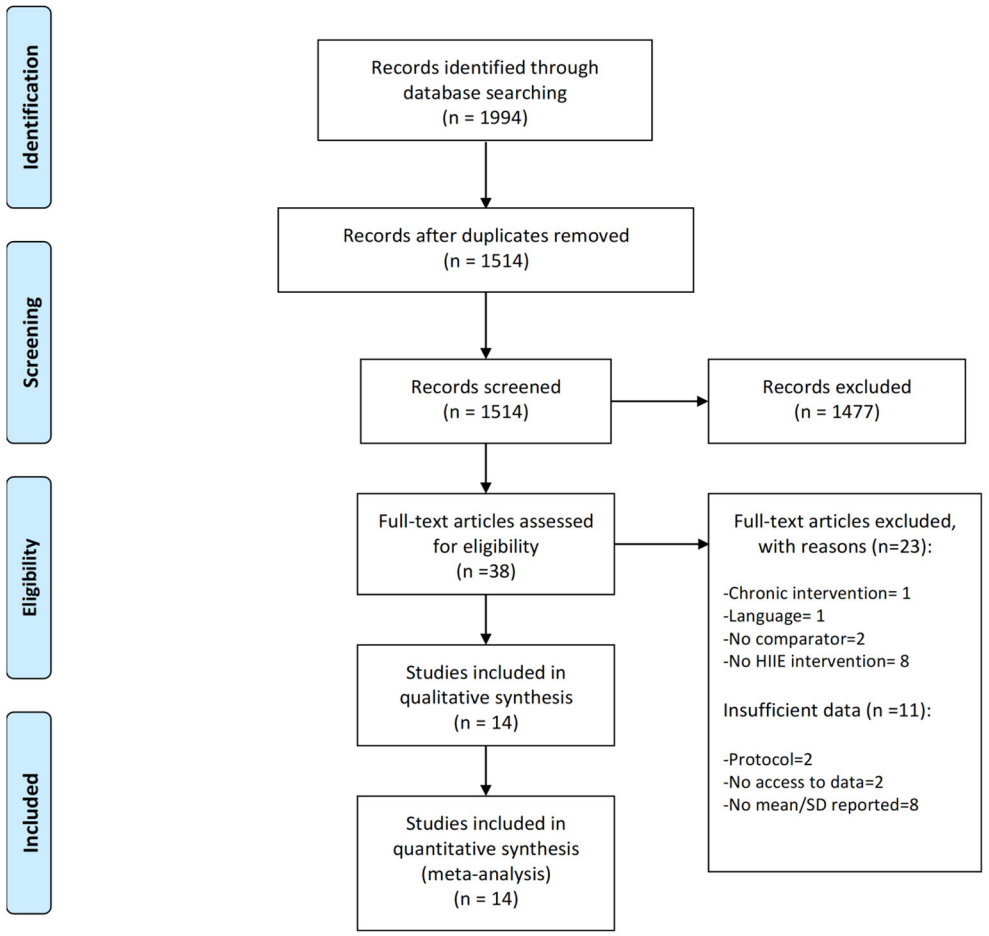

FIGURE 1 | Prisma flow diagram depicting the study selection process.

in the final meta-analysis. Three studies (Angadi et al., 2015; Morales-palomo et al., 2017; Ramirez-Jimenez et al., 2017) included multiple HIIE interventions or more than one patient group (i.e., a normotensive and hypertensive group). As a result, 18 comparisons were included in the final analysis.

Risk of Bias Within and Across Studies

The risk of bias is depicted in **Figure 2**. The kappa correlation showed a good overall agreement between both reviewers ($k = 0.656$; 95% CI 0.680–0.852; $p < 0.001$). Two studies did not report on the randomization sequence (Mourot et al., 2004; Tordi et al., 2010) and one study lacked a proper description of the eligibility criteria (Angadi et al., 2015). None of the studies explicitly stated that researchers were blinded, and all studies were thus classified as unclear for the risk "blinding of outcome assessment." Seven studies reported that office BP measurements were performed by an automated device (Rossow et al., 2009; Tordi et al., 2010; Angadi et al., 2015; Costa et al., 2016; Graham et al., 2016; Morales-palomo et al., 2017; Silva et al., 2018), and all four studies measuring ambulatory BP used an automated device (Ciolac et al., 2009; de Carvalho et al., 2014; Sosner et al., 2016; Ramirez-Jimenez et al., 2017). The remaining two studies used a manual device to measure office BP (Seeger et al., 2014; Pimenta et al., 2019) and one did not specify the device (de Carvalho et al., 2014). The intervention protocol of one study (Pimenta et al., 2019) was not sufficiently detailed to allow replication and was unclear in another study (Ramirez-Jimenez et al., 2017). All studies reported point and variability measures for BP and presented all BP data. As shown in **Supplementary File 2** in Supplementary Material, visual inspection of the funnel plots did not reveal any publication bias. Duval and Tweedie's correction model were applied to the overall sample for both systolic and diastolic office BP; no trimmed studies were observed.

Study and Participant Characteristics

Table 1 shows an overview of the study and participant characteristics. All studies were published between 2004 and 2019 and conducted in Brazil ($n = 5$) (Ciolac et al., 2009; de Carvalho et al., 2014; Costa et al., 2016; Silva et al., 2018; Pimenta et al., 2019), France ($n = 3$) (Mourot et al., 2004; Tordi et al., 2010; Sosner et al., 2016), Spain ($n = 2$) (Morales-palomo et al.,

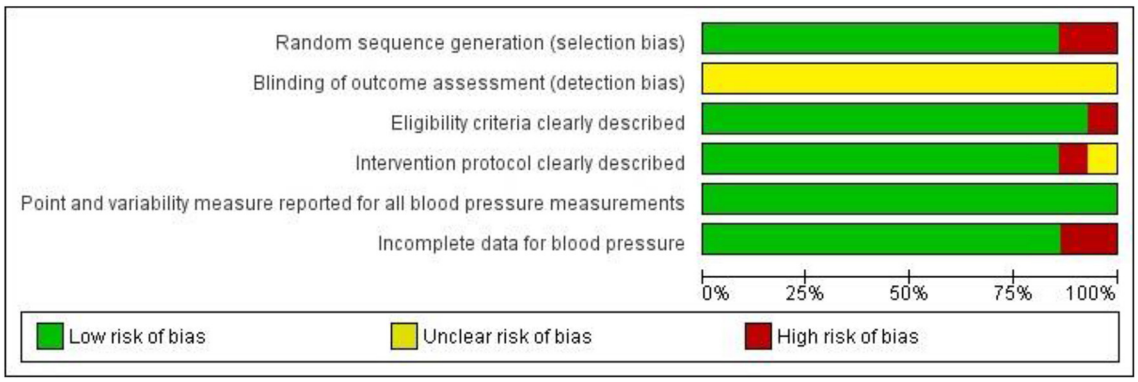

FIGURE 2 | Summary of risk of bias for each item presented as a percentage across all included studies.

2017; Ramirez-Jimenez et al., 2017), the United States ($n = 2$) (Rossow et al., 2009; Angadi et al., 2015), the United Kingdom ($n = 1$) (Seeger et al., 2014), and New Zealand ($n = 1$) (Graham et al., 2016). Twelve studies used a randomized cross-over design (Mourot et al., 2004; Rossow et al., 2009; Tordi et al., 2010; de Carvalho et al., 2014; Seeger et al., 2014; Angadi et al., 2015; Costa et al., 2016; Graham et al., 2016; Morales-palomo et al., 2017; Ramirez-Jimenez et al., 2017; Silva et al., 2018; Pimenta et al., 2019) while the remaining two applied a randomized parallel design (Ciolac et al., 2009; Sosner et al., 2016). A total sample of 276 individuals (193 males; 83 females) was included in this meta-analysis. Five studies included only men (Mourot et al., 2004; Rossow et al., 2009; Tordi et al., 2010; Costa et al., 2016; Graham et al., 2016), and nine studies included both men and women (Ciolac et al., 2009; Rossow et al., 2009; Tordi et al., 2010; de Carvalho et al., 2014; Angadi et al., 2015; Costa et al., 2016; Sosner et al., 2016; Morales-palomo et al., 2017; Ramirez-Jimenez et al., 2017). Mean age of participants ranged from 22.5 to 69.5 years. Based on resting office BP, 10 study groups involved normotensive individuals (Mourot et al., 2004; Rossow et al., 2009; Tordi et al., 2010; Seeger et al., 2014; Angadi et al., 2015; Costa et al., 2016; Graham et al., 2016; Silva et al., 2018), four study groups included hypertensive patients (Rossow et al., 2009; Tordi et al., 2010; Costa et al., 2016; Pimenta et al., 2019), and four study groups included both normotensive and hypertensive participants (Morales-palomo et al., 2017; Ramirez-Jimenez et al., 2017).

Ten studies (Mourot et al., 2004; Ciolac et al., 2009; Rossow et al., 2009; Tordi et al., 2010; Seeger et al., 2014; Angadi et al., 2015; Graham et al., 2016; Sosner et al., 2016; Morales-palomo et al., 2017; Ramirez-Jimenez et al., 2017) performed the exercise protocol on a cycle ergometer whereas the remaining four used a treadmill (de Carvalho et al., 2014; Costa et al., 2016; Silva et al., 2018; Pimenta et al., 2019). The exercise intensity was set as % of heart rate reserve (Ciolac et al., 2009), % of maximum heart rate (Tordi et al., 2010; Angadi et al., 2015; Morales-palomo et al., 2017; Ramirez-Jimenez et al., 2017), % of maximum load (Seeger et al., 2014; Costa et al., 2016), % of peak VO2 (de Carvalho et al., 2014; Silva et al., 2018), % of reserve VO2 (Pimenta et al., 2019), and power output (Sosner et al., 2016) or watts (Mourot et al., 2004; Rossow et al., 2009; Graham et al., 2016). MICE sessions lasted 18–65 min and HIIE lasted 15–45 min. Two studies reported that the HIIE and MICE bouts were isocaloric (∼460 kcal) (Morales-palomo et al., 2017; Ramirez-Jimenez et al., 2017). The exercise intensity for MICE sessions ranged between 40 and 77.5% of heart rate (reserve and/or maximum). Within the HIIE sessions, the number of bouts ranged from 4 to 40, with 15 to 240 s of high-intensity activity interspaced with 15–270 s of active or passive recovery. The high-intensity bouts during HIIE ranged between 80 and 100%, while the intensity during active recovery was 70% of heart rate (reserve and/or maximum). Warm-up and cool-down time were excluded from the total duration of the sessions.

As shown in **Table 1**, office BP was measured pre-exercise and then 30 ($n = 5$ studies) (Rossow et al., 2009; Tordi et al., 2010; de Carvalho et al., 2014; Seeger et al., 2014; Morales-palomo et al., 2017) and 60 min ($n = 8$ studies) (Mourot et al., 2004; Angadi et al., 2015; Costa et al., 2016; Graham et al., 2016; Morales-palomo et al., 2017; Silva et al., 2018; Pimenta et al., 2019) post-exercise by means of an automated device ($n = 6$) (Rossow et al., 2009; Tordi et al., 2010; Costa et al., 2016; Graham et al., 2016; Ramirez-Jimenez et al., 2017; Silva et al., 2018), manual auscultatory method ($n = 2$) (Seeger et al., 2014; Pimenta et al., 2019) or by means of the Finapress ($n = 1$) (Graham et al., 2016). Four (Ciolac et al., 2009; de Carvalho et al., 2014; Sosner et al., 2016; Ramirez-Jimenez et al., 2017) studies used automatic ambulatory BP monitors of which three studies (Mourot et al., 2004; Ciolac et al., 2009; Sosner et al., 2016) reported 24 h ambulatory BP after exercise, four studies reported only day-time BP (Ciolac et al., 2009; de Carvalho et al., 2014; Sosner et al., 2016; Ramirez-Jimenez et al., 2017), and three studies (Ciolac et al., 2009; de Carvalho et al., 2014; Sosner et al., 2016) presented night-time BP.

Office Blood Pressure

Pooling data from five studies ($n =$ six study groups) evaluating systolic BP and diastolic BP 30 min following completion of the exercise sessions showed no difference between HIIE and MICE [−0.24 mmHg (−3.9 to +3.4; $I^2 = 52.3$; $p = 0.89$)/−1.07 mmHg (−2.98 to +0.84); $I^2 = 0$; $p = 0.27$] (**Figures 3A,B**).

TABLE 1 | Overview of the general characteristics of the study and participants.

Study (author, year, country)	Design	Subjects analyzed [(N) M + (N) F]	BP category	Age	Office SBP/DBP	Modality	HIIE characteristics	MICE characteristics	BP measurement (device)	Time point BP measurements
Ambulatory Blood Pressure										
Carvalho et al. 2014, Brazil (de Carvalho et al., 2014)	Crossover	8M/12F	Medicated Hypertensives	≥60 yrs	143.45 ± 10.18/88.50 ± 7.11 mmHg	Treadmill	**Time:** 42 min **Work-bout:** 4 min at the RCP **Recovery:** 2 min at 40%VO2peak	**Time:** 42 min **Intensity:** VAT	Ambulatory BP (Spacelabs® 90207)	20 h post-exercise
Ciolac et al. 2009, Brazil (Ciolac et al., 2009)	Parallel	HIIE: 18M/8F MICE: 16M/10F	Medicated Hypertensives	HIIE:44 ± 9 yrs MICE:48 ± 7 yrs	HIIE: 129.3 ± 0.8/84.8 ± 6 mmHg MICE:129.9 ± 10/85.8 ± 10.4 mmHg	Cycle	**Time:** 30 min **Work-bout:** 2 min at 50% HRreserve **Recovery:** 1 min at 80%HRreserve	**Time:** 30 min **Intensity:** 60% HRres	Ambulatory BP (Spacelabs 90207)	24 h post-exercise
Sosner et al. 2016, France (Sosner et al., 2016)	Parallel	HIIE: 9M/5F MICE: 8M/6F	High Normal/ Hypertensive	HIIE: 65 ± 8 yrs MICE:65 ± 6 yrs	HIIE:144.2 ± 17.3/87.6 ± 11.6 mmHg MICE:142.4 ± 11.4/81.9 ± 6.2 mmHg	Cycle	**Time:** 20 min **Work-bout:** 2 sets (10 min) of 15 s at 100% Power Output **Recovery:** 15 s of passive recovery (4 min passive recovery between the sets)	**Time:** 24 min **Intensity:** 50% Peak Power Output	Ambulatory BP (Mobil-O-Graph PWA)	24 h post-exercise
Ramirez-Jimenez et al. 2017, Spain (Ramirez-Jimenez et al., 2017)	Crossover	G1:5M/3F G2:8M/3F	G1($n = 8$): Normotensive G2 ($n = 11$): High normal/ hypertensive	G1: 53.3 ± 9.5yrs G2: 56.5 ± 6.2yrs	G1:116 ± 7/65 ± 7 mmHg G2:135 ± 17/86 ± 7mmHg	Cycle	**Total Time:** 28 min **Work-bout:** 4 × 4min at 90%HRpeak **Recovery:** 3 min at 70%HRpeak	**Time:** 53 ± 6 min **Intensity:** 60%HRpeak	Ambulatory BP (Oscar2, SunTech, Morrisville, NC, USA)	14 h post- exercise
Office Blood Pressure										
Angadi et al. 2015, USA (Angadi et al., 2015)	Crossover	10M/1F	Normotensive	24.0 ± 3.7 yrs	122 ± 11/68 ± 7 mmHg	Cycle	**Total Time**: G1:28 min (HIIE near maximal) G2:15 min (HIIE supra-maximal) **Work bout:**4 × 4min at G1: 90–95%HRmax or G2: 6 × 30 s "all out" **Recovery:** G1: 3 min at 50%Hrmax or G2:4 min active recovery	**Time:** 30 min **Intensity:** 75–80% HRmax	Automatic Dinamap oscillometric BP monitor (GE Healthcare, Waukesha, WI, USA)	Every 15 min post-exercise for 3 h
Costa et al. 2016, Brazil (Costa et al., 2016)	Crossover	14M	Normotensive	24.9 ± 4.1 yrs	120.5 ± 8.1/69.5 ± 6 mmHg	Treadmill	**Total Time:** 20 min **Work-bout:** 10 × 60 s at 90% MTV **Recovery:** 60 s at 30% of MTV	**Time:** 20 min **Intensity:** 60% MTV	Automatic - Oscillometric device (Omron®HEM-780-E, Kyoto,Japan)	Every 10 min for 60 min post-exercise
Graham et al. 2016, New Zealand (Graham et al., 2016)	Crossover	12M	Normotensive	23 ± 3 yrs	116.3 ± 11.6/62.4 ± 9.4 mmHg	Cycle	**Total Time:** 20.3 min: 5 × 60 s (*all out)* **Recovery:** 4.5 min at 30W (legs) - 15W(arms)	**Time:** 50 min **Intensity:** 65% VO2max	Finometer (Finapress Medical Systems, The Netherlands)	30, 60, and 180 min post-exercise

(Continued)

TABLE 1 | Continued

Study (author, year, country)	Design	Subjects analyzed [(N) M + (N) F]	BP category	Age	Office SBP/DBP	Modality	HIIE characteristics	MICE characteristics	BP measurement (device)	Time point BP measurements
Mourot et al. 2004, France (Mourot et al., 2004)	Crossover	10M	Normotensive	24.6 ± 0.6 yrs	130.6 ± 7.1/71.7 ± 6.1 mmHg	Cycle	**Total Time:** 45 min **Work-bout:** 1 min peak work-rate **Recovery:** 4 min at base work-rate	**Time:** 45 min **Intensity:** power at 1st ventilatory threshold	Automatic- Office (BP-8800, Colin Electronics, Japan)	20 and 60 min post-exercise
Palomo et al. 2017, Spain (Morales-palomo et al., 2017)	Crossover	11M/3F	G1 ($n = 7$): Hypertensive; G2($n = 7$): Normotensive	Hypertensive: 59 ± 6 yrs Normotensive: 55 ± 9 yrs	Hypertensive: 135 ± 18.2/81 ± 7.9 Normotensive: 122.1 ± 9/75.2 ± 6	Cycle	**Time:** ∼460 kcal **Work-bout:** 5 × 4 min at 90%HRpeak **Recovery:** 3 min at 70%HRpeak	**Time:** ∼460 kcal **Intensity:** 60% HRpeak for 70 ± 5 min	Automatic – Office (Tango^{TM} SunTech Medical, Inc., Morrisville, NC, USA)	Pre-exercise and post-exercise
Pimenta et al. 2019, Brazil (Pimenta et al., 2019)	Crossover	5M/15F	Medicated Hypertensive	51 ± 8 yrs	HIIE:127 ± 09/83 ± 08 mmHg MCE: 128 ± 15/83 ± 10 mmHg	Treadmill	**Time:** 30 min **Work-bout:** 5 × 3 min 85–95% of VO2reserve **Recovery:** 2 min active recovery at 50–60% VO2reserve	**Time:** 35 min **Intensity:** 60–70% VO2reserve	Manual	Every 10 min one single measure for 60 min post-exercise
Rossow et al. 2010, USA (Rossow et al., 2009)	Crossover	15M/10F	Normotensive	25.5 ± 1.1	117 ± 8/63.4 ± 7 mmHg	Cycle	**Total Time:** 25 min **Work-bout:** 4 × 30 s "all-out" cycle sprint (∼500W) **Recovery:** 4.5 min (<50rpm/30W)	**Time:** 60 min **Intensity:** 60% HRreserve	Automatic Oscillometric cuff (HEM-907 XL;Omrom, Shimane, Japan)	Post 30 min; Post 60 min
Seeger et al. 2014, United Kingdom (Seeger et al., 2014)	Crossover	10M/7F	Normotensive	23 ± 4 yrs	121 ± 9/73 ± 8 mmHg	Cycle	**Total time:** 28 min **Work-bout:** 10 × 1 min at 100% Maximum workload **Recovery:** 2 min at 25% maximum workload	**Time:** 28 min **Intensity:** 50% of maximum workload	Manual	At 30 min post-exercise
Silva et al. 2018, Brazil (Silva et al., 2018)	Crossover	23M	Normotensive	24.2 ± 2.8 yrs	118.2 ± 9.1/70.3 ± 7.0 mmHg	Treadmill	**Total Time:** 18 min **Work-bout:** 6 × 90 s at 80% VO2peak **Recovery:** 90 s at 40% Vo2peak	**Time:** 18 min **Intensity:** 40% VO2peak	Automatic – Sphygmomanometric device (OMROM – HEM 7200, Kyoto, Japan)	Every 10 min for 1 h post-exercise
Tordi et al. 2010, France (Tordi et al., 2010)	Crossover	11M	Normotensive	22.5 ± 0.7 yrs	118.1 ± 4.8/65.5 ± 4.1 mmHg	Cycle	**Total Time:** 30 min **Work-bout:** 6 × 5 min 4 min at 65% HRmax **Recovery:** 1 min at 85% HRmax	**Time:** 30 min **Intensity:** the average HR achieved during HIIE	Automatic -Dinamap® GE Medical Systems, Bc, France	At 30 min post-exercise

Data are reported as mean ± SD. BP, blood pressure; DBP, diastolic blood pressure; F, female; HIIE, high-intensity interval exercise; HR, heart rate; HRmax, maximal heart rate; M, male; MCE, moderate-intensity continuous exercise; Min, minutes; MVT, maximal treadmill velocity; N, number of participants; RCT, respiratory compensation threshold; s, seconds; SBP, systolic blood pressure; VAT, ventilatory anaerobic threshold; VO2, uptake oxygen.

An I^2 of 52.3% suggested high heterogeneity for systolic BP. Though, leave one out sensitivity analysis for systolic BP did not change the results (systolic BP ranged between +0.08 and −1.6; $p > 0.30$ for all). Similarly, pooled data from eight studies (11 study groups) found no differences in PEH between both exercise modalities 60 min after ending the session [−1.5 mmHg (−3.91 to +0.85); $I^2 = 12.77$; $p = 0.20$/−0.76 (−2.47 to +0.95); $I^2 = 7.47\%$; $p = 0.38$] (**Figures 3C,D**). A sensitivity analysis omitting the two hypertensive subgroups did not change the results [−1.14 mmHg (–3.64 to +1.36); $I^2 = 13.1$; $p = 0.21$/−0.43 mmHg (−2.3 to + 1.47); $I^2 = 10.3\%$; $p = 0.22$]. $I^2 < 15\%$ suggested low heterogeneity. An overview of the BP changes at the individual study level is presented in **Supplementary File 3** in Supplementary Material. Effect sizes calculated as SMD were small with pooled values of −0.037 and −0.12 for systolic and diastolic BP after 30 min recovery and −0.18 and −0.10 for systolic and diastolic BP after 60 min of recovery.

Ambulatory Blood Pressure

Compared with MICE, HIIE reduced daytime systolic and diastolic ambulatory BP by −5.3 mmHg (−7.3 to −3.3; $I^2 = 0\%$; $p =< 0.001$) (**Figure 4A**) and −1.63 mmHg (−3.00 to −0.26; $I^2 = 0\%$; $p = 0.02$), respectively (**Figure 4B**). However, nighttime ambulatory BP after HIIE was not significantly lower than MICE for both systolic [−2.4 mmHg (−5.7 to +0.87); $I^2 = 14.6$; $p = 0.1$] (**Figure 4C**) and diastolic BP [−1.6 mmHg (−3.9 to +0.55); $I^2 = 0$; $p = 0.14$] (**Figure 4D**). Heterogeneity was low for both daytime and nighttime BP. Three studies reported 24 h ambulatory BP and found no differences in systolic [−2.2mmHg (−5.9 to +1.48), $p = 0.23$] and diastolic BP [−0.76 (−4.0 to +2.51), $p = 0.64$] between HIIE and MICE, yet heterogeneity was high with $I^2 = 42\%$ and $I^2 = 53\%$, respectively. An overview of the ambulatory BP changes at the individual study level is presented in **Table 1**. Pooled SMD showed a medium effect (−0.60) for daytime SBP whereas effect sizes for daytime DBP (−0.31) and nighttime SBP/DBP (−0.2/−0.185) were small.

DISCUSSION

The main aim of this systematic review and meta-analysis was to examine whether BP changes following a session of HIIE are more pronounced compared to a session of MICE. Findings of this meta-analysis suggest that a single session of HIIE is associated with a statistically significant and clinically meaningful larger reduction in daytime ambulatory BP compared to a single session of MICE.

Previous research suggested that exercise intensity had little impact on the manifestation of PEH when BP is measured for a short time period after exercise (Cornelissen and Fagard, 2004). Our results are in line with these older studies showing that office BP responses, measured in a quiet sitting or supine position, are not substantially different during the first 30 and 60 min after completion of a session of HIIE or MICE. Concordant to our results, a recent systematic review investigating acute cardiovascular response to HIIE also found that cardiovascular responses were quite similar within 1 h of completion of a session of HIIE or MICE (Price et al., 2020). In addition, meta-analytic research investigating the effect of a single session of dynamic resistance exercise on PEH (Casonatto et al., 2016) found no major impact of intensity on systolic and diastolic PEH after 60–90 min of exercise completion.

On the other hand, when PEH was analyzed by means of ambulatory BP monitoring during the daytime and/or nighttime hours following the exercise sessions, the present meta-analysis suggests that a single session of HIIE has a more pronounced and most likely longer lasting effect than a single session of MICE. Our findings are consistent with a previous study evaluating PEH over 9 h after single sessions of low, moderate, or vigorous exercise in 45 men (age 18–55 years) with elevated awake ambulatory BP, which found that although all exercise sessions (low, moderate, or vigorous) reduced the BP when compared to a non-exercise control session, the PEH occurred in a dose-response way with higher intensity exercise inducing a larger and more sustained BP reduction (Eicher et al., 2010). Previously, it was found that PEH following exercise has a strong correlation with BP lowering effect of chronic exercise training (Hecksteden et al., 2013). In that sense, our results are in contrast to the meta-analysis in adults of any health status performed by Way et al. (2019) who compared chronic effects (≥4 weeks) of both exercise interventions documenting a significant blood pressure reduction in favor of HIIE at night-time diastolic BP (−0.826 to −0.086 mmHg), and near significant difference for systolic BP day-time (−0.740 to 0.041 mmHg) and diastolic BP day-time (−0.717 to 0.020 mmHg).

Regarding the mechanisms associated with PEH, insufficient data did not permit us to quantitatively summarize potential differences in underlying mechanisms. In summary, Lacombe et al. (2011) showed that HIIE promoted greater changes in baroreflex sensitivity and HR variability compared to MICE. A single session of HIIE also promoted a larger reduction in stroke volume and a more pronounced increase in HR compared to MICE (Morales-palomo et al., 2017). Additionally, greater reductions on systematic vascular resistance and cutaneous vascular resistance have been observed following a single session of HIIE (Morales-palomo et al., 2017). In line, Costa et al. (2020) showed a significant decrease in systemic vascular resistance following HIIE compared to a control condition. The same authors (Costa et al., 2020) also found a lower vascular impedance after both MICE and HIIE sessions compared to the control session. The reduction in systematic vascular resistance, total vascular impedance, and pulse pressure, mainly after HIIE, might be explained by a sustained post-exercise vasodilation in the vascular beds of the lower limbs in treadmill exercise protocols (Costa et al., 2020). A complex interaction between neural and local vasodilatory mechanisms (e.g., sympathoinhibition due to baroreflex resetting, blunted transduction of sympathetic outflow to vasoconstriction, and histamine receptors activation) mediates the sustained post-exercise vasodilation (Halliwill et al., 2013; Hecksteden et al., 2013). During exercise, the likely higher increase of blood flow toward the active muscle following HIIE vs. MICE promotes increased shear stress (mechanical stimulus) on the endothelium, which mediates the release of vasodilatory substances, such as histamines, promoting a

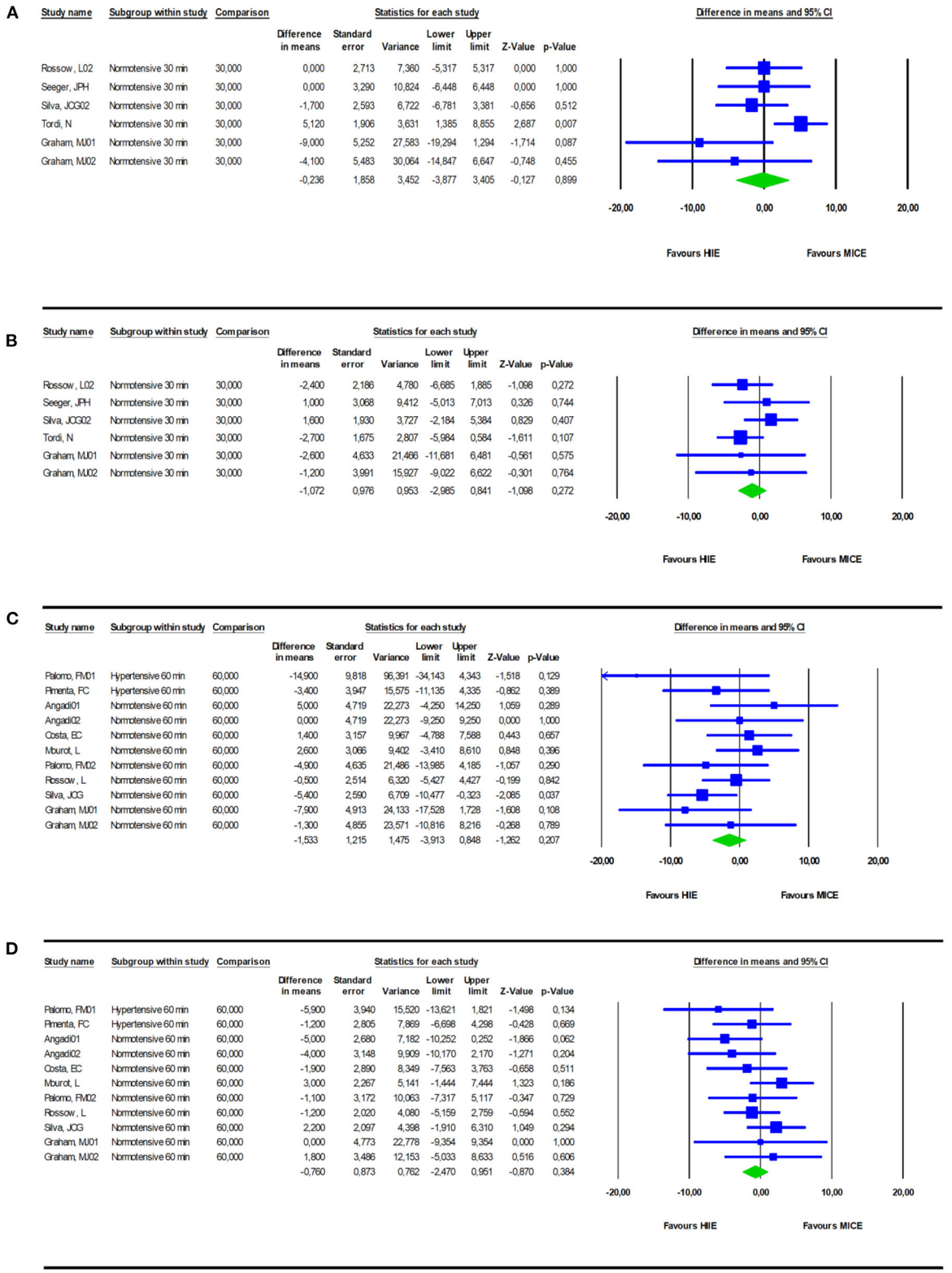

FIGURE 3 | Comparison of PEH, measured as office BP at 30 [SBP **(A)**- DBP **(B)**] or 60 min [SBP **(C)**- DBP **(D)**] after completion of a bout of HIIE vs. a bout of MICE.

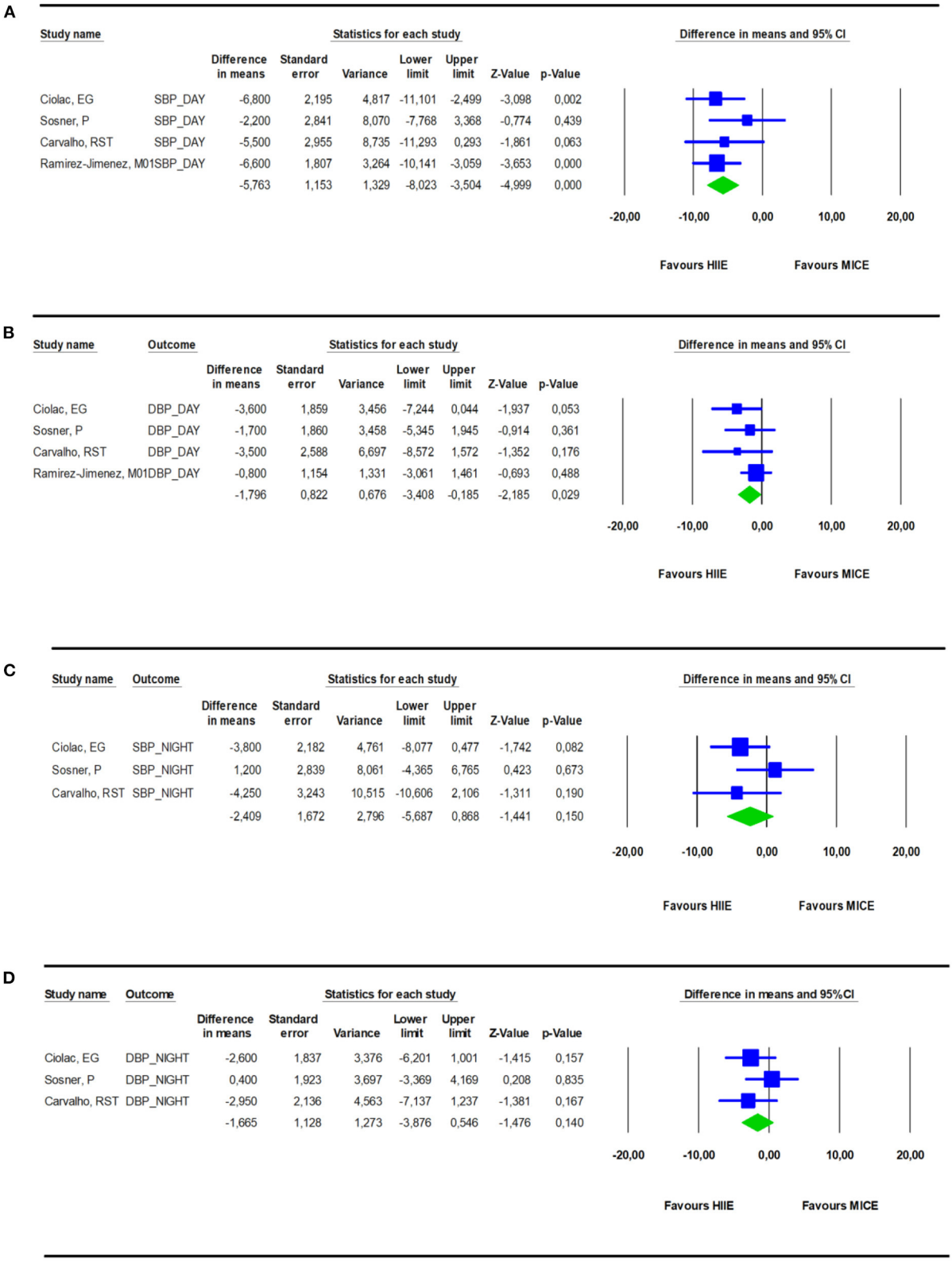

FIGURE 4 | Effect of a bout of HIIE on daytime SBP **(A)** and DBP **(B)** monitoring compared to a bout of MICE. Effect of a bout of HIIE on nighttime SBP **(C)** and DBP **(D)** monitoring compared to a bout of MICE.

sustained vasodilatory response and reducing systemic vascular resistance (Halliwill et al., 2013; Hecksteden et al., 2013). Further studies should address these vasodilatory responses after different exercise intensities, as these mechanisms might explain in part a more sustained PEH following HIIE.

Further, the studies analyzing autonomic function reported higher heart rate post 30 min (Tordi et al., 2010), post the first hours (Morales-palomo et al., 2017), and post 20 h (de Carvalho et al., 2014) after HIIE than MICE sessions. This is in accordance with Abreu et al. (2019) in a systematic review ($n = 193$) who showed an improvement in parasympathetic and/or sympathetic modulation after HIIE ($\geq$2 weeks) when evaluated by linear and non-linear indexes of heart rate variability (Abreu et al., 2019). Along with the improvement in endothelium responses as mentioned above (i.e., stimulating nitric oxide syntheses), the authors found HIIE superiority vs. MICE in cardiac autonomic variables due to greater degrees of distensibility of carotid artery which seems to be associated with improvements in baroreflex sensitivity, improving mitochondrial function and, consequently, capacity of skeletal muscle as well as improving maximal volume uptake, which may be correlated to the predominance of rest vagal modulation after HIIE (Abreu et al., 2019). On the other hand, Mourot et al. (2004) demonstrated that mean R-R interval measured by heart rate variability were lower 1 h after HIIE compared to MICE, but not post 24 or 48 h, suggesting that short-term heart rate variability depend on the type of exercise (i.e., intensity), contrary to the long-term recovery (i.e., total physical work performed during exercise) (Mourot et al., 2004).

Limitations

This systematic review with meta-analysis has some limitations that need to be acknowledged. First, the number of randomized trials and their sample sizes was low. Moreover, studies evaluating office PEH shortly after exercise mainly involved normotensive individuals, whereas the four trials that assessed ambulatory BP included patients with hypertension under pharmacological treatment (two studies) or included only untreated individuals with stage 1 hypertension (two studies). Moreover, except for two trials, recruited participants were all younger than 60 years. In this context, one should be careful with generalizing present results to all hypertensive patients. We also observed a large variety of HIIE protocols, which ranged from the well-known Norwegian protocol of 4 $\times$ 4 min (Ramirez-Jimenez et al., 2017) to 10 $\times$ 1 min at 100% of maximal load (Seeger et al., 2014). Unfortunately, given the small number of studies, no subgroup analysis could be performed on the type of HIIE protocol. As only two trials reported that their exercise interventions were isocaloric, we cannot be 100% confident that the observed difference is due to a difference in intensity or a difference in volume. Therefore, this study emphasizes the need for more research investigating the role of HIIE on PEH and its mechanisms across all BP and age categories to maximize personalization of BP management for the growing group of older hypertensive patients.

CONCLUSION

In summary, HIIE and MICE were similarly effective for promoting short-time PEH measured by office BP. On the other hand, HIIE showed larger PEH than MICE during daytime ambulatory BP monitoring. These findings suggest that HIIE may be a more time-efficient and beneficial antihypertensive tool compared to MICE. However, the number of studies assessing PEH by ambulatory BP was low and the office BP data were mainly derived from young normotensive/prehypertensive populations. Thus, future studies incorporating ambulatory BP monitoring, as well as including more hypertensive and older individuals, are needed to confirm HIIE's superiority as a safe BP lowering intervention in daily clinical practice.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

VC, IM, KG, and RB contributed to conception and design of the manuscript. KG and IM performed data search and data extraction. JC, KG, and IM performed data-analysis. VC, IM, and KG drafted the manuscript. JC, EC, RB, VC, IM, and KG critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2021.675289/full#supplementary-material

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The Effects of Acute Aerobic Exercise on Blood Pressure, Arterial Function, and Heart Rate Variability in Men Living With HIV

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Purpose: This study aims to investigate the effects of acute cycling on blood pressure (BP), arterial function, and heart rate variability (HRV) in men living with HIV (MLHIV) using combined antiretroviral therapy (cART).

Methods: Twelve MLHIV (48.7 ± 9.2 years; 25.2 ± 2.8 kg m^{-2}) and 13 healthy controls (41.2 ± 9.9 years; 26.3 ± 2.9 kg m^{-2}) performed a cycling bout (ES) (intensity: 50% oxygen uptake reserve; duration: time to achieve 150 kcal—MLHIV: 24.1 ± 5.5 vs. controls: 23.1 ± 3.0 min; $p = 0.45$), and a 20-min non-exercise session (NES).

Results: At rest ($p < 0.05$), MLHIV presented higher brachial systolic/diastolic BP (SBP/DBP: 123.2 ± 14.2/76.8 ± 6.3 vs. 114.3 ± 5.1/71.6 ± 2.6 mmHg) and central BP (cSBP/cDBP: 108.3 ± 9.3/76.5 ± 6.5 vs. 101.6 ± 4.9/71.3 ± 4.4 mmHg) vs. controls but lower absolute maximal oxygen uptake (2.1 ± 0.5 vs. 2.5 ± 0.3 L min^{-1}) and HRV indices reflecting overall/vagal modulation (SDNN: 24.8 ± 7.1 vs. 42.9 ± 21.3 ms; rMSSD: 20.5 ± 8.5 vs. 38.1 ± 22.8 ms; pNN50: 3.6 ± 4.2 vs. 13.6 ± 11.3%). DBP postexercise lowered in controls vs. MLHIV (∼4 mmHg, $p < 0.001$; ES: 0.6). Moreover, controls vs. MLHIV had greater reductions ($p < 0.05$) in augmentation index (−13.6 ± 13.7 vs. −3.1 ± 7.2% min^{-1}; ES: 2.4), and HRV indices up to 5 min (rMSSD: −111.8 ± 32.1 vs. −75.9 ± 22.2 ms min^{-1}; ES: 3.8; pNN50: −76.3 ± 28.3 vs. −19.0 ± 13.7% min^{-1}; ES: 4.4). Within-group (ES vs. NES; $p < 0.05$) reductions occurred in controls for SBP (∼10 mmHg, 2 h), DBP (∼6 mmHg, 20, 30, and 70 min), cSBP (∼9 mmHg, 30 min), cDBP (∼7 mmHg, 30 and 70 min), augmentation index (∼10%, 30 min), and pNN50 (∼20%; up to 2 h), while in MLHIV only cSBP (∼6 mmHg, 70 min) and cDBP (∼4 mmHg, 30 min) decreased. Similar increases (up to 5 min)

in heart rate (∼22 bpm) and decreases in SDNN (∼18 ms) and rMSSD (∼20 ms) occurred in both groups.

Conclusion: MLHIV under cART exhibited attenuated postexercise hypotension vs. healthy controls, which seemed to relate with impairments in vascular function.

Keywords: post-exercise hypotension, acquired immunodeficiency syndrome (AIDS), ambulatory blood pressure monitoring (ABPM), heart rate variability (HRV), autonomic nervous system (ANS), health

INTRODUCTION

The acquired immune deficiency syndrome (AIDS) caused by the human immunodeficiency virus (HIV) is a major public health issue. Up to 2020, 35 million people have died because of AIDS and 1.7 million were newly infected in 2019 (UNAIDS, 2020; World Health Organization, 2020). Although AIDS mortality has dramatically decreased since the introduction of combined antirretroviral therapy (cART), there is compelling evidence demonstrating that the HIV infection associated to prolonged cART increases the cardiovascular risk in people living with HIV (Feinstein et al., 2019).

On the other hand, it is well documented that regular physical exercise is capable of reducing cardiovascular risk and blood pressure levels (Pescatello et al., 2004a; Cornelissen and Fagard, 2005). The potential mechanisms of blood pressure decline due to exercise training seem to be linked to repeated reductions following single exercise bouts (Carpio-Rivera et al., 2016), which is referred to as postexercise hypotension (PEH) (Kenney and Seals, 1993). Although the mechanisms underlying PEH are not fully understood, it is accepted that this phenomenon results from a persistent drop in systemic vascular resistance induced by neural and vascular factors, which is not completely offset by increases in cardiac output (Halliwill et al., 2013).

People living with HIV usually present impaired autonomic modulation at rest (Glück et al., 2000; Neild et al., 2000; Correia et al., 2006; Lebech et al., 2007; Compostella et al., 2008) and after exercise (Borges et al., 2012). In addition, endothelial dysfunction has been described in this population (Lopes et al., 2019), even in early stages of HIV infection (Bush et al., 2019), which predisposes to increased arterial stiffness (Ferraioli et al., 2011; Anand et al., 2018). It is therefore feasible to suppose that blood pressure responses to acute exercise might be altered in those patients. We could find a single trial investigating this issue (Domingues et al., 2018), which failed to identify PEH after resistance exercise in women living with HIV. However, in what extent a single bout of aerobic exercise might induce blood pressure reduction among these patients is uncertain. A better understanding on this matter would be relevant to provide insights into supporting therapies counteracting cardiovascular damages induced by HIV infection and cART.

Given this gap in the literature, we aimed to investigate the effects of acute aerobic cycling exercise on blood pressure, arterial function, and cardiac autonomic modulation in men living with HIV (MLHIV) vs. age-matched non-infected counterparts. We hypothesized that PEH would be more likely to occur in healthy controls than among MLHIV.

MATERIALS AND METHODS

Ethical Approval

All volunteers provided informed written consent before participation in the study, which complied with the recommendations laid on the Helsinki Declaration and gained approval from the Ethics Review Board of the Pedro Ernesto University Hospital (Rio de Janeiro, RJ, Brazil, CCAE 87616418.2.0000.5259).

Subjects

Twelve MLHIV [age: 48.7 ± 9.2 years; body mass index (BMI): 25.3 ± 2.7 kg m^{-2}] followed up at a tertiary-care university hospital, and 13 men without HIV/AIDS (controls) (age: 41.2 ± 9.9 years; BMI: 26.3 ± 2.9 kg m^{-2}) were randomly recruited from the staff of the same institution to participate in this study. Eligible MLHIV should have been diagnosed with HIV/AIDS (Centers for Disease Control and Prevention, 1993) but should be asymptomatic and free from opportunist infections. Exclusion criteria were as follows: (a) use of cART for less than 6 months; (b) resting blood pressure ≥ 140/90 mmHg; (c) history of hypertension, coronary artery disease, ischemic disease, pulmonary disease, diabetes mellitus, Chagas disease, tuberculosis, or heart failure; (d) malnutrition; and (e) use of antidepressant or antihypertensive medication. Controls were screened for items b, c, d, and e.

Experimental Design

The study was conducted during three visits to the laboratory, interspersed with 72-h intervals. Participants were instructed to avoid physical exercise in the 48 h and caffeine or alcohol in the 12 h prior to experimental sessions. All procedures took place at the same time of the day (7–8 a.m.) to minimize potential circadian effects on the outcomes, in a quiet temperature-controlled environment (21–22°C).

On the first visit, subjects underwent blood collection after 8 h fasting. After a light standardized breakfast, they were connected in supine position to an oxygen uptake (VO_2) analyzer. The cuff for blood pressure measurement and belt for heart rate monitoring were positioned on the participant's arm and chest, respectively. Brachial and central (aortic) blood pressure rates were measured after 30 min of rest, during which the heart rate variability (HRV) was assessed. Subsequently, a maximal cardiopulmonary exercise testing (CPET) was performed.

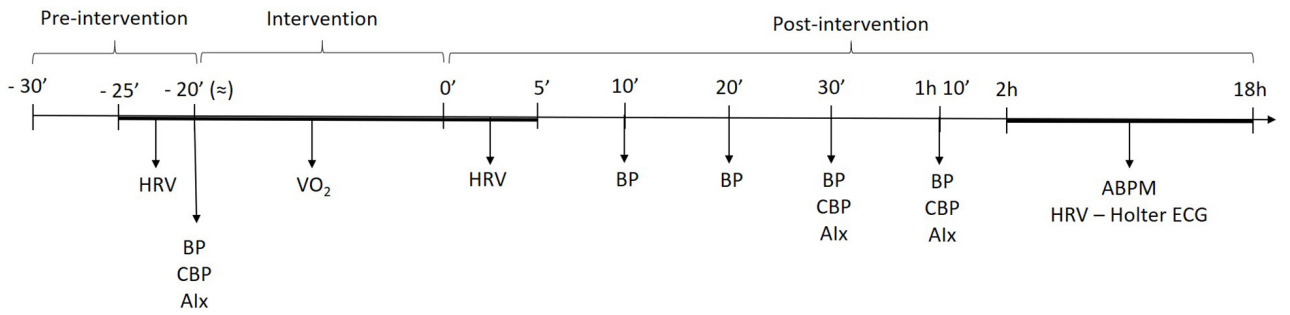

FIGURE 1 | Timeline of measurements across submaximal exercise and non-exercise sessions. HRV, heart rate variability; BP, blood pressure; cBP, central blood pressure, AIx, augmentation index; ABPM, ambulatory blood pressure monitoring.

On second and third visits, non-exercise and aerobic exercise sessions were performed in a random counterbalanced order. Initially, the experimental setup of the first visit was mounted, with participants remaining at rest for 10 min. HRV, brachial, and central blood pressure assessments were repeated. Aerobic exercise sessions consisted of pedaling on cycle ergometer at intensity corresponding to 50% of oxygen uptake reserve (VO_2R). The exercise went until energy expenditure of 150 kcal. In the non-exercise sessions, participants remained seated for 20 min mimicking the duration of the aerobic bout. Immediately after the experimental sessions, brachial blood pressure (10, 20, 30, and 70 min), central blood pressure, augmentation index (AIx) (30 and 70 min), and HRV (each 60 s up to 5 min) were assessed in supine position throughout 70-min recovery. The ambulatory blood pressure monitoring (ABPM) and Holter ECG System devices were placed 2 h after the end of the experimental sessions and returned 16 h later (next morning). **Figure 1** summarizes the timeline of assessments during exercise and non-exercise sessions.

Resting VO_2 Assessment and Cardiopulmonary Exercise Testing

Breath-by-breath pulmonary gas exchanges were determined using a VO2000 analyzer (Medical Graphics^{TM}, Saint Louis, MO, United States). Data were 30-s stationary time averaged, which provided a good compromise between removing noise while maintaining the underlying trend (Midgley et al., 2007). Prior to each test, the gas analyzers were calibrated according to the manufacturer's instructions, using a certified standard mixture of oxygen (17.01%) and carbon dioxide (5.00%), balanced with nitrogen (AGA^{TM}, Rio de Janeiro, RJ, Brazil). Ambient temperature and relative humidity ranged from 20 to 24°C and 50–70%, respectively. Resting and maximal VO_2 were determined to calculate the percentage of VO_2R, as described elsewhere (Fonseca et al., 2018; Cunha et al., 2020). The VO_2 at rest was assessed following strict recommendations (Compher et al., 2006). Maximal CPET was performed on an electronic braked cycle ergometer (Cateye EC-1600, Cateye^{TM}, Tokyo, Japan), using a ramp protocol designed to elicit maximal volitional effort within 8–12 min (Cunha et al., 2015a). Tests were considered maximal in the presence of at least three of the five following criteria (Howley et al., 1995): (a) maximum voluntary exhaustion; (b) ≥95% predicted maximal heart rate (HR) (220—age) or presence of heart rate (HR) plateau (ΔHR between two consecutive work rates ≤ 4 beats min^{-1}); (c) presence of VO_2 plateau (ΔVO_2 between two consecutive work rates < 2.1 ml kg^{-1} min^{-1}); (d) respiratory exchange ratio > 1.1; and (e) score of 10 on the Borg CR -10 scale.

Submaximal Exercise Bout

Cycling bouts were performed at an intensity corresponding to 50% VO_2R. The absolute VO_2 corresponding to a given%VO_2R was used to calculate the associated cycling power by applying the equation: VO_2 cycling = 3.5 + 12.24 × power × body weight, where VO_2 is in milliliters per kilogram per minute, power is in Watts, and body weight is in kilograms (American College of Sports Medicine, 2018). Cycling cadence was kept at 65 rpm, and the power output was adjusted whenever necessary to maintain the target intensity. The energy expenditure was calculated individually from the VO_2 and VCO_2 in liters per minute, using the Weir equation: Energy expenditure in kcal = [(3.941 × average VO_2) + (1.106 × average VCO_2)] × exercise time in minutes (Weir, 1949). The exercise bouts were terminated when participants achieved a total energy expenditure of 150 kcal, which represents the minimum threshold per session recommended by the ACSM to promote health (American College of Sports Medicine, 2018).

Outcomes

Brachial Blood Pressure

At-office measurements of brachial blood pressure were performed in triplicate with 1-min intervals by the same trained professional, using a digital sphygmomanometer (Omron^{TM}, HEM 7200, Matsusaka, Japan). ABPM was assessed on the non-dominant arm to obtain records from 2- to 18-h postinterventions (Welch Allyn model 6100, Poznań, Poland), every 20 min during daytime and every 30 min at night. Participants were instructed not to shower, perform physical exercise, or change their daily activities during the test, which was considered satisfactory when at least 70% of blood pressure readings were valid.

All participants were given a standardized activity diary to register any unusual physical or emotional events. Patients were also asked to record the sleep and wake times during the recording.

Central (Aortic) Blood Pressure and Augmentation Index

Central blood pressure and AIx were assessed non-invasively by applanation tonometry, using the SphygmoCor System (AtCor Medical™, Sydney, NSW, Australia). Radial artery waveforms were recorded from the radial artery at the wrist, and the sensor transmitting the pulse of the radial artery was placed over the radial artery for 10 s. The corresponding aortic waveforms were automatically generated from the radial artery waveform by a validated transfer function. The central blood pressure was computed from the radial artery pressure curve and calibrated with brachial blood pressure, as previously reported (Miyashita, 2012). Briefly, central augmentation pressure (AP) was calculated as the difference between the first and second systolic peaks on the central pressure waveform. The AIx—a measure of composite vascular function (Wilkinson et al., 1998, 2000; Ring et al., 2014)—was calculated as AP divided by central pulse pressure × 100 to give a percentage. The quality of the recordings was assured by discarding all SphygmoCor recordings with an operator index below 90.

Autonomic Modulation

Beat-to-beat HR was continuously recorded using a Polar RS800CX monitor (Polar Electro™, Kempele, Finland), and signals were transferred to the Polar Precision Performance Software (Polar Electro, Kempele, Finland). After replacing the non-sinus beats by interpolated data derived from adjacent normal RR intervals, times series data were exported to a HRV analysis software (Kubios™ HRV software, Biosignal Analysis and Medical Imaging Group, University of Kuopio, Kuopio, Finland). A Holter ECG system (CardioLight Digital™, Cardio Sistema Ltda, São Paulo, SP, Brazil) was used to obtain HRV between 2- and 18-h postinterventions, through the CardioSmart™ Institutional CS 550 software (Cardio Sistema Ltda, São Paulo, SP, Brazil).

In the present study, the following indices in time domain were assessed: standard deviation of the NN intervals (SDNN), square root of the mean squared successive differences from adjacent RR intervals (rMSSD), and percent number of pairs of adjacent RR intervals differing by more than 50 ms (pNN50). The SDNN reflects total variability, while rMSSD and pNN50 are estimates of short-term components of HRV reflecting the parasympathetic modulation (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). HR recording and HRV analysis were performed as previously recommended (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Bourdillon et al., 2017; Shaffer and Ginsberg, 2017). All devices were installed by the same trained professional, and data were analyzed on a single computer.

Statistical Analysis

A total of eight individuals in each group was estimated as necessary, according to sample size *a priori* calculations performed using the G*Power™ 3.0.10 software (Kiel University, Kiel, Germany) considering 80% power, 5% significance level, and effect size of 0.44 based on acute exercise-induced change in blood pressure of −3.1 mmHg (Carpio-Rivera et al., 2016). Data normality was ratified by Shapiro–Wilk statistics, and therefore data were expressed as mean ± standard deviation.

Differences between MLHIV and controls at baseline were tested by unpaired *t*-tests. Linear mixed models adjusted for baseline values were fitted to evaluate the effects of exercise on changes from baseline in MLHIV and controls. The following approaches were adopted: (a) within-between group analysis, with models including group, time, session (non-exercise or aerobic exercise) as fixed effects and group × time × session interaction (power: 60%); (b) within-group analysis, with models including time and session (non-exercise or aerobic exercise) as fixed effects, and time × session interaction (power: 76%). The adjustment of models were evaluated based on Bosker/Snijders *R*-squared values (Recchia, 2010), and rate of changes between sessions was expressed by β coefficients. Additionally, Cohen's *d* effect sizes (ES) were calculated for significant differences between sessions.

Due to the probable insufficient statistical power of the three-way interaction model, between-group analysis was complemented by comparing the areas under the curves (AUCs) of exercise net effects [(post-pre-exercise session) - (post-pre-non-exercise session)] on outcomes in MLHIV and controls, using unpaired *t*-tests. In all cases, statistical analyses were performed using the Stata 13.0 software (StataCorp, College Station, TX, United States), and significance level was fixed at $p \leq 0.05$.

RESULTS

Baseline Sample Characteristics and Submaximal Exercise Bouts

Clinical, cardiovascular, and autonomic variables at rest are presented in **Table 1**. No difference was detected between groups for age, height, body mass, body mass index, abdominal circumference, LDL cholesterol, triglycerides, relative maximal VO_2, HR at rest, and AIx. However, MLHIV presented higher glucose and lower absolute maximum VO_2, total cholesterol, and HDL cholesterol than controls. As for cardiovascular and autonomic outcomes, MLHIV exhibited higher brachial and central blood pressure and lower SDNN, rMSSD, and pNN50 than controls. Moreover, 66% of patients were using nucleoside reverse transcriptase inhibitors, 66% non-nucleoside reverse transcriptase inhibitors, 41% protease inhibitors, and 25% integrase inhibitors.

Table 2 depicts data for total duration, HR, and VO_2 elicited by the acute exercise bouts, which were similar between groups.

TABLE 1 | Clinical, cardiovascular, and autonomic parameters at rest in controls and men living with HIV (MLHIV).

	Controls (n = 13)	MLHIV (n = 12)	p-value*
Clinical parameters			
Age (years)	41.2 (9.9)	48.7 (9.2)	0.07
Height (cm)	177.9 (4.9)	178.6 (5.4)	0.75
Body mass (kg)	83.4 (11.9)	80.9 (11.2)	0.59
Body mass index (kg m^{-2})	26.3 (2.9)	25.2 (2.8)	0.39
Abdominal circumference (cm)	90.1 (9.1)	92.3 (9.3)	0.60
Glucose (mg dl^{-1})	89.4 (9.8)	97.2 (6.2)	**0.05**
Total cholesterol (mg dl^{-1})	205.2 (34.7)	170.6 (28.7)	**<0.01**
LDL cholesterol (mg dl^{-1})	126.2 (29.1)	107.5 (28.9)	0.12
HDL cholesterol (mg dl^{-1})	52.5 (10.8)	37.5 (7.9)	**<0.01**
Triglycerides (mg dl^{-1})	132.6 (81.8)	180.5 (86.7)	0.17
Maximal oxygen uptake (L min^{-1})	2.5 (0.3)	2.1 (0.5)	**0.03**
Maximal oxygen uptake (ml kg^{-1} min^{-1})	30.4 (6.1)	26.4 (4.3)	0.07
Years diagnosed with HIV	–	17.3 (6.6)	–
Years taking cART	–	17.1 (7.4)	–
T CD4 (cell mm^{-3})	–	683.6 (271.7)	–
T CD8 (cell mm^{-3})	–	857.2 (419.8)	–
Undetectable viral load (n, %)	–	12 (100)	–
Cardiovascular and autonomic parameters			
Heart rate (bpm)	64.9 (8.8)	71.2 (12.5)	0.15
Systolic blood pressure (mmHg)	114.3 (5.1)	123.2 (14.2)	**0.04**
Diastolic blood pressure (mmHg)	71.6 (2.6)	76.8 (6.3)	**0.01**
Central systolic blood pressure (mmHg)	101.6 (4.9)	108.3 (9.3)	**0.03**
Central diastolic blood pressure (mmHg)	71.3 (4.4)	76.5 (6.5)	**0.03**
Augmentation index (%)	14.3 (10.7)	15.2 (12.3)	0.85
SDNN (ms)	42.9 (21.3)	24.8 (7.1)	**0.01**
rMSSD (ms)	38.1 (22.8)	20.5 (8.5)	**0.02**
pNN50 (%)	13.6 (11.3)	3.6 (4.2)	**0.01**

**Student t-test. Data expressed as mean (SD). cART, combined antiretroviral therapy; SDNN, standard deviation of normal to normal intervals; rMSSD, root mean square of successive differences between normal intervals; pNN50, percentage of differences between adjacent normal intervals. p-values in bold denote statistical significant differences.*

TABLE 2 | Characteristics of submaximal exercise session in controls and men living with HIV (MLHIV).

	Controls (n = 13)	MLHIV (n = 12)	p-value*
Duration (min)	23.2 (3.1)	24.9 (5.6)	0.45
Heart rate (bpm)	122.7 (10.2)	125.3 (14.4)	0.61
Oxygen uptake (% reserve)	53.2 (3.9)	55.7 (4.9)	0.19

**Student t-test. Data expressed as mean (SD).*

Acute Effects of Submaximal Aerobic Exercise

Residual plots for all models were visually examined and did not demonstrate deviations from the regression assumptions. As expected, the linear model including group as fixed effect (three-way interaction) lacked significance for all outcomes ($p \geq 0.08$), while the approach including time and session proved to be significant ($p \leq 0.03$). Bosker/Snijders R-squared for within-group models discriminated by outcome were always non-negative (controls: 0.13–0.85; MLHIV: 0.45–0.96), indicating low chances of misspecification giving the explanatory variables added to the models. Detailed R-squared data per outcome and group are presented in **Supplementary Table 1**.

Brachial Blood Pressure

Resting blood pressure measured on the first visit and before the experimental conditions (exercise and non-exercise) was similar in controls (114.3/71.6 vs. 112.3/69.9 vs. 112.9/71.4 mmHg, respectively; $p > 0.38$) and MLHIV (123.2/76.8 vs. 121.2/75.5 vs. 121.1/76.0 mmHg, respectively; $p > 0.59$). **Figure 2** presents absolute values of at-office and ambulatory brachial blood pressure after the experimental sessions in controls (**Figure 2A**) and MLHIV (**Figure 2B**), and exercise net effects on systolic blood pressure (SBP, **Figure 2C**) and diastolic blood pressure (DBP, **Figure 2D**). In both groups, no difference between sessions was detected for SBP, except for controls that presented lower values 2 h postexercise vs. non-exercise sessions (123.6 ± 9.3 vs. 132.7 ± 8.7 mmHg; β = −9.73; 95% CI = −18.6 to −0.8; $p = 0.03$; ES: 1.5). Controls showed lower DBP after 20 min (115.2 ± 4.0 vs. 118.3 ± 8.0 mmHg; β = −6.69; 95% CI = −11.4 to −1.9; $p < 0.01$; ES: 0.55), 30 min (115.4 ± 5.0 vs. 118.0 ± 8.6 mmHg; β = −5.84; 95% CI = −10.5 to −1.1; $p = 0.01$; ES: 0.80), and 70 min (115.6 ± 9.5 vs. 118.6 ± 10.1 mmHg; β = −6.53; 95% CI = −11.2 to −1.7; $p < 0.01$; ES: 1.3) after exercise vs. non-exercise sessions, while no difference was detected for MLHIV.

There was no difference between controls and MLHIV with regard to AUCs of exercise net effects on SBP (**Figure 2C**) (overall: −11.3 ± 23.0 vs. −4.5 ± 12.8 mmHg min^{-1}; $p = 0.37$). On the other hand, greater reductions in DBP (**Figure 2D**) were found in controls vs. MLHIV along the first 70 min of recovery (−19.6 ± 12.5 vs. −5.0 ± 7.0 mmHg min^{-1}; $p < 0.01$; ES: 0.7), ABPM (−16.0 ± 18.1 vs. 7.6 ± 6.8 mmHg min^{-1}; $p < 0.001$; ES: 0.4), and total follow-up (−42.8 ± 22.8 vs. 0.9 ± 11.3 mmHg min^{-1}; $p < 0.0001$; ES: 0.6). This corresponded to an overall average difference of −4 mmHg between groups.

Central Blood Pressure and Augmentation Index

Figure 3 depicts absolute values and exercise net effects on central (aortic) blood pressure (**Figures 3A–F**) and AIx (**Figures 3G–I**) in controls and MLHIV. In the within-group analysis, controls had lower cSBP at 30 min (100.8 ± 4.3 vs. 108.4 ± 13.6 mmHg; β = −8.21; 95% CI = −15.6 to −0.7; $p = 0.03$; ES: 0.7), and lower

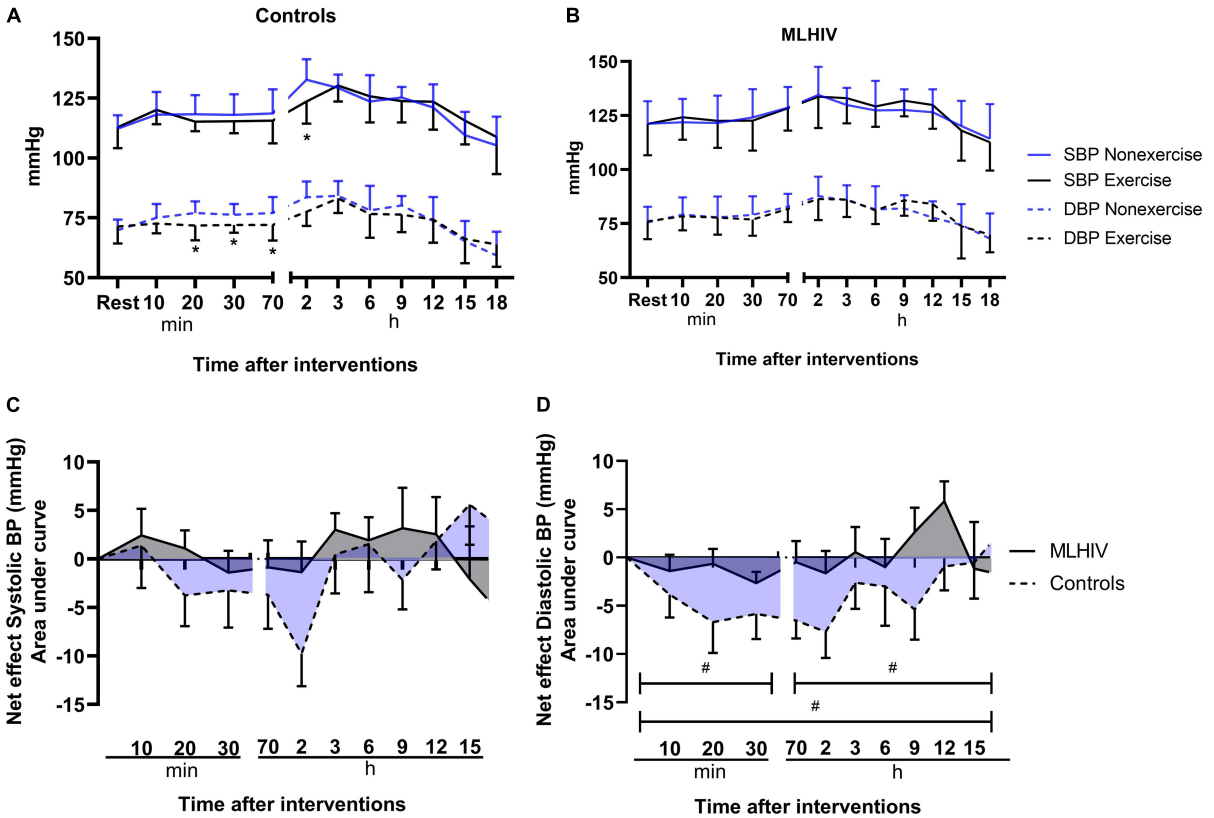

FIGURE 2 | Blood pressure after submaximal exercise or non-exercise sessions in controls **(A)** and men living with HIV **(B)** and exercise net effects on systolic **(C)** and diastolic **(D)** blood pressure. SBP, systolic blood pressure; DBP, diastolic blood pressure. $^{*}p < 0.05$ for changes from baseline (exercise vs. non-exercise session) using linear mixed models. $^{\#}p < 0.05$ for differences between areas under the curves of controls vs. MLHIV.

cDBP at 30 min (72.5 ± 3.3 vs. 78, 8 ± 9.0 mmHg; β = −7.58; 95% CI = −12.6 to −2.4; $p < 0.01$; ES: 0.8), and 70 min (72.6 ± 6.8 vs. 77.5 ± 6.3 mmHg; β = −6.18; 95% CI = −11.2 to −1.0; $p = 0.01$; ES: 2.0) after exercise vs. non-exercise sessions. In MLHIV, reductions in postexercise vs. non-exercise sessions were detected for cSBP at 70 min (116.7 ± 11.1 vs. 113.9 ± 9.4 mmHg; β = −6.53; 95% CI = −12.6 to −0.3; $p = 0.03$; ES: 0.3) and cDBP at 30 min (78.3 ± 8.1 vs. 82.5 ± 7.7 mmHg; β = −4.20; 95% CI = −7.6 to −0.7; $p = 0.01$; ES: 0.95). Lower AIx was found for controls at 30 min postexercise vs. non-exercise sessions (4.7 ± 14.7 vs. 15.7 ± 13.1%; β = −10.53; 95% CI = −18.9 to −2.0; $p = 0.01$; ES: 1.0), while no difference between sessions occurred for MLHIV.

No statistical difference between controls and MLHIV occurred for AUCs of exercise net effects on cSBP (−12.5 ± 15.7 vs. −6.5 ± 7.8 mmHg min^{-1}; $p = 0.24$) and cDBP (−10.7 ± 9.0 vs. −5.0 ± 4.9 mmHg min^{-1}; $p = 0.06$). On the other hand, the AIx reduction was greater in controls vs. MLHIV (−13.6 ± 13.7 vs. −3.1 ± 7.2% min^{-1}; $p = 0.02$; ES: 2.4).

Heart Rate and Heart Rate Variability

Figure 4 shows HR and HRV data from baseline up to 5 min (300 s) following the experimental sessions. Both groups presented higher HR and lower SDNN and rMSSD in all time points after exercise vs. non-exercise sessions, but only controls exhibited lower pNN50. **Figure 5** presents absolute values for HR and HRV between 2 and 18 h after the experimental conditions. In both groups, HR, SDNN, and rMSSD were similar in exercise and non-exercise sessions. The only exception was the lower pNN50 in controls vs. MLHIV after 2 h postexercise vs. non-exercise sessions (14.5 ± 7.2 vs. 17.9 ± 9.4%; β = −11.27; 95% CI = −20.5 to −1.9; $p = 0.01$; ES: 0.4).

Exercise net effects for HR and HRV are presented in **Figure 6**. Comparisons of AUCs in the first 300 s revealed that controls had greater reductions vs. MLHIV in rMSSD (−111.8 ± 32.1 vs. −75.9 ± 22.2 ms min^{-1}; $p < 0.01$; ES: 3.8) and pNN50 (−76.3 ± 28.3 vs. −19.0 ± 13.7% min^{-1}; $p < 0.0001$; ES: 4.4). On the other hand, the Holter analysis showed greater rMSDD reduction postexercise in MLHIV than controls (−45.7 ± 26.1 vs. −13.6 ± 24.5 ms min^{-1}; $p < 0.01$; ES: 0.7).

DISCUSSION

The present study compared the blood pressure, vascular function, and cardiac autonomic modulation after exercise and non-exercise sessions in MLHIV and non-infected controls. To the best of our knowledge, this is the first controlled trial

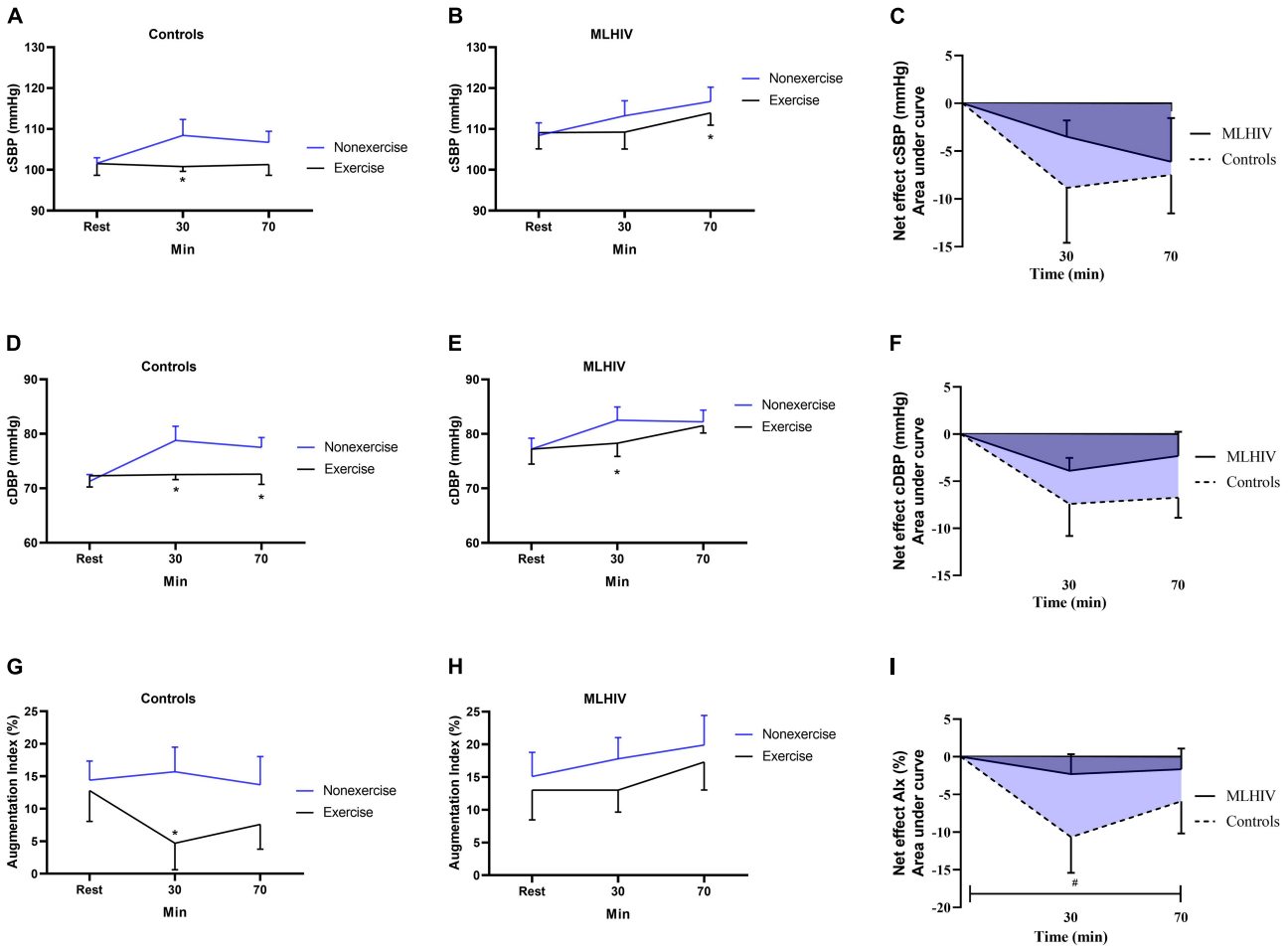

FIGURE 3 | Absolute values and exercise net effects of central systolic blood pressure **(A–C)**, central diastolic blood pressure **(D–F)**, and augmentation index **(G–I)** after exercise and non-exercise sessions in controls and men living with HIV (MLHIV). cSBP, central systolic blood pressure; cDBP, central diastolic blood pressure. $^{*}p < 0.05$ for changes from baseline (exercise vs. non-exercise session) using linear mixed models. $^{\#}p < 0.05$ for differences between areas under the curves of controls vs. MLHIV.

describing cardiovascular responses to acute aerobic exercise in MLHIV, since prior studies addressing vascular function in these patients reported only data at rest (Leite et al., 2017). The major finding was that PEH was attenuated in MLHIV vs. healthy controls—while reductions after exercise have been detected in brachial diastolic blood pressure in controls, changes did not occur in MLHIV. Postexercise decreases in AIx and HRV markers reflecting vagal modulation were also greater in controls vs. MLHIV.

Our data concur with a prior study (Domingues et al., 2018) that failed to identify PEH after resistance exercise in women living with HIV. In that study, five responders out of 12 patients (decreases in SBP > 4 mmHg) had lower CD4/CD8 ratio and used cART for shorter periods. This suggests that the attenuated PEH presently observed in MLHIV might have been influenced by the prolonged use of cART. The average blood pressure reduction in the first 2 h of postexercise recovery was approximately 3.0/4.5 mmHg (SBP/DBP) in controls, which is consistent with values reported for individuals with normal blood pressure (∼4.5/2.6 mmHg) (Perrier-Melo et al., 2020) and higher than decreases in MLHIV (∼0/1 mmHg). Prior research has suggested that the length and magnitude of postexercise hypotension may be influenced by exercise session characteristics, such as duration, intensity, or volume (Brito et al., 2018; Fonseca et al., 2018). Therefore, at least in theory, longer (>25 min) and more intense (>50% of VO_2R) exercise would elicit greater hypotensive responses (de Brito et al., 2019). Our exercise protocol was defined based on recommendations from the ACSM for minimum energy expenditure during health-oriented exercise sessions (American College of Sports Medicine, 2018). Nevertheless, from a clinical perspective, epidemiological studies indicate that a decrease of 2 to 5 mmHg in SBP could reduce the mortality due to cardiovascular causes by 6–14% (Carpio-Rivera et al., 2016).

An important aspect of our study is the inclusion of a non-exercise session to control time effects on blood pressure (de Brito et al., 2019). Due to the circadian variation, blood pressure increases progressively in the morning before showing a decrease

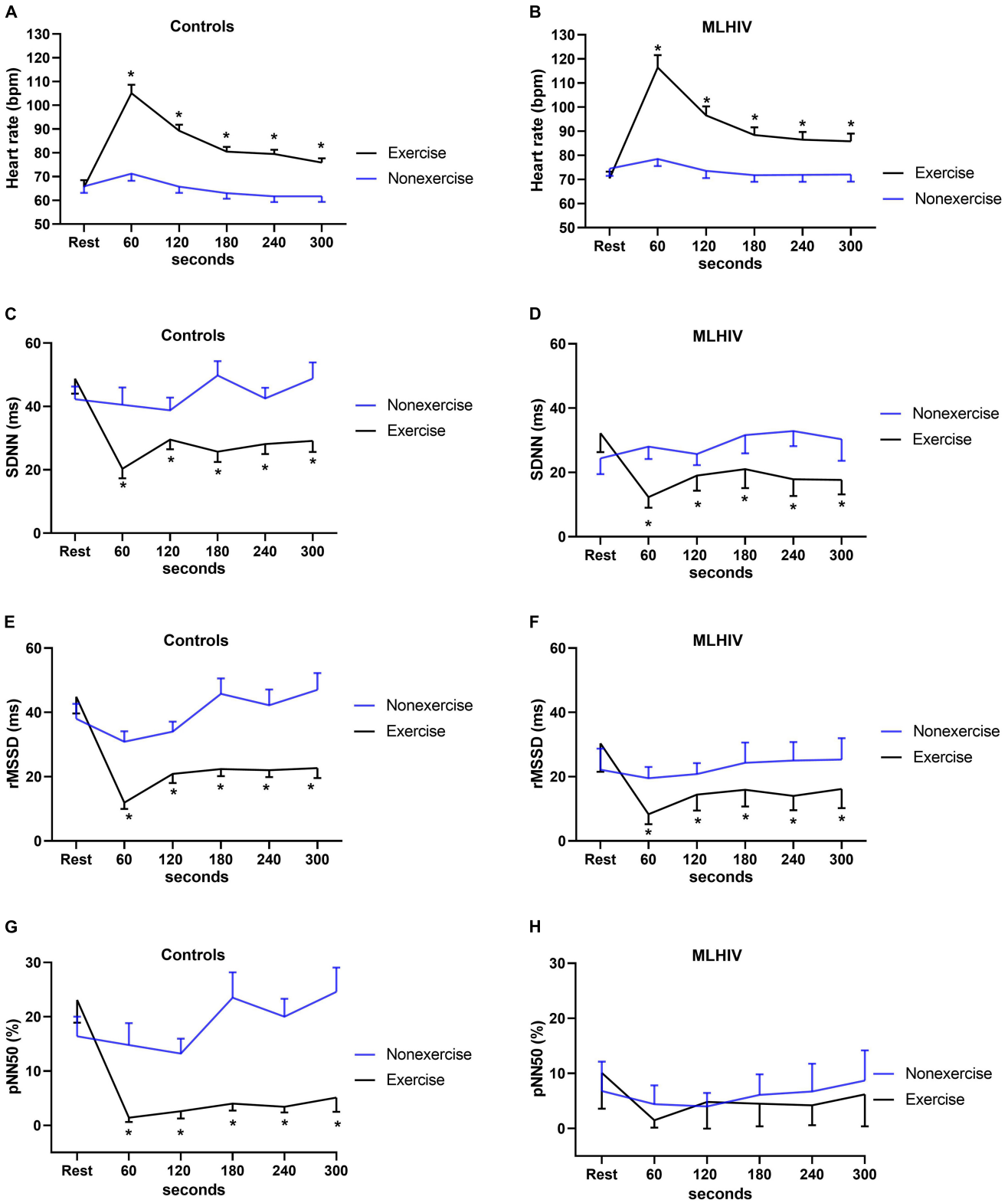

FIGURE 4 | Heart rate **(A,B)** and heart rate variability indices **(C–H)** from baseline to 5 min after exercise or non-exercise sessions in controls and men living with HIV (MLHIV). SDNN, standard deviation of normal to normal intervals; rMSSD, root mean square of successive differences between normal intervals; pNN50, percentage of differences between adjacent normal intervals. *$p < 0.05$ for changes from baseline (exercise vs. non-exercise session) using linear mixed models.

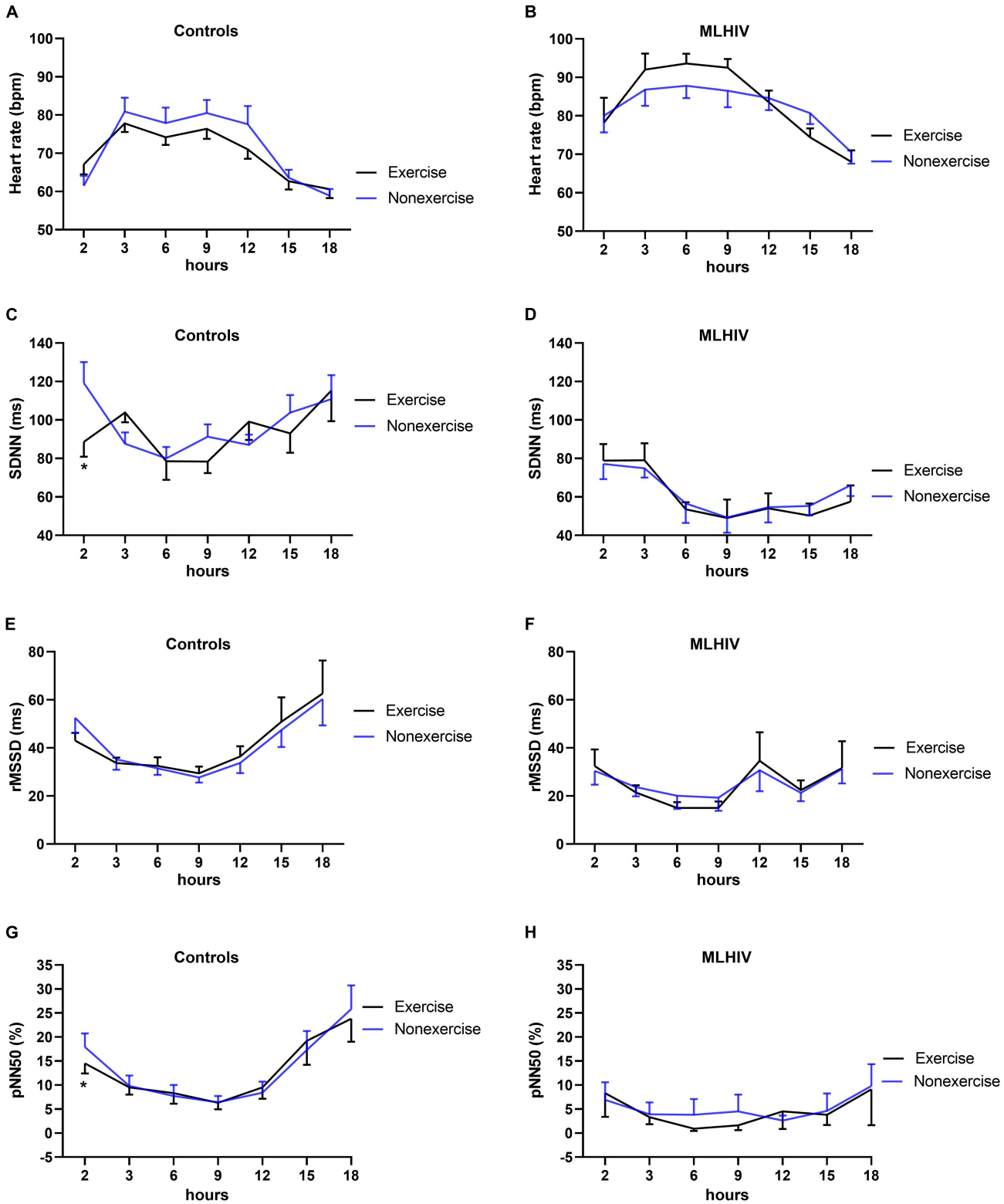

FIGURE 5 | Heart rate **(A,B)** and heart rate variability indices **(C–H)** during 18 h ambulatory blood pressure monitoring after exercise or non-exercise sessions in controls and men living with HIV (MLHIV). SDNN, standard deviation of normal to normal intervals; rMSSD, root mean square of successive differences between normal intervals; pNN50, percentage of differences between adjacent normal intervals. *$p < 0.05$ for changes from baseline (exercise vs. non-exercise session) using linear mixed models.

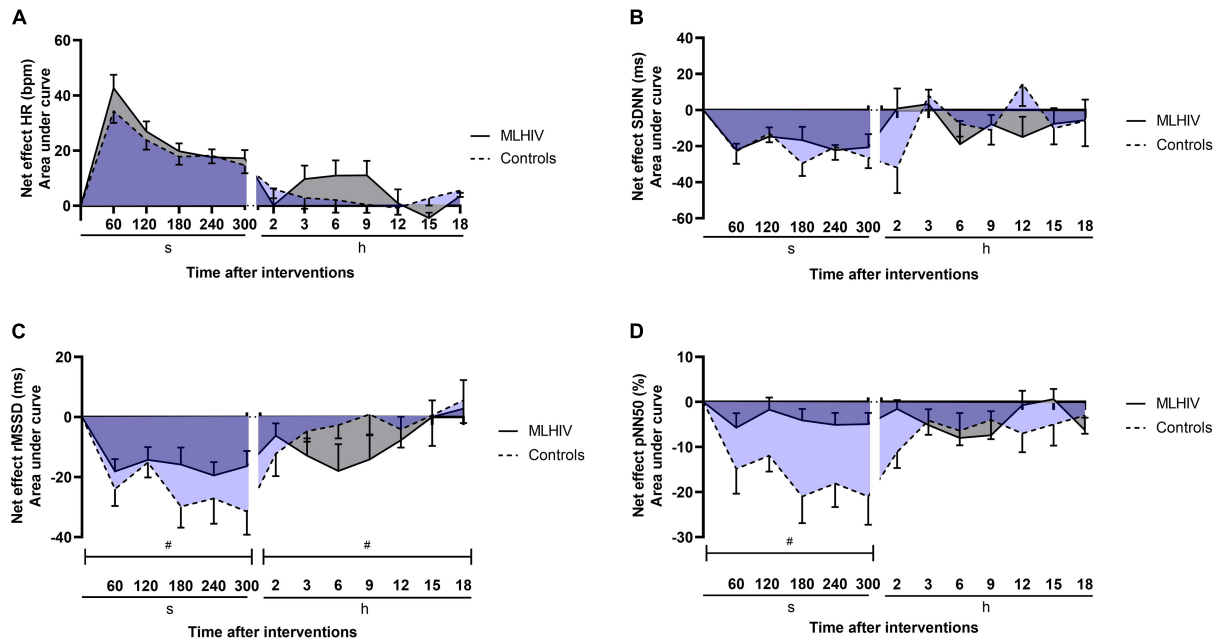

FIGURE 6 | Exercise net effects on heart rate **(A)** and heart rate variability indices **(B–D)** in controls and men living with HIV (MLHIV). SDNN, standard deviation of normal to normal intervals; rMSSD, root mean square of successive differences between normal intervals; pNN50, percentage of differences between adjacent normal intervals. $^{\#}p < 0.05$ for differences between areas under the curves of controls vs. MLHIV.

(Hermida et al., 2007). This is consistent with our data from non-exercise sessions in both groups. Apparently, the exercise session lowered this circadian effect on blood pressure in controls, as previously reported (Cucato et al., 2015; de Brito et al., 2015; Queiroz et al., 2017). It is also worth mentioning that the exercise bouts have been matched for the overall energy expenditure, therefore negating the influence of exercise volume on the magnitude and duration of acute blood pressure reduction (Jones et al., 2007; Fonseca et al., 2018). This strategy resulted from the premise that central baroreflex plays an important role in eliciting PEH. During exercise, vascular smooth muscle (myogenic tone) (Phan et al., 2021) and muscle afferent fibers (exercise pressor reflex) contribute to reset the blood pressure to a higher level (Halliwill et al., 2013). When exercise is terminated, a decrease in sympathetic activity resets the baroreflex to a lower level, contributing to the acute blood pressure reduction (Chen and Bonham, 2010; Halliwill et al., 2013). A greater amount of muscle work—in other words, exercise volume—increases the exercise pressor response (Halliwill et al., 2013). Thus, it is feasible to speculate that the exercise volume would be a major determinant of the PEH phenomenon.

Several studies investigating PEH did not match exercise sessions performed with different intensity for the total amount of work (Forjaz et al., 2004; Pescatello et al., 2004b; Eicher et al., 2010; Casonatto et al., 2011), and this helps on explaining why one of them failed to detect hypotensive responses (Casonatto et al., 2011), while others claimed that intensity would be more determinant than duration to produce PEH (Forjaz et al., 2004; Pescatello et al., 2004b; Eicher et al., 2010). Trials assessing the blood pressure after acute aerobic exercise bouts performed with different intensities, but similar volume (energy expenditure, time × intensity, etc.) have consistently reported similar hypotensive effects (Jones et al., 2007; Fonseca et al., 2018; Cunha et al., 2020).

It is well accepted that PEH is more likely to occur in individuals with high than normal blood pressure (Brito et al., 2014). However, although MLHIV presented higher brachial and central blood pressure at rest than controls, in both groups, those outcomes felt within the normal range (Reboussin et al., 2018). According to the American Heart Association, studies are inconsistent on whether the prevalence of hypertension is higher in patients with treated HIV vs. uninfected individuals (Feinstein et al., 2019). However, less controversial is the association between HIV infection and autonomic dysfunction—the accumulated evidence suggests a shift toward sympathetic dominance (McIntosh, 2016), which concurs with our data.

Besides predisposing patients to higher cardiovascular risk (McIntosh, 2016), autonomic dysfunction also seem to influence parasympathetic reactivation after exercise (Cunha et al., 2015b). In this sense, Cunha et al. (2015b) reported that individuals with lower vagal modulation at rest tend to exhibit slower postexercise parasympathetic reactivation. We could not confirm a delayed vagal reactivation and sympathetic withdrawal within 5 min of recovery after the exercise performed by MLHIV, but rather an attenuated vagal withdrawal. Borges et al. (2012) observed that people living with HIV exhibited lower vagal modulation during the first 30 min of postexercise recovery in comparison with healthy controls. However, since

the vagal modulation at rest was already different between groups, and no data have been provided demonstrating in what extent vagal modulation was reactivated in comparison with baseline, assumptions on how fast vagal reactivation and sympathetic withdrawal occurred after exercise could not be made. Our results indicate that the time course of autonomic responses during recovery did not affect the effects of acute exercise on blood pressure. However, the contribution of autonomic dysfunction in precluding the occurrence of PEH among MLHIV cannot be discarded, since only the parasympathetic modulation has been indirectly assessed. Further research is warranted to confirm these findings, including direct assessments of both sympathetic and parasympathetic activities.

The role of changes in cardiac autonomic control to produce PEH remains controversial even among uninfected individuals. While some studies reported a reduction in sympathetic activity associated with increased vagal activity (Park et al., 2006), others reported no changes (Park et al., 2008; Anunciacao et al., 2016) or observed increased sympathetic activity (Teixeira et al., 2011; Cunha et al., 2016). It has been suggested that an increase in sympathetic outflow concomitant to PEH would be a reflex response to counteract the reduction in blood pressure and the baroreflex resetting (MacDonald, 2002). Our findings partially concur with this premise, since during postexercise recovery the HR was higher and indices reflecting vagal modulation were lower vs. pre-exercise in both MLHIV and controls. Moreover, the greater decrease in DBP was concomitant with lower RMSSD and pNN50 in controls vs. MLHIV. It is therefore feasible to speculate that PEH among controls was not mediated by increased vagal activity (or by opposition, lowered sympathetic activity). In this case, the hypotensive response to exercise would rely on the ability of local vasodilator mechanisms to override the effects of sympathetic activation (Fonseca et al., 2018). This is again in agreement with our results in regards to AIx. Acute reductions in sympathetic vasoconstrictor activity have been reported in exercising muscles (i.e., functional sympatholysis) (Moynes et al., 2013). This phenomenon is thought to be mediated by locally released substances that modulate the effect of noradrenaline on α-receptors, such as histamine, opioids, nitric oxide, prostaglandins, or ATP (Halliwill, 2001), which are yet to be properly assessed in MLHIV.

There is strong accumulated evidence indicating a decrease in arterial stiffness following acute aerobic exercise (Mutter et al., 2017; Pierce et al., 2018). Arterial stiffness depends on several factors, such as endothelial function, smooth muscular vascular tone, and structural features (Martinez-Ayala et al., 2020). It has been proposed that a relaxation of vascular smooth muscle transfers stress from the less extensive collagen fibers to elastin, which could partially account for decreases in arterial stiffness after exercise (Mutter et al., 2017). Evidence demonstrates that changes in immune activity due to HIV infection may increase the pulse wave velocity (Boccara et al., 2006; Rider et al., 2014), disrupting the activity of the matrix metalloproteinase (MMPs) (Misse et al., 2001) and degrading collagen, elastin, laminin, and fibrillin within the arterial wall (Martinez-Ayala et al., 2020). The consequent increasing in vascular resistance limits the vasodilation response during exercise. Accordingly, in the present study, greater postexercise reduction in AIx was found in controls vs. MLHIV. This is suggestive that vascular mechanisms could partially explain the PEH detected in controls, but not in MLHIV.

The major limitation of the present study was the lack of data regarding additional hemodynamic outcomes (e.g., stroke volume, cardiac output, and peripheral resistance), which precluded further analysis on whether the attenuated PEH in MLHIV resulted from central or peripheral mechanisms. Second, despite being compatible with health-oriented exercise prescription (American College of Sports Medicine, 2018), the exercise bout was of relatively short duration and moderate intensity, which limits the generalization of our findings to exercise settings with greater volume (vigorous intensity and/or longer duration). Another important feature refers to the relatively small sample of men only. The small sample probably contributed to the lack of significance of the linear mixed model including "group" as fixed effect, which would be the optimal approach. The exclusive participation of men in the study limits its external validity. However, the inclusion of women might introduce a confounding factor due to differences in sex hormones affecting the autonomic nervous system and blood pressure responses to acute exercise (Carpio-Rivera et al., 2016).

CONCLUSION

An aerobic cycling bout performed with moderate intensity and relatively short duration seemed to be capable to induce PEH in non-infected controls, but not in MLHIV using cART. Although MLHIV presented autonomic dysfunction at rest, no evidence was found of delayed vagal reactivation and sympathetic withdrawal within 5 min after exercise in this group. The acute reduction in DBP among controls was concomitant with greater postexercise decreases in HRV indices reflecting vagal modulation vs. MLHIV. Although no changes between groups were detected for central blood pressure, controls exhibited greater reductions in AIx after exercise than MLHIV.

Overall, these data are indicative of the role of vascular responses to produce PEH, and that the attenuated postexercise blood pressure reduction in MLHIV may have resulted from vascular dysfunction limiting vasodilation. In practical terms, our findings suggest that aerobic exercise sessions with appropriate volume may contribute to reduce blood pressure and cardiovascular risk in MLHIV. However, further studies investigating the effects of acute exercise performed with different intensities and durations on cardiovascular responses in people living with HIV under cART are warranted, to provide information to optimize exercise prescription aiming to reduce blood pressure, improve autonomic control, and prevent vascular dysfunction in those patients.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Review Board of the Pedro Ernesto University Hospital/Rio de Janeiro State University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JBa, TP, WM, FC, PF, and JBo were involved in the conception and design of the research. JBa, TP, and MR collected the data. JBo and MM analyzed the data. JBa, JBo, and PF drafted the manuscript. All authors revised, edited, and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2021.685306/full#supplementary-material

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Sex Differences in Post-exercise Hypotension, Ambulatory Blood Pressure Variability, and Endothelial Function After a Power Training Session in Older Adults

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Background: The efficacy of power training (PT) to acutely reduce blood pressure (BP) in participants with hypertension is controversial, and no studies have assessed the influence of sex on post-exercise hypotension and its mechanisms in older adults.

Purpose: The aims of this secondary, exploratory analysis were to compare the effects of a single bout of PT on post-exercise hypotension, BP variability, and endothelial function between older men and women with hypertension.

Methods: Twenty-four participants with hypertension (12 men and 12 women aged to >60 years old) took part in this crossover study and randomly performed two experimental sessions: power exercise training (PT) and non-exercising control session (Con). The PT protocol was composed of 3 sets of 8–10 repetitions of five exercises performed in the following order: leg press, bench press, knee extension, upright row, and knee flexion, using an intensity corresponding to 50% of one repetition maximal test (1RM) and 2-min intervals between sets and exercises. The concentric phase of exercises during each repetition was performed "as fast as possible," while the eccentric phase lasted 1 to 2 s. During Con, the participants remained at seated rest on the same exercise machines, but without any exercise. Each protocol lasted 40 min. Office BP, flow-mediated dilatation (FMD), 24-h ambulatory BP, and the average real variability (ARV) of systolic and diastolic BP were assessed before and after experimental sessions.

Results: Comparing PT with Con, a reduced office BP after exercise was found in men (systolic BP—average post 1 h: −14 mmHg, $p < 0.001$; diastolic BP—average post 1 h: −8 mmHg, $p < 0.001$) and only a reduced systolic BP in women (average post 1 h: −7 mmHg, $p = 0.04$). Comparing men and women, a reduced systolic BP (post 60': −15 mmHg, $p = 0.048$; average post 1 h: −7 mmHg, $p = 0.046$) and diastolic BP (post 60': −9 mmHg, $p = 0.049$) after the first hour were found in men. In relation to 24-h

ambulatory BP, ARV, and FMD, no statistically significant differences were found between men and women.

Conclusion: In older adults with hypertension, the office BP response after the experimental sessions was different in men and women, showing that the PT protocol is more effective to acutely reduce BP in men. Additionally, the mechanisms behind this reduction remain unclear. This finding suggests that sex cannot be combined to analyze post-exercise hypotension.

Clinical Trial Registration: ClinicalTrials.gov, Identifier: NCT03615625.

Keywords: aging, high blood pressure, blood pressure variability, post exercise hypotension, flow-mediated dilatation, high-velocity resistance training

INTRODUCTION

Resistance training is a cornerstone intervention to counteract age-related declines in physical function (Peterson et al., 2010), improving independence, and reducing the risk of chronic diseases such as hypertension (Mcleod et al., 2019). In particular, power training (PT) has been recommended to improve muscular strength, power and functionality in older adults as it could achieve a greater improvement in functional performance when compared to traditional resistance training (Bottaro et al., 2007). Good levels of functional capacity in older adults are related to a better quality of life, reducing the increase risk of falling, fractures, and hospitalization (Cadore et al., 2013). The characteristics of PT exercises (i.e., low volume and low intensity per set; Chodzko-Zajko et al., 2009) could also attenuate blood pressure (BP) and rate-pressure product responses during exercise (Schimitt et al., 2020), reducing the risk of acute adverse events among individuals with hypertension.

Arterial blood pressure increases during exercise but is depressed after the completion of exercise (Ferrari et al., 2020). This so-called post-exercise hypotension (PEH) is believed to play a major role in BP management as the magnitude of PEH is associated with chronic reductions in BP induced by regular exercise programs (Wegmann et al., 2018). The initial BP level, as well as intensity/volume/type of exercises, can influence both the magnitude and duration of PEH (Pescatello et al., 2004; Domingues et al., 2020). Physiological mechanisms underlying PEH have been under the investigation. The majority of the available studies indicate that the primary factor driving PEH is the reduction in systemic vascular resistance, but a decrease in cardiac output is pointed out as a contributing factor to PEH in older adults (Brito et al., 2014).

Traditional resistance exercises and high-velocity resistance exercise (i.e., PT) are effective strategies to induce PEH under laboratory conditions (Casonatto et al., 2016; Coelho-Júnior et al., 2017; Domingues et al., 2020; Machado Filho et al., 2020). However, few data have demonstrated that this hypotensive effect is not sustained when BP is assessed throughout long periods and under usual conditions in patients with essential hypertension (Queiroz et al., 2015; Oliveira-Dantas et al., 2020; Schimitt et al., 2020). Additionally, a PT session seems to increase the bioavailability of nitric oxide in older women (Coelho-Júnior et al., 2017; Orsano et al., 2018), but studies assessing mechanisms related to PEH after PT in older men are lacking and warrant further investigation. In fact, sex differences exist in the prevalence, awareness, therapy, and prognosis of hypertension and underlying mechanisms responsible for hypertension (Song et al., 2020). The sex influence on PEH was recently described in half-marathon runners (Mourot et al., 2020), attributed to different hemodynamic mechanisms associated with PEH. More specifically, PEH appears to be induced by a reduction in cardiac output in men (Huxley, 2007) whereas a decrease in systemic vascular resistance seems to be a driving factor in women (Parker et al., 2007). TKO

Currently, studies evaluating PT exercise on PEH are scarce and its efficacy remains controversial (Oliveira-Dantas et al., 2020; Schimitt et al., 2020). We have reported no statistically significant differences between PT and Con on ambulatory BP, but a trend toward reduction in daytime ($p = 0.063$) and nighttime ($p = 0.062$) diastolic BP was found after the PT session (Schimitt et al., 2020). Based on this result and considering the potential biological differences between men and women that seems to impact BP responses (Maranon and Reckelhoff, 2013), we decided to run an exploratory analysis, assessing the office and ambulatory BP data separated by sex, and comparing possible differences between older men and women. Additionally, studies comparing acute BP between older men and women are absent, and important sex differences in hemodynamic responses after a single bout of resistance exercise were found in middle-aged adults with normal BP (Mariano et al., 2019). Accordingly, the aims of this secondary, exploratory analysis were to compare the effects of a single bout of PT on PEH, BP variability, and endothelial function between older men and women with hypertension.

MATERIALS AND METHODS

Study Design and Participants

This is an exploratory sub-study of a previously published randomized clinical trial with crossover design (Schimitt et al., 2020) and was conducted in order to compare the sex differences in PEH and its mechanisms after a PT session in older adults. Men and women aged 60 to 75 years with previously diagnosed hypertension by a physician were recruited. Exclusion criteria included previous diagnosis of ischemic heart disease, heart failure, current smokers or ex-smokers for less than 6 months,

body mass index over 39.9 kg/m^2, musculoskeletal problems that restrained them from exercising, changes in antihypertensive medications throughout the trial, diabetes with retinopathy, and participation in structured exercise programs in the last 3 months.

The study was conducted from June 12, 2018, to July 20, 2019, at a tertiary referral hospital in southern Brazil. All participants read and signed an informed consent form before beginning the study. Participation was voluntary, and all ethical principles of confidentiality and data protection were followed. The study protocol was conducted according to the principles of the Declaration of Helsinki and in compliance with the Brazilian legal and regulatory framework for research involving human beings (NR 466/12). The study protocol was approved by the Institutional Review Board of Hospital de Clínicas de Porto Alegre, Brazil, and registered on clinicaltrials.gov under identifier number NCT03615625. The protocol followed the CONSORT guidelines for non-pharmacological treatment (Boutron et al., 2017).

Preliminary Sessions

Each participant completed a clinical screening and underwent electrocardiogram, BP and heart rate measurements with oscillometric monitor, and anthropometric evaluation in the research laboratory as previously described (Schimitt et al., 2020). The rate-pressure product was calculated using the systolic BP and heart rate values (systolic blood pressure × heart rate). Since most participants included in the study had no previous experience with power exercise training, we implemented two familiarization sessions to ensure that participants perform the prescribed exercises properly. Participants were familiarized with power exercises involved in PT and maximal strength testing during the first two sessions. During the third preliminary session, participant's maximal strength was evaluated using one repetition maximal strength test (1-RM) in 5 resistance exercises: leg press, bench press, knee extension, upright row, and knee flexion. A specific warm-up composed of 2 sets of 10 and 5 repetitions, using 50 and 75% of estimated 1-RM load was performed prior to the test. After the first attempt, the load was adjusted through Lombardi coefficients, if necessary. Each participant's 1RM was determined with no more than three attempts with a five-minute recovery between attempts and a two-minute recovery between exercises. These results were used to determine the intensity or load of the experimental sessions. The same trained investigator conducted the tests. Before the test, resting BP was assessed after 20 min of rest in supine position, and these values were used to describe the baseline characteristics of participants.

Experimental Sessions

The participants performed two experimental sessions in a random order: a power training session (PT) and a non-exercising control session (Con). An epidemiologist generated the randomization list composed of random block sizes of four participants using a computer software. This epidemiologist did not participate in the recruitment or assignment to the experimental sessions. The participants and the research team were blinded to the randomization list until the moment of assignment. Participants were instructed to avoid physical exercise for 24 h before the experimental sessions, keep their usual dietary intake, avoid drinking alcohol and coffee before the experimental sessions, and have the same meal 4 h before each session.

Both experimental sessions started between 2 and 3 PM (at the same time of the day to account for potential diurnal variation in BP and residual effects of antihypertensive medications) and lasted approximately 2 h. A washout period of 5–10 days was implemented between the sessions. Each session was composed of 20 min of rest in the supine position, 40 min of PT or Con protocols followed by 60 min of rest in supine position. Standardized office BP and endothelium-dependent brachial vascular function were assessed before and during the first hour (in intervals of 15 min: post 15', post 30', post 45', and post 60') after exercise and control sessions. Afterwards, participants underwent 24 h ambulatory BP monitoring.

The PT protocol was composed of 3 sets of 10 repetitions of five exercises performed in the following order: leg press, bench press, knee extension, upright row, and knee flexion, using an intensity corresponding to 50% of 1-RM and 2-min intervals between sets and exercises. The concentric phase of exercises during each repetition was performed "as fast as possible," while the eccentric phase lasted 1 to 2 s. During Con, the participants remained at seated rest on the same exercise equipment, but without any exercise.

Assessments

Office systolic and diastolic BP was assessed under laboratory conditions using an automatic oscillometric device (Dinamap 1846 SX/P; Critikon, FL, United States; Whincup et al., 1992) according to the Brazilian Guideline of Arterial Hypertension (Malachias et al., 2016). Participants were instructed to remain in supine position and in silence without using any electronic device (i.e., smartphones, notebooks). The use of a supine position to data collection is because BP assessment was performed simultaneously to the flow-mediated dilation (FMD) measurement. A properly-sized cuff was placed on the arm about 2 cm above the antecubital fossa. BP was measured on both arms with a 1-min interval between measures. The arm with the highest B*p* value was used in the characterization, as well as in the pre-and post-intervention evaluation, and the mean BP was calculated automatically by Dinamap.

The 24-h systolic and diastolic BP was assessed through ambulatory BP monitoring (90,702, Spacelabs Medical, WA, United States) after each experiment session in men and women. BP measurements were taken every 15 min at daytime and every 20 min at nighttime. The first daytime period started between 4 and 5 PM (immediately after laboratory session), nighttime between 11 PM and 7 AM, and the second daytime finished at 5 PM on the day after the experimental session. Participants filled a diary about physical activities, symptoms, sleep, and wake-up time. Each examination was considered valid when at least 70% of the expected readings were available and recorded (O'Brien et al., 2013), and the mean BP was calculated automatically by Spacelabs.

Consecutive reading-to-reading BP measurements assessed during ambulatory monitoring were included in a computer

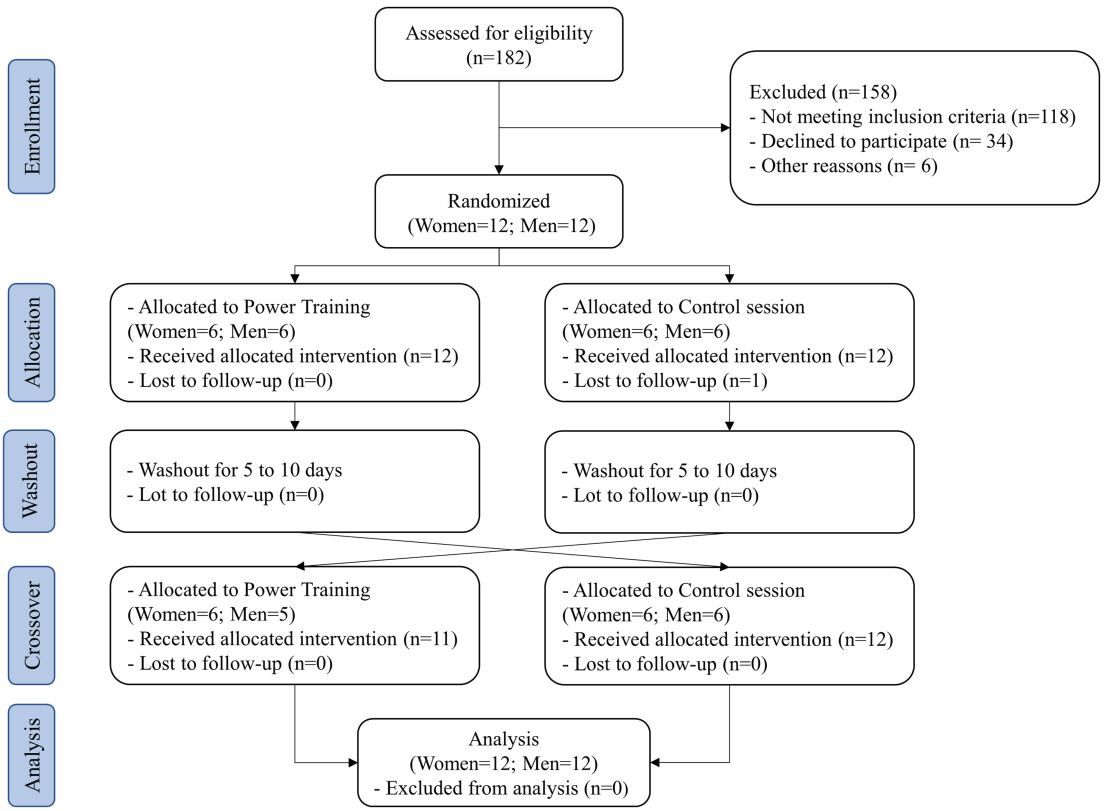

FIGURE 1 | Flow diagram of participants.

software to calculate the average real variability (ARV) (Farrag et al., 2019). ARV weighted for the time interval between consecutive readings was also calculated for both systolic and diastolic BP within the daytime, nighttime, and 24-h periods (Coccina et al., 2019).

The endothelium-dependent brachial vascular function was evaluated using the FMD technique according to guideline (Corretti et al., 2002). Participants were instructed to remain in supine position, and then a BP cuff was placed on the proximal third of the arm (5 cm from the cubital fossa). Baseline longitudinal brachial artery diameters were measured along with pulsed doppler signals for flow velocity analysis. After baseline recordings were completed, reactive hyperemia was induced by inflation of a BP cuff to 50 mmHg above previously measured systolic BP, and cuff inflation was maintained for 5 min. Two-dimensional images of the brachial artery were acquired using a linear-array multi-frequency transducer (7–12 MHz) connected to a high-resolution ultrasound system (HD7XE, Phillips, United States). The time of each image acquisition during the cardiac cycle was determined from simultaneous ECG recording. During image acquisition, anatomical landmarks such as veins and fascial planes were observed to help maintain the same image of the artery throughout the study. The longitudinal image of the brachial artery was recorded continuously for 30 s before (baseline image) to 2 min after cuff deflation (peak diameter). FMD was expressed as the percentage change in arterial diameter from baseline: FMD (%) = (peak diameter − baseline diameter)/baseline diameter × 100. All image analyses were performed offline using the computer software (Brachial Analyzer, Vascular Tools, Medical Imaging Applications, Coralville, IA United States) by an expert evaluator blinded to the sequence of interventions (DeVan et al., 2011).

Sample Size and Statistical Analyses

This article presents a secondary exploratory analyses, and the original sample size was estimated based on the original hypothesis, considering an initial sample size of 24 individuals with hypertension (12 women and 12 men), able to detect a difference of 5 mmHg in 24-h systolic BP among protocols with 80% of statistical power and a type I error rate of 5%, allowing a dropout rate of up to 10% (Schimitt et al., 2020). Data were entered in duplicate by three different researchers. The statistician did not participate in the recruitment or assignment to the experimental sessions and was blinded to the interventions. The assumption of normality was evaluated through the use of the Shapiro–Wilk test. Results were expressed as means and standard deviation (**Table 1**) or standard error (**Tables 2, 3**, and **4**) for variables with normal distribution. In office BP data, average total 1 h was calculated using the average of the 4 values measured after the sessions ((post 15'+ post 30' + post 45' + post 60')/4). The post-FMD values were calculated using the average of 2 consecutive values measured after the sessions (post media 30' = (post 15' + post 30')/2; post media 60' = (post 45' + post 60')/2). Delta office

TABLE 1 | Selected participant characteristics.

	Men (n = 12)	Woman (n = 12)	p value
Age, years (±SD)	67 (5)	67 (4)	0.785
Race/Ethnicity, n (%)			0.237
White	12 (100)	9 (75)	
Black	0 (0.0)	2 (17)	
Asian	0 (0.0)	1 (8)	
Anthropometric measures			
Body weight, kg (range)	92 (79–100)	70 (66–74)	**0.001**
Height, cm (range)	171 (164–174)	157 (155–159)	**<0.001**
BMI, kg/m^2 (SD)	31 (4)	28.2 (3)	**0.047**
Waist circumference, cm (SD)	107 (13)	92 (9)	**0.003**
Anti-hypertensive medications, n (range)	2 (1–4)	2 (1–4)	
Diuretics, n (%)	9 (75)	10 (83)	0.721
β blockers, n (%)	3 (25)	4 (33)	0.423
ACE inhibitors, n (%)	4 (33)	4 (33)	0.833
Angiotensin receptor antagonists, n (%)	9 (75)	5 (42)	0.374
Calcium channel blockers, n (%)	1 (8)	4 (33)	0.174
Hemodynamic measures (± SD)			
Systolic BP, (mmHg)	133 (12)	133 (14)	0.964
Diastolic BP (mmHg)	76 (9)	76 (8)	0.846
Mean BP, (mmHg)	96 (8)	98 (8)	0.567
Heart rate, (bpm)	65 (12)	68 (11)	0.634
RPP, (mmHg*bpm)	8,661 (1721)	8,987 (1796)	0.654
1-RM muscle strength tests, Kg (± SD)			
Leg Press	170.2 (61)	105.0 (27)	**0.003**
Knee Extension	103.3 (29)	69.8 (14)	**0.003**
Knee Flexion	65.9 (17)	41.1 (10)	**0.001**
Bench Press	50.0 (11)	25.9 (6)	**<0.001**
Upright row	38.2 (17)	21.4 (5)	**<0.001**
Total load lifted (kg)	427.6 (121)	263.3 (53)	**<0.001**
Total load/body weight	4.6 (0.9)	3.8 (0.7)	**0.011**

Values are means ± standard derivation (SD) for parametric data, and medians ± interquartile interval (range) for nonparametric data; BMI, body mass index; ACE, angiotensin-converting enzyme; BP, blood pressure; RPP, rate-pressure product; 1-RM, repetition maximal strength. Total load lifted: sum of the 1RM test values.

BP was calculated through the difference between PT and Con sessions in each time-point after intervention (i.e., post 15', post 30', post 45', post 60, and average post 1 h), adjusted for baseline (pre) BP values [(post-exercise BP–pre-exercise BP)–(post-control BP–pre-control BP)] in men and women.

Generalized estimating equations (GEE) analyses were used to assess main effects between experimental sessions (2 sessions: PT and Con) by time in men and women (session*time). To compare the sex differences, we run an additional GEE analysis including a new factor (sex: men *vs.* women), adjusted for BMI, since we found a difference in BMI between men (31 kg.m^{-2}) and women (28 kg.m^{-2}) that can affect BP values (session* time*sex). Post-hoc comparisons were performed using Bonferroni tests. Statistical significance was set *a priori* at $p < 0.05$, and a borderline significance was detected for p-values ranging from 0.05 to 0.10. All statistical analyses were performed using SPSS Statistics for Windows version 22.0 (IBM, Armonk, NY, United States).

RESULTS

A flowchart of the experiments is presented in **Figure 1**. Participants' characteristics at baseline, assessed during the preliminary sessions, are shown in **Table 1**. There were no reported adverse events during the PT or Con session. All participants performed the same amount of exercise during the PT protocol (i.e., 3 × 10 at 50%1RM in 5 resistance exercises). The quality of the ambulatory BP recorded was considered satisfactory in all patients. Additionally, the participants reported no adverse symptoms or difficulties to sleep throughout the study.

Office BP data are presented in **Table 2.** Time*session*sex interaction was found in office BP for systolic BP ($p < 0.001$) and diastolic BP ($p < 0.001$). The BP values before the PT and Con sessions were similar, and no difference between men and women was found at baseline ($p > 0.05$). Comparing the BP values in the first hour after each experimental session with the corresponding baseline BP, no significant change was found after PT, while an increased BP after Con was found ($p < 0.05$). Comparing PT with Con, a reduced systolic BP was found at post 30' ($p = 0.001$), post 45' ($p = 0.031$), post 60' ($p < 0.001$), and average total 1 h ($p < 0.001$) in men, and at post 15' ($p < 0.001$) and average total 1 h ($p = 0.046$) in women. Additionally, a reduced diastolic BP was found after PT when compared with Con at post 15' ($p = 0.043$), post 30' ($p = 0.003$), post 45' ($p = 0.004$), post 60' ($p = 0.001$), and average total 1 h ($p < 0.001$) only in men. Comparing BP response after the first hour between men and women, a reduced systolic BP at post 60' ($p = 0.048$) and average total 1 h ($p = 0.046$), and a reduced diastolic BP at post 60' ($p = 0.049$) were found in men.

Ambulatory BP data are presented in **Tables 3** and **4**. No time*session*sex interaction was found in systolic ($p = 0.335$) and diastolic ($p = 0.208$) ambulatory BP (**Table 3**). Additionally, we run an exploratory analysis to assess the main effects between PT and Con in men and women separately. Time*session interaction was found in ambulatory BP for systolic ($p = 0.041$), and a borderline time*session interaction was found for diastolic BP ($p = 0.050$) in men but not in women. Compared with Con, 24-h diastolic BP decreased after PT in men. Nighttime systolic and diastolic BP also decreased after PT in men. In women, no statistically significant differences were found between PT and Con sessions for daytime, nighttime, and 24-h systolic/diastolic BP (**Table 3**).

BP variability and FMD data are presented in **Table 5**. No time*session*sex interaction was found for BP variability and FMD data.

DISCUSSION

To the best of our knowledge, no previous studies have evaluated sex differences in acute blood pressure and hemodynamic responses after the PT session in older adults with essential hypertension. A salient finding of this exploratory study was a reduced office BP values after exercise in men than women, highlighting important differences between older men and women on PEH after the PT protocol. Additionally, no significant

TABLE 2 | Office blood pressure measures before (pre) and after (for 1 h) the power training and control sessions in men and women.

Variables	Control	Power training	Intervention		Sex	
			ΔBP (mmHg)	*p* value	ΔBP (mmHg)	*p* value
Systolic						
Pre						
Men	130.4 ± 4.0	129.0 ± 3.5	−1.4 ± 2.9	0.622	3.6 ± 5.3	0.191
Women	134.5 ± 3.5	129.5 ± 4.4	−5.0 ± 3.8	0.191		
Post 15'						
Men	136.6 ± 4.6	131.7 ± 5.1	−4.9 ± 3.4	0.151	5.4 ± 7.3	0.437
Women	142.4 ± 5.9	132.1 ± 5.2	−10.3 ± 2.5	**<0.001**		
Post 30'						
Men	141.5 ± 5.4	132.2 ± 4.6	−9.3 ± 2.9	**0.001**	−3.3 ± 6.4	0.400
Women	143.6 ± 5.1	137.6 ± 4.5	−6.0 ± 3.4	0.074		
Post 45'						
Men	145.1 ± 5.5	122.1 ± 11.3	−23.0 ± 10.7	**0.031**	−16.9 ± 12.7	0.103
Women	148.9 ± 4.9	142.8 ± 5.7	−6.1 ± 4.5	0.178		
Post 60'						
Men	150.0 ± 5.4	131.3 ± 4.5	−18.7 ± 3.6	**<0.001**	−15.0 ± 7.2	**0.048**
Women	149.1 ± 4.8	145.5 ± 5.6	−3.7 ± 3.3	0.260		
Average post 1 h						
Men	143.3 ± 4.9	129.3 ± 5.7	−13.9 ± 4.4	**<0.001**	−7.4 ± 4.9	**0.046**
Women	146.0 ± 5.0	139.5 ± 4.9	−6.5 ± 2.8	**0.046**		
Diastolic						
Pre						
Men	76.4 ± 3.1	75.3 ± 2.1	−1.1 ± 1.7	0.516	0.7 ± 3.5	0.491
Women	74.6 ± 2.9	72.8 ± 2.9	−1.8 ± 2.9	0.554		
Post 15'						
Men	80.2 ± 3.5	74.7 ± 3.0	−5.5 ± 2.7	**0.043**	−2.6 ± 4.3	0.537
Women	77.3 ± 3.1	74.4 ± 3.1	−2.9 ± 2.3	0.202		
Post 30'						
Men	81.8 ± 3.4	74.7 ± 2.9	−7.1 ± 2.4	**0.003**	−6.6 ± 4.7	0.079
Women	77.8 ± 3.3	77.3 ± 2.8	−0.5 ± 2.4	0.861		
Post 45'						
Men	82.6 ± 3.4	76.2 ± 3.3	−6.5 ± 2.3	**0.004**	−5.0 ± 4.5	0.352
Women	78.4 ± 3.0	76.9 ± 3.1	−1.5 ± 2.9	0.601		
Post 60'						
Men	87.0 ± 3.5	76.0 ± 2.8	−11.0 ± 1.7	**0.001**	−9.2 ± 4.9	**0.049**
Women	78.4 ± 3.4	79.2 ± 3.1	1.8 ± 2.9	0.752		
Average post 1 h						
Men	82.9 ± 3.3	75.4 ± 2.8	−7.5 ± 2.2	**<0.001**	−6.0 ± 2.2	0.052
Women	77.9 ± 3.0	76.9 ± 2.9	−1.0 ± 2.2	0.638		

Values: mean ± SE; BP, blood pressure. p-value in the intervention is comparing the interventions separately in men and women (power training vs control). p-value in the sex is comparing the results of the sexes in the interventions (men vs women).

difference between men and women was found in ambulatory BP, endothelial function as assessed by FMD, and short-term BP variability. Given the limited sample size of the present study, further studies are necessary to understand how PEH is mediated in older hypertensive individuals. The differences in BP responses to PT between older men and women are highlighted and deserve further studies to deepen the physiological mechanisms associated with PEH.

Scarcity data have suggested that men and women presented similar BP responses after a single bout of resistance training (Senitko et al., 2002; Queiroz et al., 2013). Controversially, a recent study assessing PEH after a traditional resistance exercise protocol in middle-aged men and women with normal BP found BP reduction in men but not in women (Mariano et al., 2019). In the present study, we specifically explore differences between older men and women using office and ambulatory BP data. To the best of our knowledge, this is the first study to compare older men and women with hypertension in PEH induced by PT. We found differences between older men and women on PEH after PT in office BP. Systolic and diastolic BP was lower in men than women after the first hour (post 60' systolic BP: −15 mmHg, $p = 0.048$; Post 60' diastolic BP: −9 mmHg, $p = 0,049$).

TABLE 3 | Ambulatory blood pressure measures after the power training and control sessions in men and women.

Variables	Control	Power training	Intervention		Sex	
			ΔBP (mmHg)	*p* value	ΔBP (mmHg)	*p* value
Systolic BP						
24-h						
Men	130.8 ± 4.2	130.7 ± 3.4	−0.1 ± 2.7	0.973	−0.3 ± 4.8	0.835
Women	130.9 ± 3.6	131.1 ± 3.4	0.2 ± 1.6	0.915		
Daytime						
Men	134.2 ± 4.3	136.1 ± 3.7	1.2 ± 2.5	0.447	−0.2 ± 5.0	0.511
Women	133.2 ± 4.0	134.2 ± 3.4	1.0 ± 1.3	0.451		
Nighttime						
Men	122.2 ± 4.9	119.0 ± 4.9	−3.2 ± 2.9	0.272	−1.3 ± 5.4	0.401
Women	125.4 ± 3.7	123.5 ± 3.6	−1.9 ± 3.2	0.543		
Diastolic BP						
24-h						
Men	77.6 ± 3.2	75.4 ± 3.1	−2.2 ± 1.6	0.178	−2.4 ± 4.1	0.709
Women	76.0 ± 2.6	76.2 ± 2.7	0.2 ± 0.8	0.833		
Daytime						
Men	80.3 ± 3.4	79.3 ± 3.0	−1.0 ± 1.3	0.427	−1.8 ± 4.1	0.366
Women	78.7 ± 2.9	79.4 ± 2.7	0.8 ± 0.7	0.309		
Nighttime						
Men	69.8 ± 2.9	67.0 ± 3.2	−2.8 ± 2.1	0.180	−1.4 ± 4.2	0.608
Women	70.6 ± 2.2	69.2 ± 2.7	−1.4 ± 1.9	0.457		

Values: mean ± SE; BP, blood pressure (mmHg); Δ: net effect. Intervention: Δ BP and p-value corresponding to the individual differences between control and power training sessions in each sex. Sex: Δ BP and P value corresponding to the differences between men and women.

TABLE 4 | Exploratory analyses of ambulatory blood pressure, separated by sex, after the power training and control sessions.

Variables	Control	Power training	Intervention	
			ΔBP (mmHg)	*p* value
Systolic				
24-h				
Men	132.5 ± 6.6	129.8 ± 4.5	−2.8 ± 2.9	0.336
Women	129.7 ± 3.0	129.6 ± 2.3	−0.1 ± 1.6	0.943
Daytime				
Men	135.5 ± 6.7	135.1 ± 5.2	−0.4 ± 2.6	0.891
Women	131.8 ± 3.4	132.7 ± 2.4	0.9 ± 1.4	0.505
Nighttime				
Men	123.7 ± 7.5	117.4 ± 4.9	−6.3 ± 3.1	**0.042**
Women	124.7 ± 3.7	122.1 ± 2.6	−2.6 ± 3.1	0.398
Diastolic				
24-h				
Men	78.1 ± 4.1	74.2 ± 3.1	−3.9 ± 1.9	**0.036**
Women	75.1 ± 1.9	75.1 ± 2.0	0.0 ± 0.8	0.973
Daytime				
Men	80.3 ± 4.2	78.1 ± 3.2	−2.2 ± 1.3	0.109
Women	77.6 ± 2.3	78.4 ± 2.0	0.8 ± 0.7	0.244
Nighttime				
Men	70.7 ± 3.7	65.5 ± 3.0	−5.2 ± 2.5	**0.036**
Women	69.9 ± 2.1	68.1 ± 2.1	−1.9 ± 1.9	0.319

Values: mean ± SE; BP, blood pressure. p-value in the intervention is comparing the interventions separately in men and women (power training vs control).

The magnitude and duration of PEH seem to be influenced by intensity/volume of exercise (Pescatello et al., 2004; Domingues et al., 2020), and differences in total overload (sets × repetitions × total load lifted × number of exercises x time under tension) can be a key component in predicting the magnitude and duration of PEH after different resistance exercise protocols. In our study, the relative amount of exercise performed during the PT protocol was identical between men and women (3 × 8–10 - 50%1RM - 5 exercises). However, men performed higher total overload than women due to their greater values of maximal strength (i.e., 1RM tests; **Table 1**). We believe that the total overload performed during the PT session (i.e., sets × repetitions × number of exercises × total load lifted × time under tension) seems to be the main factor that helps to explain the above-mentioned differences between men and women, influencing the magnitude and duration of PEH after PT in older adults.

Ambulatory BP monitoring is the best strategy to observe and understand the BP behavior throughout daily living activities and sleeping periods (Grossman, 2013). Only two studies have evaluated ambulatory BP after a single bout of PT in older adults with hypertension (Oliveira-Dantas et al., 2020; Schimitt et al., 2020). In the study of Oliveira-Dantas et al. (2020), a PT protocol (i.e., three sets of six repetitions in eight exercises using elastic bands) was performed by 14 hypertensive older women and no significant difference between PT and Con in 24-h, daytime, and nighttime BP was found. In the present study, no statistical differences in men and women were found in daytime, nighttime, and 24-h BP when

TABLE 5 | Short-term blood pressure variability and endothelial function measures after the power training and control sessions in men and women.

Variables	Control	Power training	Intervention		Sex	
			ΔBP (mmHg)	*p* value	ΔBP (mmHg)	*p* value
Systolic BP variability						
24-h						
Men	8.6 ± 0.4	8.4 ± 0.4	0.2 ± 0.4	0.240	0.4 ± 0.6	0.351
Women	8.8 ± 0.3	8.9 ± 0.4	0.2 ± 0.4	0.618		
Daytime						
Men	9.2 ± 0.6	8.6 ± 0.4	0.7 ± 0.6	0.077	−1.0 ± 0.6	0.106
Women	9.2 ± 0.4	9.5 ± 0.4	0.3 ± 0.5	0.589		
Nighttime						
Men	7.7 ± 0.4	7.9 ± 0.5	0.2 ± 0.3	0.839	0.3 ± 0.8	0.718
Women	8.2 ± 0.6	8.1 ± 0.6	0.1 ± 1.0	0.928		
Diastolic BP variability						
24-h						
Men	6.9 ± 0.3	6.6 ± 0.3	0.3 ± 0.4	0.457	0.2 ± 0.6	0.667
Women	6.9 ± 0.5	6.9 ± 0.5	0.1 ± 0.5	0.827		
Daytime						
Men	7.1 ± 0.3	6.5 ± 0.4	0.6 ± 0.3	0.062	0.3 ± 0.7	0.409
Women	7.4 ± 0.5	7.1 ± 0.6	0.3 ± 0.5	0.478		
Nighttime						
Men	6.9 ± 0.4	7.1 ± 0.6	0.3 ± 0.7	0.591	0.4 ± 0.8	0.681
Women	6.1 ± 0.7	6.8 ± 0.5	0.7 ± 0.7	0.398		
Flow-mediated dilatation (%)						
Pre						
Men	4.8 ± 0.3	4.9 ± 0.3	0.1 ± 0.2	0.564	0.8 ± 1.2	0.575
Women	6.8 ± 0.8	6.1 ± 1.4	0.7 ± 1.1	0.515		
Post media 30'						
Men	4.6 ± 0.5	5.1 ± 0.3	0.5 ± 0.6	0.374	0.3 ± 1.1	0.517
Women	6.3 ± 0.7	6.5 ± 0.7	0.2 ± 0.8	0.778		
Post media 60'						
Men	5.7 ± 0.3	5.0 ± 0.3	0.7 ± 0.5	0.153	1.7 ± 1.7	0.825
Women	5.8 ± 0.5	6.8 ± 1.5	1.0 ± 1.0	0.354		

Values: mean ± SE; BP, blood pressure (mmHg); ARV, average real variability (mmHg); Δ: net effect. Intervention: Δ BP and p-value corresponding to the individual differences between control and power training sessions in each sex. Sex: Δ BP and p-value corresponding to the differences between men and women.

using the three factors in the same GEE analysis (session*time*sex). Additionally, we run an exploratory analysis (**Table 4**), splitting our sample and assessing the ambulatory BP data separated by sex (session*time), and found significant reduction in 24-h diastolic BP after PT when compared with Con in older men but not in women, as well as nighttime ambulatory BP reduction only in men. We assumed that the inclusion of an extra factor in our analysis, using a limited sample size, reduced the statistical power of the study. Based on the limitation of this exploratory analysis, future studies should include a larger sample size to confirm the present results.

In an attempt to provide insight into physiological mechanisms, we assessed endothelium-dependent vasodilation using FMD, and short-term BP variability as an index of cardiovagal baroreflex sensitivity (Floras et al., 1988). The improvement in endothelial function after exercising is one of the potential mechanisms that could help explaining the occurrence of PEH (Halliwill et al., 2013). We found no significant difference in endothelial function between the PT and Con sessions. Additionally, changes in blood pressure were not associated with the corresponding changes in FMD. Similar results have been reported in previous studies that also evaluated FMD at different times after exercise sessions as they did not observe decreases in this variable (Birk et al., 2013; Katayama et al., 2013). Short-term BP variability has an important association with autonomic cardiovascular system, and higher BP fluctuations can be associated to impairments on autonomic nervous system that results in high BP levels (Nardin et al., 2019). Few studies have evaluated the acute effects of exercise on ambulatory BP variability (Caminiti et al., 2019; Batista et al., 2020; Matias et al., 2020), and no previous studies have compared BP variability between older men and women after a single bout of exercise. A previous study demonstrated reduction in 24 h and daytime systolic (~2 mmHg) and diastolic (~1 mmHg) BP variability after a single bout of combined aerobic and resistance exercise in postmenopausal women with hypertension (Matias et al., 2020). However, the present study did not find reductions on ambulatory BP variability after PT. Further studies are necessary to deepen the physiological mechanisms associated with PEH.

Some limitations of the present study should be taken into account in order to properly interpret the present results.

The limited number of participants enrolled in this study is due to the hypothesis tested in the original trial (Schimitt et al., 2020). However, most of the previous data assessing PEH have also used similar sample sizes. Clearly, a larger sample size trial is mandatory to confirm the present results. The endothelium-dependent brachial vascular function assessment using the FMD technique and recording data throughout 2 min after releasing the cuff could also be considered a limitation, since a recent guideline suggests that time to peak dilation in sedentary older adults can occur after the 2-min period (Thijssen et al., 2019). The enrollment of untrained participants aged 60–75 years may have limited the generalization of our findings to younger adults or trained older adults. However, the analyses of well-functioning and untrained older adults are more likely to represent the elderly population. Our study provides important implications for the exercise prescription targeted to aging individuals with essential hypertension. The use of a resistance exercise protocol is highly recommended to older adults (Fragala et al., 2019), exploring potential sex differences on PEH that should be taken into account in order to prescribe PT for hypertensive older adults. Additionally, considering that the magnitude of PEH after exercise is directly related to the baseline BP (Queiroz et al., 2015), it is reasonable to assume that the PT protocol could be more effective in reducing BP in participants with uncontrolled hypertension. The use of researchers blinded to interventions for outcome assessment and analysis and the BP assessment using ambulatory BP monitoring, the gold-standard method to assess PEH, are also strengths of this study.

CONCLUSION

In older adults with hypertension, the office BP response after the experimental sessions was different in men and women, showing that the PT protocol is more effective to acutely reduce BP in men. Additionally, the mechanisms behind this result remain unclear. Moreover, the exploratory results for ambulatory BP suggest the need of further studies to assess the potential difference between men and women.

This finding highlights the relevance of this type of resistance training as a non-pharmacological strategy to acutely reduce BP in older men with hypertension and reduced physical capacity. In women, however, the duration of PEH after our PT protocol was very limited. Different PT protocols might be necessary to induce benefits among women. Our findings have important implications for exercise prescription targeting older individuals with hypertension in that sex cannot be combined to analyze PEH.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Hospital de Clínicas de Porto Alegre, Brazil. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LC: conceptualization, investigation, and writing—original draft. RS and LD: investigation, formal analysis, and writing—review and editing. TA, HT, and SF: formal analysis and writing—review and editing. RF: conceptualization, investigation, formal analysis, funding acquisition, writing—original draft, and writing—review and editing. All authors contributed to the article and approved the submitted version.

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Post-dynamic Resistance Exercise Hypotension: Exploring Individual Responses and Predictors

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Background: Post-dynamic resistance exercise hypotension (PREH) has been largely demonstrated. However, little is known regarding the interindividual variation of PREH magnitude and its predictors (i.e. factors of influence).

Aims: To assess the interindividual variation of PREH and its predictors related to the characteristics of the individuals and the exercise protocol.

Methods: This study retrospectively analysed data from 131 subjects included in seven controlled trials about PREH (including at least one dynamic resistance exercise and one control session) conducted by two research laboratories. The interindividual variation was assessed by the standard deviation of the individual responses (SD_{IR}), and linear regression analyses were conducted to explore the predictors.

Results: PREH showed moderate interindividual variation for systolic (SBP, SD_{IR} = 4.4 mmHg; 0.35 standardised units) and diastolic blood pressures (DBP, SD_{IR} = 3.6 mmHg; 0.32 standardised units). For systolic PREH, multivariate regression analysis (R^2 = 0.069) revealed higher baseline SBP (B = −0.157, p = 0.008) and higher number of sets (B = −3.910, p = 0.041) as significant predictors. For diastolic PREH, multivariate regression analysis (R^2 = 0.174) revealed higher baseline DBP (B = −0.191, p = 0.001) and higher exercise volume (i.e. number of exercises *sets per exercise *repetitions per sets >150; B = −4.212, p = 0.001) as significant predictors.

Conclusion: PREH has a considerable interindividual variation. Greater PREH magnitude is observed in individuals with higher baseline blood pressure and after exercise protocols that comprehend higher number of sets and exercise volume.

Keywords: blood pressure, interindividual, between-subjects variation, moderators, strength exercise

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INTRODUCTION

Arterial blood pressure (BP) decreases significantly after the execution of different types of exercise (Brito et al., 2018), which has been called post-exercise hypotension (Kenney and Seals, 1993). A recent meta-analysis reported reductions of significant magnitude in clinic as well as 24-h ambulatory BPs after the execution of a single session of dynamic resistance

exercise (Casonatto et al., 2016), showing that post-resistance exercise hypotension (PREH) may be clinically relevant. In addition, PREH magnitude seems to be associated with the chronic reductions observed in BP after a period of dynamic resistance training (Tibana et al., 2014; Moreira et al., 2016), suggesting that this acute response may be used to predict BP responsiveness to training.

However, PREH magnitude varies considerably among the studies in the literature. The meta-analysis conducted by Casonatto et al. (2016) reported a significant heterogeneity between the studies' results for systolic and diastolic PREH. Some studies suggest that variation in PREH magnitude may be influenced by factors related to the population and/or the exercise protocol characteristics. Along this line, Queiroz et al. (2015) found greater magnitude of PREH in hypertensives than normotensives, and greater PREH has been reported after dynamic resistance exercises involving larger muscle mass (Polito and Farinatti, 2009) and multiple sets (Polito and Farinatti, 2009; De Brito et al., 2014; Figueiredo et al., 2015b). Nevertheless, the influence of these factors on PREH has been mainly defined based on comparisons of mean responses (i.e. comparing averages between conditions: hypertensives vs. normotensives; larger vs. smaller mass; and single vs. multiple sets) and not analysing whether there is a real interindividual variation in the response to exercise.

Recently, in the exercise physiology research field, a growing interest has showed up regarding the investigation of the interindividual responses to exercise, which may be relevant for individualizing exercise prescription (Hecksteden et al., 2015). For example, a former study (Lima et al., 2015) explored the interindividual variability of PREH and showed that 46 and 38% of the subjects actually presented systolic and diastolic PREH, respectively. However, this study provided no information about the heterogeneity of the individuals' responses to a control intervention, which is relevant since it has been proposed (Atkinson and Batterham, 2015; Hopkins, 2015) that a true interindividual variation in physiological responses to exercise can only be accepted if the variation (i.e. standard deviation) of the changes in the exercise condition is larger than obtained in a control condition. Importantly, only when a true interindividual variation is demonstrated, it is logical to perform analyses regarding the individual responses, such as identifying responders to exercise or exploring predictors of responsiveness (Atkinson and Batterham, 2015; Hopkins, 2015). Nevertheless, to the best of our knowledge, no previous study has investigated the magnitude of interindividual variation of PREH before evaluating responsiveness or predictors.

Considering this background, it could be noted that despite PREH occurrence has already been well documented in the literature, its magnitude seems to vary among the subjects (i.e. interindividual variation), being important to detect whether this variation actually occurs using appropriate and new statistical approaches and, if so, which factors can influence this response. Therefore, the current study was designed to explore the interindividual variation of PREH and its predictors using a two-step approach. First, the magnitude of the interindividual variation in PREH was determined to confirm whether there was a variation among the subjects' responses. Second, analyses were carried out to explore the potential predictors of PREH, considering factors related to the individuals' and the exercise protocol's characteristics.

MATERIALS AND METHODS

Experimental Design

This is a retrospective study that pooled data from seven previous trials (Rezk et al., 2006; Queiroz et al., 2009, 2013, 2015; Teixeira et al., 2011; Prista et al., 2013; Freire et al., 2018) conducted by two different research laboratories (i.e. the Exercise Hemodynamic Laboratory from the School of Physical Education and Sport of the University of São Paulo and the Research Group on Acute and Chronic Effects of Exercise from the Department of Physical Education of the Federal University of Rio Grande do Norte) between 2006 and 2018.

The included trials attended the following criteria as: (1) were designed to evaluate PREH; (2) presented at least one dynamic resistance exercise session and one control session; (3) had clinic BP as outcome (i.e. BP measurements taken at rest before and after the exercise and control interventions); (4) employed a crossover design; (5) evaluated subjects free of cardiovascular disease except for arterial hypertension; and (6) evaluated subjects not receiving anti-hypertensive medications.

Data Analysis

From each trial, the following individuals' characteristics were extracted for each subject: gender (male or female); age (years); body mass index (BMI, kg/m^2); diagnosis of hypertension (presence or absence); and baseline BP (defined as the average of the clinic BP values assessed before the exercise and control interventions). Additionally, the following exercise protocol data were extracted: time of day (morning or afternoon/evening); exercise intensity ($\geq$70% of 1RM or $<$70% of 1RM; Casonatto et al., 2016); number of exercises ($\geq$7 or $<$7; Queiroz et al., 2015); number of sets (single or multiple); and number of repetitions ($\geq$12 or $<$12; i.e. median value of the current data). Resistance exercise volume was calculated by the product between the number of exercises, number of sets per exercise and number of repetitions per set, being classified as high $\geq$ 150 or low $<$ 150, which is a cut-off point previously employed in a PREH's meta-analysis (Casonatto et al., 2016). Total exercise load was calculated by the product between exercise volume and exercise intensity, being classified as high $\geq$ 105 or low $\leq$ 105, which corresponds to the previous exercise volume of 150 multiplied by the previous intensity of 70% 1RM.

Finally, PREH was calculated for each subject in each trial by the net effect of the exercise, i.e. the difference between BP responses observed in the exercise and the control sessions, calculated as: PREH net effect = [(post-exercise BP – baseline BP in the exercise session) – (post-control BP – baseline BP in the control session)] (Fecchio et al., 2020).

To avoid duplicated data from the same subject, the following procedures were adopted. In trials that had evaluated

post-exercise BP at multiple moments (e.g. 45, 60 and 90 min after the exercise), the moment of greatest PREH was considered for data analysis. Regarding the trials that had compared different sessions of dynamic resistance exercise (e.g. exercises with different intensities), the session used for data analysis was raffled to avoid any selection bias.

Statistical Analyses

Data distribution was confirmed by Shapiro-Wilk tests. PREH occurrence in the whole sample was checked by comparing the net effect with zero using paired t-tests.

The interindividual variation of PREH (aim 1) was calculated by the standard deviation of the individual responses (SD_{IR}) as previously reported (Atkinson and Batterham, 2015; Hopkins, 2015). SD_{IR} represents the true magnitude of the interindividual variation of PREH adjusted for the random variations derived from biological and measurement sources, being calculated by the formula: $SD_{IR} = \sqrt{\left(SD_{ercercise^2} - SD_{control^2}\right)}$ where $SD_{exercise}$ and $SD_{control}$ are the standard deviations of BP responses (i.e. the difference between BP measured before and after the intervention) observed in the exercise and the control sessions, respectively. Then, to a qualitative evaluation of the variation magnitude, SD_{IR} was expressed in standardised units, calculated by dividing SD_{IR} by the standard deviation of baseline BP and the results were interpreted using the following cut-off points: <0.30 = low; 0.30 to 0.59 = moderate; and > 0.60 = high variation (Hopkins, 2015).

When moderate or high variations were found, further analyses were conducted to explore the potential predictors of PREH (aim 2) using simple and multiple linear regressions. Firstly, attendance to statistical assumptions of linear regression modelling were checked. Linear relationship between continuous independent factors and PREH as well absence of heteroscedasticity were checked by scatter graphs. Normal distribution of standardised residuals was checked through histograms of residuals and normal probability plots. Independence of residuals was assessed by Durbin-Watson test accepting values between 1.0 and 3.0. Absence of multi-collinearity among the variables was confirmed by tolerance >0.1 and variance inflation factor < 10.0. The presence of outliers was checked by the standardised predicted values and residuals, and a minimal sample size of 10 subjects for each independent factor was attended. Afterwards, single regression analyses were performed considering PREH (net effect) as the dependent variable and the individuals' (gender, age, BMI, hypertension diagnosis and baseline BP) and the exercise protocol's characteristics (intensity, number of exercises, number of sets, number of repetitions, exercise volume, total exercise load and time of day) as the independent variables. For the multiple regression analyses, a hierarchical modelling was performed with the independent variables clustered into two blocks: the primary block involved the individuals' characteristics, and the secondary block included the exercise protocol's characteristics. The inclusion of the variables in the multivariate model was performed with the forward method within each cluster.

Additionally, the proportion of responders and non-responders regarding the occurrence of PREH was calculated. For that, first, the typical error (TE) of BP measurement was calculated as: $TE = SD_{difference} / \sqrt{2}$, where $SD_{difference}$ is the standard deviation of the differences in BP measured before the interventions in the exercise and control sessions (Hopkins, 2000). Then, subjects who presented PREH greater than TE were classified as responders (Swinton et al., 2018).

Statistical analyses were conducted using the Statistical Package for the Social Sciences for Windows (IBM SPSS Statistics, version 20) and the significance level was set as $p \leq 0.05$. Continuous data were reported as mean value ± standard deviation.

RESULTS

This study included 131 subjects, mainly non-elderly (95.4%), males (62.6%), nonobese (92.3%) and without hypertension (84.0%; **Table 1**). Regarding the dynamic resistance exercise

TABLE 1 | Descriptive data of the sample ($n = 131$).

	Value
Characteristics of individuals	
Male, n	82
Age, ys	36 ± 15
Body mass index, kg/m^2	24.4 ± 3.4
Hypertension diagnosis, n	21
Baseline systolic BP, mmHg	114 ± 12
Baseline diastolic BP, mmHg	73 ± 11
Characteristics of exercise protocol	
Exercise intensity	
< 70% of 1 RM, n	108
≥ 70% of 1 RM, n	23
Number of exercises	
< 7 exercises, n	68
≥ 7 exercises, n	63
Number of sets	
Simple sets, n	22
Multiple sets, n	109
Number of repetitions	
< 12, n	70
≥ 12, n	61
Exercise volume	
Low, n	35
High, n	96
Total exercise load	
Low, n	39
High, n	92
Time of day	
Morning, n	53
Evening, n	78

Continuous values are expressed as mean ± standard deviation. BP, blood pressure; RM, repetition maximum. Exercise volume was calculated by the product between number of exercises, number of sets per exercise and number of repetitions per set, being denoted as high when ≥ 150. Total exercise load was calculated by the product between exercise volume and intensity, being denoted as high when ≥ 105.

TABLE 2 | Quantification of the interindividual variation of post-dynamic resistance exercise hypotension.

	BP response to exercise session	BP response to control session	SD_{IR} mmHg (95%CI)	SD_{IR} standardised units (95%CI)	Classification
SBP	−5.3 ± 7.3	1.5 ± 5.9	4.4 (1.9 to 5.9)	0.35 (0.15 to 0.47)	Moderate
DBP	−0.1 ± 5.6	3.1 ± 4.3	3.6 (2.0 to 4.7)	0.32 (0.18 to 0.42)	Moderate

Values are mean ± SD; BP, blood pressure; CI, confidence level; SD_{iFs} standard deviation of the individual responses; SBP, systolic blood pressure; and DBP, diastolic blood pressure.

TABLE 3 | Multiple linear regression assessing predictors of post-dynamic resistance exercise hypotension for systolic blood pressure (SBP).

	Coefficient B (unstandardized)	Coefficient β (standardised)	Value of *P*
Multivariate model (R2 = 0.069)	–	–	0.010*
Intercept	14.374 ± 7.221	–	0.049*
Baseline SBP (mmHg)	−0.157 ± 0.059	−0.233	0.008*
Multiple sets (yes or no)	−3.910 ± 1.891	−0.180	0.041*
Variables Excluded from the Model			
Male gender (yes or no)	–	−0.057	0.592
Age (years)	–	−0.016	0.858
BMI (kg/m^2)	–	−0.007	0.939
Hypertension diagnosis (yes or no)	–	0.053	0.610
Exercise intensity ≥70%1RM (yes or no)	–	0.077	0.380
N. exercises ≥7 exercises (yes or no)	–	−0.084	0.429
N. repetitions ≥12 (yes or no)	–	0.011	0.910
High exercise volume (yes or no)		0.060	0.662
High total exercise load (yes or no)		0.041	0.738
Evening (yes or no)	–	0.051	0.587

*BMI, body mass index; RM, repetition maximum; N, number; High exercise volume ≥ 150; High total exercise load ≥ 105; *significant ($p < 0.05$).*

protocols, most of the subjects executed protocols of low-intensity (82.4%), multiple sets (83.2%), high exercise volume (73.3%) and high total exercise load (70.2%), while almost half of them executed exercises in the evening (59.5%), with seven or more exercises (48.1%) and 12 or more repetitions per set (46.6%). All trials measured BP by the auscultatory method and with the subjects resting in the seated position. In five trials, post-exercise BP measurements were taken 60 min after the exercise while in the other two trials, BP was measured at 45 and 90 min. The occurrence of PREH in the whole sample (group analysis) was confirmed by significant net effects found for systolic (−6.8 ± 8.1 mmHg, $p < 0.001$) and diastolic (−3.3 ± 7.1 mmHg, $p < 0.001$) BPs.

The results related to the quantification of the interindividual variation of PREH (aim 1) are shown in **Table 2**. SD_{IR} for SBP was 4.4 mmHg and 0.35 standardised units, revealing a moderate variation. For DBP, SD_{IR} was 3.6 mmHg and 0.32 standardised units, also revealing a moderate variation.

Regarding aim 2, simple linear regressions (**Supplementary Figure 1**) showed a significant association of systolic PREH only with baseline SBP ($B = -0.131$, $p = 0.025$). In the multivariate analysis (**Table 3**), baseline SBP and number of sets were included in the final model as: systolic PREH = 14.374–0.157 (baseline SBP) – 3.910 (multiple sets: yes = 1, no = 0); $R^2 = 0.069$; $p = 0.010$. For diastolic PREH (**Supplementary Figure 2**), simple linear regressions showed significant associations with baseline DBP ($B = -0.215$; $p < 0.001$), hypertension diagnosis ($B = -3.797$; $p = 0.024$), male gender ($B = -3.862$; $p = 0.002$), high exercise volume ($B = -4.844$, $p < 0.001$) and high total exercise load ($B = -4.162$, $p = 0.002$). In the multivariate analysis (**Table 4**), baseline DBP and high exercise volume were included in the final model as: Diastolic PREH = 13.680–0.191 (baseline DBP) – 4.212 (high exercise volume: yes = 1, no = 0); $R^2 = 0.174$; $p < 0.001$.

Lastly, for the analyses of responders, TEs of baseline SBP and DBP were, respectively, 3.9 and 4.2 mmHg. Thus, 41 subjects (31.3%) were classified as non-responders regarding systolic PREH, whereas 72 subjects (55.0%) were classified as non-responders for diastolic PREH (**Figure 1**).

DISCUSSION

The current study has two main findings. First, there is a moderate interindividual variation in PREH magnitude as demonstrated by SD_{IR}'s results. Second, systolic PREH is mainly influenced by baseline BP and the number of sets executed during the dynamic resistance exercise session, while diastolic PREH is mainly influenced by baseline DBP and the exercise volume performed as demonstrated by multiple linear regression analyses.

As consistently reported in the current literature (Casonatto et al., 2016), the occurrence of PREH was also observed in the whole sample of the present study by the significant net effects demonstrated for SBP ($p < 0.001$) and DBP ($p < 0.001$). The novelty of the current study was to perform a robust quantification of the interindividual variation of PREH using recommended statistical approaches (Atkinson and Batterham, 2015; Hopkins, 2015). In this sense, the present analyses confirmed the existence of a moderate interindividual variation in PREH for both SBP and DBP based on SD_{IR} expressed in standardised units being between 0.30 and 0.59. Indeed, the current results show a considerable variation in PREH magnitude across the subjects for both systolic (net effect ± SD_{IR} = −11.2 to −2.4 mmHg) and diastolic PREH (net effect ± SD_{IR} = −6.9

TABLE 4 | Multiple linear regression assessing predictors of post-dynamic resistance exercise hypotension for diastolic blood pressure (DBP).

	Coefficient B (unstandardized)	Coefficient β (standardised)	Value of *P*
Multivariate Model (R2 = 0.174)			<0.001*
Intercept	13.680 ± 3.912	–	0.001*
Baseline DBP (mmHg)	−0.191 ± 0.053	−0.289	0.001*
High exercise volume (yes or no)	−4.212 ± 1.295	−0.264	0.001*
Variables Excluded from the Model			
Male gender (yes or no)	–	−0.162	0.081
Age (years)	–	0.107	0.216
BMI (kg/m^2)	–	0.013	0.885
Hypertension diagnosis (yes or no)	–	−0.132	0.249
Exercise intensity ≥70%1RM (yes or no)	–	−0.054	0.551
N. of exercises ≥7 exercises (yes or no)	–	0.160	0.090
Multiple sets (yes or no)		0.005	0.969
N. repetitions ≥12 (yes or no)	–	0.005	0.947
High total exercise load (yes or no)	–	0.047	0.828
Evening (yes or no)	–	−0.008	0.922

*BMI, body mass index; RM, repetition maximum; N, number; High exercise volume ≥ 150; High total exercise load ≥ 105; *significant (p < 0.05).*

to 0.3 mmHg). In addition, this pioneer demonstration of real interindividual variation on PREH allowed the exploration of its predictors related to individuals' and exercise protocol's characteristics.

Along this line, the current study firstly performed simple regression analyses to investigate individuals' characteristics associated with PREH, which showed greater systolic PREH associated with higher baseline SBP, whereas greater diastolic PREH was associated with higher baseline DBP, hypertension diagnosis and male gender. However, hypertension diagnosis and male gender were not maintained in the multivariate model, suggesting that their associations with PREH might be dependent of another factor or factors. In fact, baseline BP was the only investigated individual's characteristic that predicted PREH magnitude in the multivariate analysis, with higher baseline BP being associated with greater PREH. Previous original studies (Melo et al., 2006; Queiroz et al., 2009) have also reported significant associations between BP decrease after a dynamic resistance exercise session and the pre-exercise or baseline BP. Thus, the current result strengthens this finding by analysing data from a larger sample and employing specific statistical approaches. Importantly, the existence of such association may have clinical relevance, revealing a greater effectiveness of dynamic resistance exercise in individuals with altered BP who may benefit more from this acute post-exercise BP-lowering effect (Kenney and Seals, 1993).

Regarding the influence of exercise protocol's variables, the number of sets and the exercise volume were significant predictors of PREH, suggesting that a greater amount of exercise is associated with a greater PREH. This result contrasts with previous meta-analytic data (Casonatto et al., 2016) that found no influence of exercise volume (i.e. exercises *sets *repetitions) on PREH. The discrepancy may reflect the higher sensitivity of the statistical analyses performed with individual participant data, as used in the present study, to detect predictors' effects (Tierney et al., 2015). The greater hypotensive effect induced by protocols with higher volume may be related to a greater effect on vasculature since De Brito et al. (2014) showed a bigger decrease in forearm vascular resistance after a session of dynamic resistance exercise with higher volume (i.e. multiple versus single sets), which also resulted in a greater PREH. Differently from variables related to exercise volume, the current results did not reveal exercise intensity as a predictor of PREH. Indeed, the role of exercise intensity on PREH is controversial in the literature with original studies reporting greater PREH after high- (Duncan et al., 2014; De Brito et al., 2015a), moderate- (Figueiredo et al., 2015a) and low- (Rezk et al., 2006) intensity exercises as well as no difference between different intensities (Cavalcante et al., 2015). Lastly, the current study did not find a significant association between the time of day in which exercise was executed and PREH although such influence has been reported for aerobic exercise (De Brito et al., 2015b). Nevertheless, to the better of our knowledge, no previous study has directly compared PREH after morning and evening exercise.

The present results might have important clinical implications. Besides confirming an interindividual variability on PREH's responses, the study showed that an important fraction of the subjects did not present a relevant decrease in BP after resistance exercise (i.e. 31.3% were not responders for SBP and 55.5% for DBP), highlighting the importance of optimising exercise protocol for inducing PREH, which can be done based on the current results. In this sense, the multivariate regression analyses revealed a greater importance of exercise volume than intensity to optimise PREH, since exercise volume or sets but not total exercise load or intensity were significant predictors. In fact, the final multivariate regression models showed that exercise protocols composed by multiple sets and high exercise volume (at least 150) can potentiate systolic and diastolic PREH in approximately 4 mmHg. Importantly, it has been proposed that regular exposure to greater PREH episodes might optimise chronic BP reductions after training (Luttrell and Halliwill, 2015; Brito et al., 2018). Therefore, to increase PREH magnitude, the present study results suggest the employment of training protocols with more exercises, more sets, and more repetitions per set.

Besides employing a robust interindividual statistical technique, the main strength of the present study was to have pooled data from seven trials, including a sample of 131 individuals with different characteristics and that executed different protocols of dynamic resistance exercises, allowing for a comprehensive exploration of PREH occurrence, variation, and predictors. On the other hand, it is important to mention some limitations. First, the study is limited by its retrospective design that confines the analyse only to the predictors included in the original trials and the characteristics addressed in each

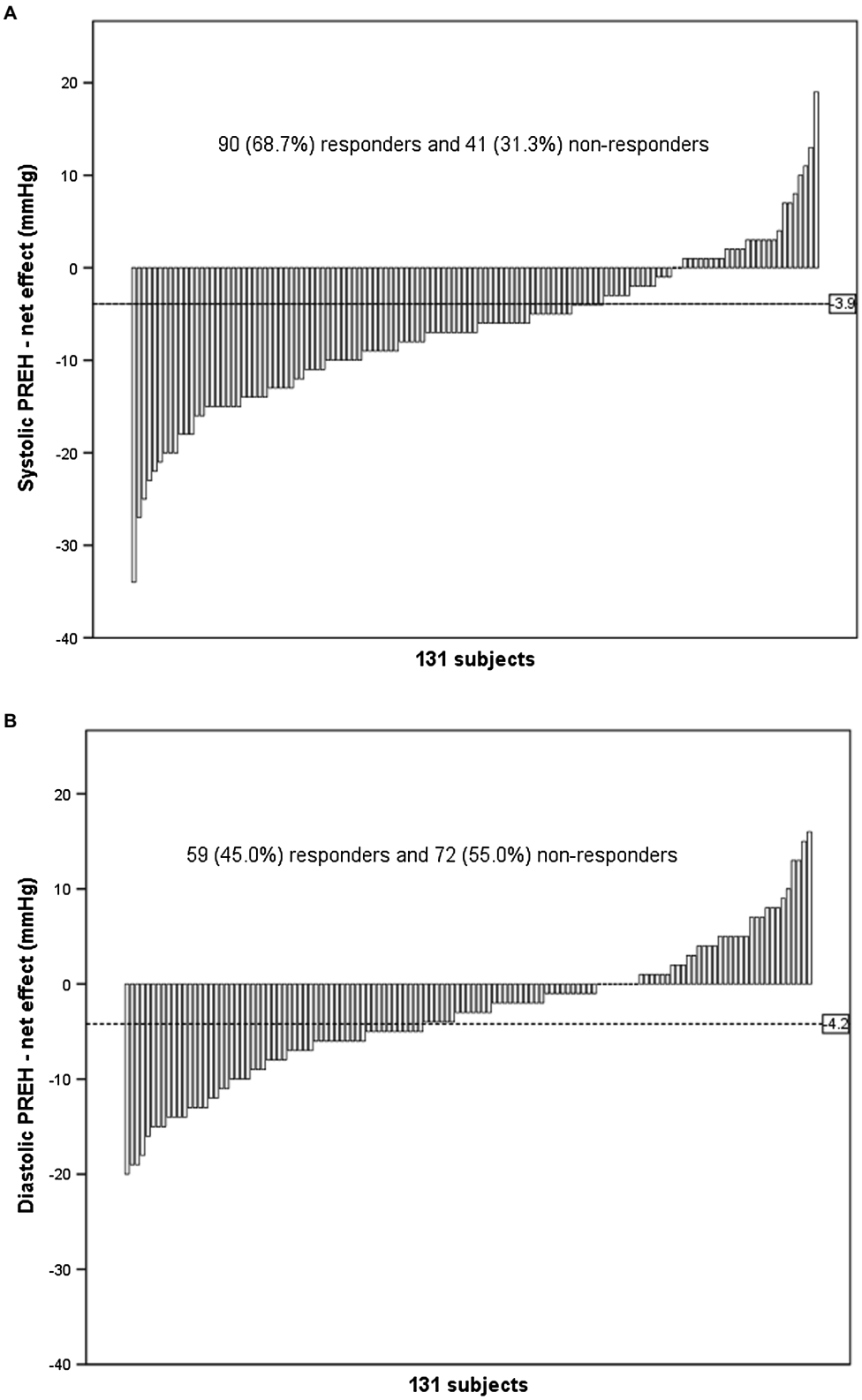

FIGURE 1 | Individual responses of post-dynamic resistance exercise (PREH) calculated by the exercise net effect [(post-exercise BP – baseline BP in the exercise session) – (post-control BP – baseline BP in the control session)]. The dashed line represents the typical error of measurement and individuals that presented PREH greater than this threshold were classified as responders.

one of them. However, the analysis of interindividual variation and predictors requires a substantial sample size (Hopkins, 2015) that is difficult to achieve in single prospective trials. Second, the present study opted to analyse the greatest BP decrease after the exercise, limiting the results to the interindividual variation of the greatest PREH. The inclusion of BP measurements performed at different time points after the exercise can be suggested as a bias. However, in a complementary analysis considering data collected at 60 min after the interventions ($n = 106$, data not shown), PREH variation remained moderate (SBP $SD_{IR} = 0.34$ and DBP $SD_{IR} = 0.32$ standardised units). Third, the multivariate models presented R^2 of 0.069 and 0.174, respectively, for SBP and DBP, explaining 7 and 17% of the PREH variations, which suggests that factors beyond those covered in the original studies included in this analysis, such as hydration status, genetic polymorphisms, race, muscle mass involved in exercise or others, may also affect PREH magnitude and should be investigated by future research. Finally, some caution is needed regarding the extrapolation of the current findings to other situations. In this sense, the present results cannot be transferred to other clinical populations, such as patients with cardiovascular disease, because they may present different cardiovascular dysfunctions that may impose a greater variation in PREH with different predictors. Additionally, results cannot be extrapolated for other types of exercise, such as aerobic exercise, in which an increase in volume prolongs a constant cardiovascular load instead of promoting a progressive cardiovascular load as observed in dynamic resistance exercise, this difference may induce a different impact on PREH variation. Future studies should investigate the interindividual variation of BP responses in these situations.

CONCLUSION

PREH presents a considerable interindividual variation with its magnitude being influenced by baseline BP, number of exercise sets and exercise volume.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, and further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical review and approval were not required for retrospective study on human participants in accordance with the local legislation and institutional requirements as original studies included in analysis have already been approved by ethics committees. Written informed consent for participation was obtained for the oiriginal trials included in this study.

AUTHOR CONTRIBUTIONS

RF: conception, design, statistical analysis, interpretation of data, and writing of the manuscript. AQ: extraction of data and revision of the manuscript. RR-D and EC: conception, design, extraction, interpretation of data, and revision of the manuscript. CF: conception, design, interpretation of data, revision of the manuscript, and final approval of the version to be submitted. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2021.787444/full#supplementary-material

Supplementary Figure 1 | Simple linear regression analyses assessing possible predictors of systolic post-dynamic resistance exercise hypotension (PREH) related to the following characteristics of the individuals and exercise protocol: baseline systolic blood pressure, SBP **(A)**; gender **(B)**; age **(C)**; body mass index, BMI **(D)**; hypertension diagnosis **(E)**; daytime of exercise **(F)**; exercise intensity **(G)**; number of exercises **(H)**; number of sets **(I)**; number of repetitions **(J)**; exercise volume **(K)**; and total exercise load **(L)**. RM, repetition maximum. *Significant moderator ($p < 0.05$). Dashed line represents the typical error of SBP (–3.9 mmHg) and individuals below this line are responders.

Supplementary Figure 2 | Simple linear regression analyses assessing possible predictors of diastolic post-dynamic resistance exercise hypotension (PREH) related to the following characteristics of the individuals and exercise protocol: baseline diastolic blood pressure, DBP **(A)**; gender **(B)**; age **(C)**; body mass index, BMI **(D)**; hypertension diagnosis **(E)**; daytime of exercise **(F)**; exercise intensity **(G)**; number of exercises **(H)**; number of sets **(I)**; number of repetitions **(J)**; exercise volume **(K)**; and total exercise load (L). RM, repetition maximum. *Significant moderator ($p < 0.05$). Dashed line represents the typical error of DBP (–4.2 mmHg) and individuals below this line are responders.

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ORIGINAL RESEARCH
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Post-exercise Hypotension in Patients With Coronary Artery Disease

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Background: Blood pressure (BP) and hemodynamic changes occurring in the recovery phase after a single bout of exercise have not been extensively studied in coronary artery patients, despite the potential clinical implications of reducing BP through exercise. This study aimed at investigating the hemodynamic and arterial baroreflex mechanisms possibly involved in post-exercise hypotension (PEH) in patients with coronary artery disease.

Methods: In 42 normotensive coronary artery patients undergone a Cardiac Rehabilitation Program, we evaluated before and after their daily exercise training session: blood pressure (BP) and heart rate (HR). In a subgroup ($n = 29$), daily BP profile was also evaluated by ambulatory BP monitoring. In those patients showing PEH ($n = 15$), we evaluated: Cardiac Output (CO), Stroke Volume (SV), total peripheral resistances (TPR), forearm (FVR) and calf (CVR) vascular resistances, and spontaneous baroreflex sensitivity (BRS).

Results: After exercise TPR was significantly reduced with a similar contribution from CVR and FVR, whereas CO and SV significantly increased. BRS showed a significant reduction mainly due to a BRS decrease in response to hypertensive stimuli. Systolic BP (SBP) was significantly reduced for 12 h after the end of a single exercise session.

Conclusion: These findings indicate that in coronary artery patients, the recovery phase after exercise is characterized by PEH which is mediated mainly by a generalized peripheral vasodilation and appears to influence BP behavior throughout the daily life. Finally, the cardiac component of the arterial baroreflex seems to contribute indirectly to BP reduction occurring after exercise.

Keywords: exercise, hypotension, baroreflex, neural regulation, hemodynamics, ischemic heart disease, post-exercise hypotension

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INTRODUCTION

It has been widely reported that after a single out of dynamic exercise, blood pressure (BP) is usually reduced below pre-exercise control value thus configuring the phenomenon indicated as post-exercise hypotension (PEH; Kenney and Seals, 1993). We reported that in hypertensives, PEH is mediated by a peripheral vasodilation, which may involve metabolic factors linked to

post-exercise hyperemia, overriding a concomitant, reflex sympathetic activation directed to the vasculature, with the possible aim to oppose excessive decreases in BP (Legramante et al., 2002). In addition, we have suggested that baroreflex mechanisms controlling heart period retain the potential for a greater opposition to hypotensive stimuli (Legramante et al., 2002), thus contributing to buffer excessive BP decreases.

Because exercise training has been shown to produce beneficial effects in many cardiovascular diseases (Fletcher et al., 1996) and to improve prognosis after myocardial infarction (O'Connor et al., 1989) nowadays, regular physical activity is recommended as a major strategy in the secondary (in addition to primary) prevention of cardiovascular disease. Thus BP reduction may be an important target of secondary prevention even in normotensive patients with established coronary artery disease (CAD), since even small reductions in BP might be useful with regard to coronary risk (Oparil, 1999).

To our knowledge, however, only one small study investigated changes in BP occurring in the recovery phase after exercise in CAD patients (Fagard and Vanhees, 2000), with no clear-cut results. Little is known as the duration of PEH, because BP monitoring was discontinued shortly after exercise and even less as the persistence of BP decrease.

Ambulatory blood pressure monitoring (ABPM) provides information about the dynamics of BP, (and heart rate as well) during daily life, and is now being increasingly recommended for both diagnostic and therapeutic purposes (Mallion and Baguet, 2006).

Accordingly, the aim of the present study was to investigate BP, hemodynamic, and autonomic (baroreflex) changes occurring after an exercise training session in CAD patients enrolled in a supervised exercise training program and whether BP lowering after a single exercise session is sustained over time while patients have continued their daily activity.

MATERIALS AND METHODS

Subjects

The study included 42 normotensive CAD male patients (mean age 59 ± 7.2) consecutively referred to our Cardiac Rehabilitation Center under reimbursement of the Italian Health Care system. Criteria for eligibility were male sex, sinus rhythm, and normal BP values (≤ 130/80 mmHg) Exclusion criteria were hypertension, congestive heart failure, residual angina, insulin-treated diabetes, major arrhythmias, age > 70 years, EF < 45%. Diet and medications were not altered during the study. The study was performed during a residential cardiac rehabilitation program. Informed consent was obtained from each subject, and the study was approved by the Ethical Committee of the Cardiac Rehabilitation Center.

Measurements

Blood Pressure and Heart Rate

In all patients, BP and HR were measured in the sitting posture, with a conventional sphygmomanometer, before and after their daily exercise training session. In a subgroup of patients ($n = 29$), a 24-h non-invasive ambulatory BP monitoring (ABPM; Spacelabs, United States) was performed twice. In order to study the baroreflex control of sinus node, in a subgroup of subjects showing PEH ($n = 15$), BP was continuously and non-invasively measured by Finapres (Finapres, Ohmeda 2,350, Englewood, CO, United States). The output of the Finapres was transmitted *via* the RS 232 serial port and processed by a software program written in our laboratory. Baroreflex sensitivity (BRS) was assessed by means of the sequences technique (Iellamo et al., 1994).

Systemic Hemodynamics

In the same subgroup of patients featuring PEH ($n = 15$), an echocardiographic (Sequoia, Acuson, United States) parasternal long-axis view was used to measure end-diastolic and end-systolic left ventricular diameters as well as the aortic ring diameter. The instantaneous flow velocity in the ascending aorta was measured using continuous-wave Doppler. Stroke volume (SV) was calculated as the product of mean time-velocity integrals and the cross-sectional area of the aortic orifice, as done in previous studies (Ihelen et al., 1984; Iellamo et al., 1994; Legramante et al., 2002). Cardiac output (CO) was calculated as the product of SV and HR. Total peripheral resistance (TPR) was calculated in dynes sec^{-1} cm^{-2} according to the following formula: TPR = 80 mean blood pressure/CO.

Regional Hemodynamics

Brachial and femoral artery ultrasound scans were obtained with a 7 MHz linear array transducer (Celermajer et al., 1992). The diameter of the arteries was measured from B-mode images over longitudinal sections. Arterial blood flow velocity was measured from pulsed Doppler signal. At least 5 measurements were averaged. Volumetric flow was calculated for each study by multiplying the angle corrected velocity time integral of the Doppler signal by the heart rate and the vessel cross-sectional area. All measurements used for flow calculations were obtained simultaneously.

Experimental Protocol

After the patients had sat quietly for 15 min, BP was measured twice, 5 min apart, and the measurements were averaged. After the instrumentation, following a 20 to 25-min adaptation period to the supine position patients underwent baseline echocardiographic, vascular echo-doppler examination, and continuous BP and HR recordings for 10 min.

After baseline measurements, patients underwent their normal exercise training session on a cycle ergometer according to their Rehabilitation Program, as previously reported (Iellamo et al., 2000). Briefly, the training program consisted of 2 daily sessions of 30 min of stationary cycling 6 times a week for 2 weeks (24 sessions overall) combined with calisthenics. Training intensity was graded according to 85% of the HR max reached in an initial exercise test.

60 min after the end of the exercise, during which patients sat quietly in the laboratory, post-exercise BP was measured by sphygmomanometer as described above.

Thereafter, the first 15 consecutive patients who exhibited PEH repeated the echocardiographic, vascular echo-doppler, and the continuous BP and HR recordings in the supine position as before exercise. BP was measured again 120 min after the end of the exercise by sphygmomanometry.

In patients ($n = 29$) who underwent ABPM, the two recordings were performed in an "exercise" and in a "control day." The patients were instructed to engage in normal daily activities and to avoid strenuous exercise during the 24-h monitoring. On the "exercise day" ABPM was initiated ~15 min before subjects carried out the regular exercise training sessions. On the "control day," the patients abstained from physical activity including the exercise training program. The participants were asked to maintain the same daily routines (including time of sleeping) as after their regular exercise training session.

All the studies were performed in the final week of the training program, and ABPMs were performed at least 3 days apart.

Spontaneous Baroreflex Analysis

Details of this analysis have been previously described (Iellamo et al., 1994, 1996, 1999, 2001). Briefly, the beat-by-beat time series of SBP and pulse interval (PI) were scanned by a computer to identify sequences of 3 or more consecutive beats in which SBP and PI changed in the same direction (either increasing, i.e., "up-sequences," or decreasing, i.e., "down-sequences"). A linear regression was applied to each sequence and the mean individual slope of the SBP/PI relationship, obtained by averaging all slopes computed within the test period, was calculated and taken as a measure of the integrated BRS (Bertinieri et al., 1988; Iellamo et al., 1994). We evaluated the occurrence of baroreflex sequences by the engagement time (eng %), which calculates the fractional occurrence of the sequences (Legramante et al., 2001).

Statistics

Each variable was checked for normality of distribution by the Kolmogorov-Smirnov test. When normality test passed, paired *t*-test or one-way ANOVA for repeated measures was used, when appropriate, to compare pre- and post-exercise values for each of the reported variables. The Wilcoxon signed rank test or the Friedman ANOVA on ranks for repeated measures were used, when appropriate, for nonnormally distributed variables. Values are expressed as means ± SEM. Differences were considered statistically significant when P was <0.05.

RESULTS

Exercise Training

The mean workload attained during the exercise training session was 74.3 ± 2.4 Watt (range 70–110 Watt) and the average HR max reached 146 ± 2.9 beats/min (87 ± 2.0% of the maximal age-predicted HR). No patients complained any symptoms during and after the exercise training sessions.

Blood Pressure

After exercise BP was lower than in baseline conditions in 76% (32 out of 42) for systolic and in 52% (22 out of 42) for diastolic values of the patients. 60 and 120 min after the end of exercise, SBP still showed a significant decrease, whereas DBP did not showed significant difference as compared to the pre-exercise values (**Figure 1**). HR did not show significant changes both at 60 and 120 min after exercise (from 69.2 ± 1.2 b/min to 69.1 ± 1.4 b/min and to 68.5 ± 1.3 b/min, $p = 0.772$).

Baseline BP did not show significant differences between the ABPM of the "control" and the "exercise day" (**Figure 2**). In the "exercise day," SBP was significantly reduced as compared to the baseline for 12 h after the end of the exercise, whereas in the "control day," no significant changes in SBP have been reported during the same time interval (**Figure 2**). SBP reductions were significantly greater during the "exercise day" as compared to the "control day" for the first 12 h after the end of the exercise training session (**Figure 3**). DBP and HR showed a similar behavior in the two experimental sessions (**Figures 2, 3**). During the night (13th-24th hours), as expected, all the cardiovascular variables showed a significant reduction that was independent from the exercise training session (**Figure 2**), even though SBP reductions were significantly greater during the "exercise day" as compared to the "control day" (**Figure 3**).

Systemic and Regional Hemodynamics

In a subgroup of patients exhibiting PEH ($n = 15$), systolic and diastolic BP reduction (**Table 1**) was accompanied by a significant and substantial decrease in TPR and by a significant increase in SV and in CO. HR was not significantly different before and after exercise (**Table 1**). The vasodilation appeared generalized including both exercising, calf (CVR), and non-exercising, forearm (FVR), muscular districts (**Table 1**).

In the same patients, BRS showed a significant ($p < 0.05$) decrease during supine recovery after exercise (7.5 ± 0.8 msec/mmHg) as compared to the pre-exercise values (9.8 ± 1.2 msec/mmHg). This decrease was mainly due to a significant BRS

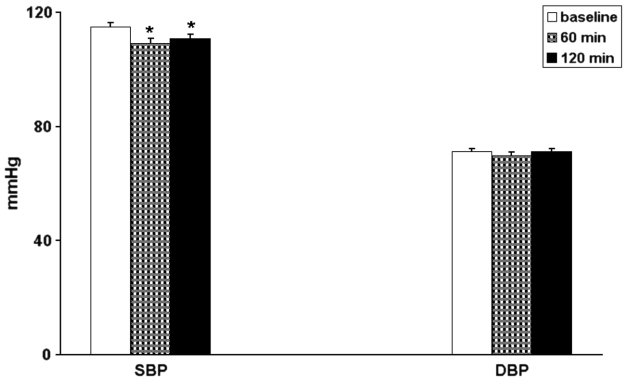

FIGURE 1 | Bar graphs showing systolic (SBP) and diastolic (DBP) blood pressure in 42 coronary artery patients in baseline conditions (**open bars**) and 60 min (**hatched bars**) and 120 min (**black bars**) after exercise. *$p < 0.05$ vs. baseline.

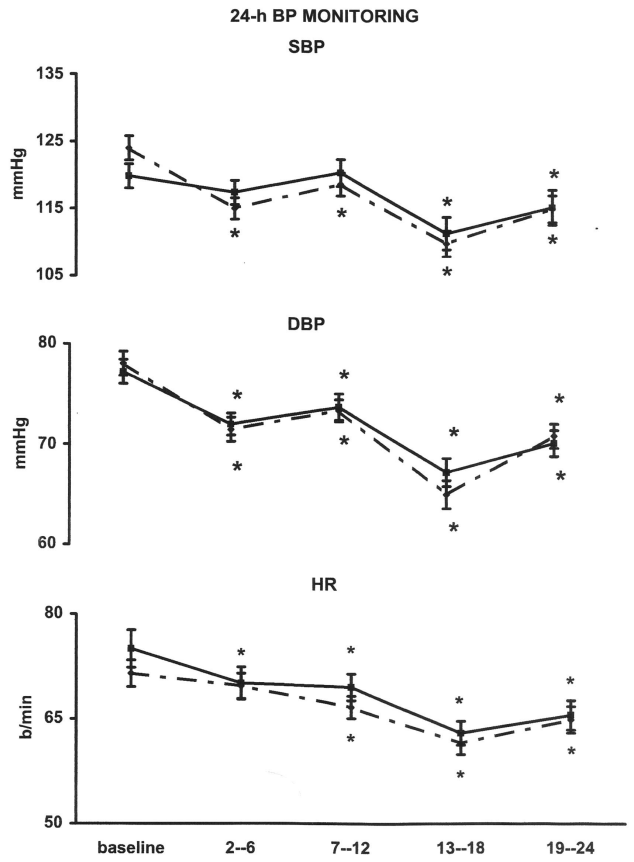

FIGURE 2 | Line graph shows average values for systolic (SBP) and diastolic (DBP) blood pressure and heart rate (HR) in 29 coronary artery patients at 2nd–6th, 7–12th, 13–18th, and 19–24th interval hours after exercise training session (♦) compared with measurements taken at the same time of day on a nonexercise control day (■). *$p < 0.05$ vs. baseline.

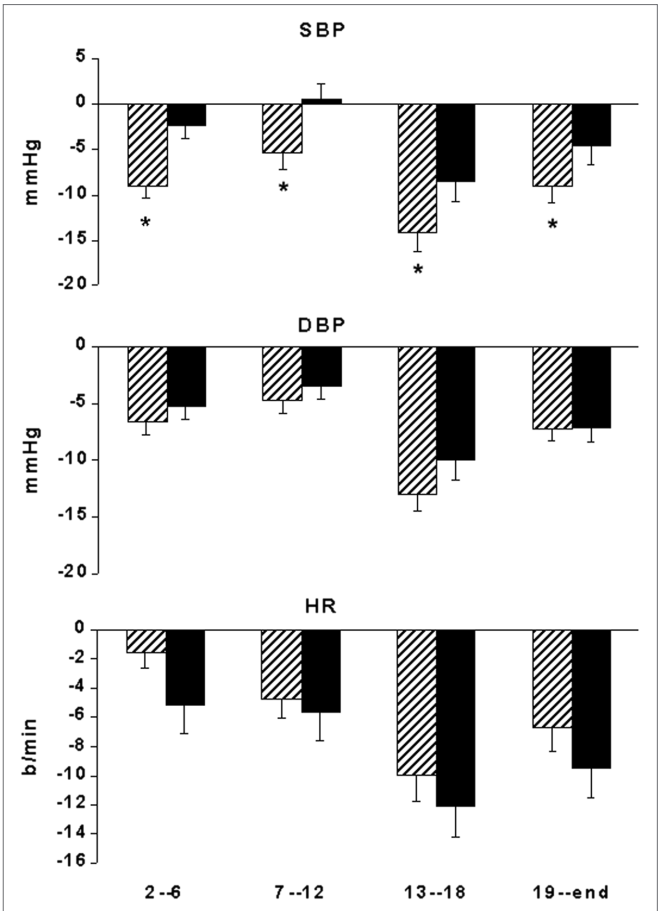

FIGURE 3 | Bar graphs showing systolic (SBP) and diastolic (DBP) blood pressure and heart rate (HR) changes from the start of ABPM in 29 coronary artery patients at 2nd–06th, 7–12th, 13–18th, and 19–24th interval hours after exercise training session (**hatched bars**) compared with measurements taken at the same time of day on a nonexercise control day (**black bars**). *$p < 0.05$ vs. nonexercise control day.

decrease in response to hypertensive stimuli (i.e., increasing BP ramps; **Figure 4**). No significant changes were observed for the occurrence of baroreflex sequences (**Figure 4**).

DISCUSSION

The novel finding of this study is that in CAD patients, the recovery period after exercise training session is characterized by a BP reduction similar to that usually observed in hypertensives. To our knowledge, this is the first study which addressed systematically BP behavior, with the attendant changes in central and peripheral hemodynamics, in the recovery phase after exercise in patients with CAD enrolled in an exercise training program.

PEH in our CAD patients differed from that observed in hypertensives in that BP showed a significant reduction only in systolic values, whereas a decrease both in systolic and in diastolic BP has been reported in hypertensives (Somers et al., 1991; Kenney and Seals, 1993; MacDonald et al., 2001; Legramante et al., 2002). The present study was not designed to define the mechanisms underlying PEH in different patients populations. Nonetheless, some observations deserve comments. Interestingly, the extent of systolic BP decrease after exercise in normotensive CAD patients was in a range similar to that reported for healthy subjects (Coats et al., 1989; Somers et al., 1991; Kenney and Seals, 1993). This observation suggests that the extent of BP decrease occurring in the recovery phase after exercise is linked to baseline BP levels. When BP is high, as in hypertensives, the cardiovascular regulatory mechanisms would allow a greater BP decrease after exercise as compared to normotensives (either healthy or CAD patients) in whom the regulatory system would act to protect from excessive BP decreases. We suggest that in CAD patients the arterial baroreflexes might play a key role in this protection (see below). The possibility that therapy (not discontinued in our patients) could have influenced the extent of BP reduction cannot be excluded. However, drugs were not withdrawn purposely for ethical reasons.

TABLE 1 | Systemic and peripheral hemodynamics in baseline condition and during post-exercise hypotension (PEH).

	BASELINE	PEH
SBP, mmHg	115.6 ± 3.0	104.7 ± 3.0*
DBP, mmHg	70.0 ± 2.0	64.4 ± 2.1*
CO, L/min	4.2 ± 0.2	4.7 ± 0.2*
SV, ml	74.5 ± 2.6	82.1 ± 2.6*
HR, b/min	56.7 ± 2.0	57.4 ± 2.0
TPR, dynes sec^{-1} cm^{-2}	1652.5 ± 71.7	1344.9 ± 44.7*
FVR, dynes sec^{-1} cm^{-2}	138.0 ± 16.1	98.2 ± 10.5*
CVR, dynes sec^{-1} cm^{-2}	48.3 ± 3.0	37.8 ± 2.6*

*Values are means ± SEM. SBP, systolic blood pressure; DBP, diastolic blood pressure; CO, cardiac output; SV, stroke volume; HR, heart rate; TPR, total peripheral resistance; FVR, forearm vascular resistance; CVR, calf vascular resistance. Hemodynamic data refer to a subgroup of patients (n = 15) exhibiting PEH. *p < 0.05 vs. baseline.*

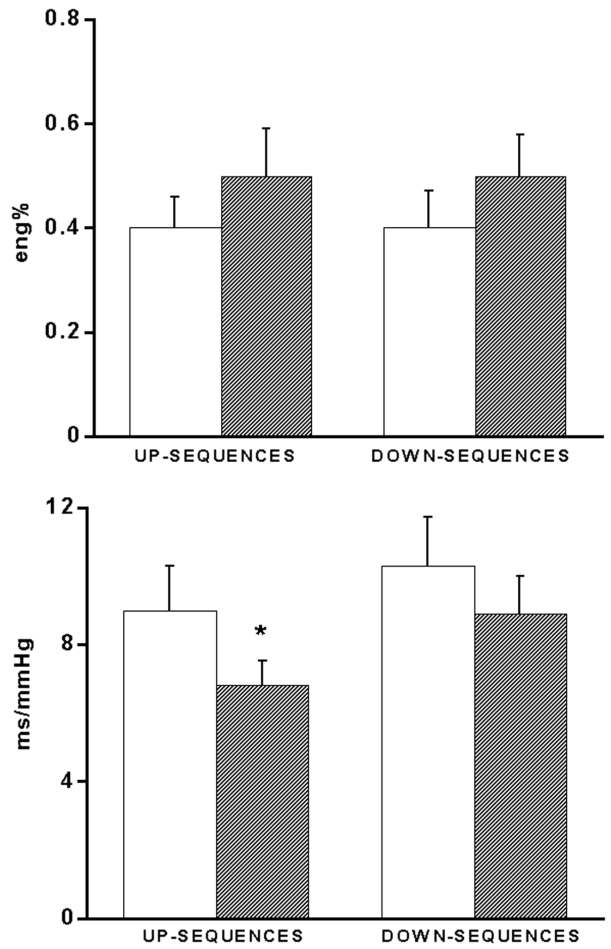

FIGURE 4 | Bar graphs showing the occurrence (eng%, see methods) of up- and down-baroreflex sequences (upper panel) and baroreflex sensitivity values calculated separately for up- and down-baroreflex sequences (bottom panel) in 15 coronary artery patients baseline conditions (**open bars**) and 60 min after exercise (**hatched bars**). *$p < 0.05$ vs. baseline.

Similarly to previous reports in hypertensives (Pescatello et al., 1991; MacDonald et al., 2001), in our study, PEH was not limited to the early recovery but was sustained throughout a substantial part of the day. SBP showed a significant long-lasting reduction (~ 12 h) during the "exercise" day as compared to the "control" day. Moreover, even the nighttime BP reduction was significantly greater in the "exercise" as compared to the "control" day.

The sustained BP-lowering effect of exercise has potentially relevant clinical implications, adding to the other benefits of physical activity programs in CAD patients, even in those not suffering from concomitant hypertension history. In fact, the control of BP levels has been widely acknowledged as a major factor positively affecting the prognosis in CAD patients and uncontrolled SBP has been reported as an independent predictor of cardiovascular outcome in patients admitted to hospital for an acute coronary event (Amar et al., 2002). In this context, the possible role played by exercise as an add-on therapy in the control of systolic BP in CAD patients should be regarded as remarkable.

Our results differ from a previous study investigating a similar group of patients which showed no evidence of PEH (Fagard and Vanhees, 2000). Even though that study used an experimental protocol similar to ours, some differences deserve further comments. First, Fagard et al. (Fagard and Vanhees, 2000) measured BP shortly after the end of the exercise (~ 20 min) when patients had changed positions from supine to sitting. The well-known effects of body posture changes on BP regulation (Blomquist and Lowell-Stone, 1983) might have influenced the BP measurements. Second, the small sample size ($n = 7$) could have provided a partial representation of the post-exercise BP behavior in CAD patients. Finally, Fagard et al. (Fagard and Vanhees, 2000) studied patients participating in an outpatient cardiac rehabilitation program, whereas our patients resided in the Cardiac Rehabilitation Center, thus sharing the same daily routines and allowing us to carefully check their activities during the whole duration of the study.

Central and Peripheral Hemodynamics

In keeping with most of the studies performed so far in hypertensives (Pescatello et al., 1991; Hara and Floras, 1995; Legramante et al., 2002), the present investigation confirms that also in CAD patients the decrease in TPR is the main mechanism sustaining PEH. However, at variance with hypertensives in which vasodilation would be limited to the previously active limb, that is, the lower legs (Legramante et al., 2002), in our CAD patients, the vasomotor responses appear similar in different regional vascular beds, being characterized by a significant and marked decrease in both CVR (i.e., the active limbs) and FVR (i.e., the non-active limbs), thus suggesting a generalized vasodilation. This latter was associated with an increase in SV, which may explain the observation of an increased CO despite an unchanged HR as compared to pre-exercise values. This finding suggests the indirect improvement in cardiac performance as an after-effect of a single exercise training session, at least in CAD patients with preserved left ventricular function, in line with previous observations in hypertensives (Cléroux

et al., 1992; Hara and Floras, 1995; Legramante et al., 2002). This could also provide a temptative explanation of the improved left ventricular function reported in CAD patients undergone exercise training (Belardinelli et al., 1998).

Spontaneous Baroreflex

A number of studies (Bennet et al., 1984; Somers et al., 1985; Hagberg et al., 1987; Convertino and Adams, 1991; Legramante et al., 2002) reported a lack of tachycardia during early PEH in hypertensives, raising the question of an alteration in arterial baroreflex modulation of HR. This prompted us to investigate whether this phenomenon is peculiar to hypertensives which have defective baroreflex control mechanisms (Pagani et al., 1988) or whether this phenomenon is generalized to other patients' populations. Also in our CAD patients, BP decrease was not accompanied by the anticipated reflex tachycardia, and this was associated to a leftward shift in the baroreceptor-cardiac stimulus-response relationship to the lower BP level of post-exercise recovery, with a decreased overall BRS from pre-exercise value. This finding would suggest that the arterial baroreflex would be not simply reset (Pagani et al., 1988) along the prevailing (decreased) BP values of the post-exercise period [i.e., a pressure-dependent, acute "baroreceptor" resetting (Sagawa, 1983; Chapleau et al., 1989)], but would also actively contribute to maintain lower HR values through a decrease in baroreceptor-cardiac reflex gain, thus contributing to maintain low BP values by buffering the expected reflex tachycardia. However, BP decrease remained within safety level during recovery and our data suggest that the arterial baroreflex could contribute to this protective effect. In fact, the reduced BRS, due to the decrease in response to hypertensive stimuli (i.e., the increasing BP ramps), attempts to limit the bradycardia resulting from baroreceptors engagement on a recurring basis by spontaneous fluctuations in BP above the mean levels. This attenuated bradycardic pattern would contribute to prevent excessive BP decreases and could also exert a cardioprotective role in the setting of an acute decrease in BP after exercise, by avoiding an increase in myocardial oxygen consumption ensuing from a reflex tachycardia.

It thus appears that the lack of tachycardia during PEH is not limited to hypertensive patients but is a generalized phenomenon, which may indirectly contribute to the maintenance of post-exercise decrease in BP. Although more subtle differences in baroreflex regulation of sinus node may exist between different patients population (Legramante et al., 2002), overall, baroreflex control of HR seems to play substantially a permissive role in PEH also in CAD patients.

It is worth of note, however, that the arterial baroreflex appears capable of buffering excessive PEH by using different strategies. In fact, in hypertensives (Legramante et al., 2002) BRS has been shown to increase in response to *hypotensive* stimuli (i.e., decreasing BP ramps), whereas in the CAD patients of this study, BRS was decreased in response to *hypertensive* stimuli (i.e., increasing BP ramps). These findings suggest that the arterial baroreflex seeks the better strategy to maintain a homeostatic control of the cardiovascular system, and outline the plasticity of the neural networks.

Limitations of the Study

One possible limitation of this study is the lack of a control group of non-CAD subjects. However, our interest was to test the hypothesis that PEH would occur in normotensive CAD patients and the mechanisms underlying PEH in this widely diffused patients' population. Indeed, several studies have already demonstrated the occurrence of PEH in healthy subjects (in addition to hypertensives). Second, we did not evaluate CAD patients not featuring PEH, so we would not been able to ascertain whether baroreflex responses were returned to normal at 60 min, in line with BP recovery, This, however, would not detract from the novelty of the study. Third, stroke volume was measured by echocardiography, and this might have been a source of mistakes. However, our echocardiographers had a long experience; therefore, we are confident of our results. This study included only male CAD patients, and hence, our results cannot be generalized to females. Moreover, we employed only the aerobic continuous exercise modality. This choice was dictated by current guidelines that recommend aerobic exercise as the preferred training modality (Piepoli et al., 2016) Therefore, it is possible that different training modalities (e.g., resistance, combined, and high intensity interval training) could produce different results as far as PEH and its mechanisms is concerned (Iellamo et al., 2021). Finally, we cannot exclude the possibility that the prevalence of lower blood pressure values we observed might had been different if assessment had been performed at different times during the course of the training period. The last week of the training program was chosen because at that time, the patients had a lower likelihood to be deconditioned and this would have prevented from performing an effective training session.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee IRCCS San Raffaele Pisana, Roma. The patients/participants provided their written informed consent to participate in this study.

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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Effects of Aquatic Exercise in Post-exercise Hypotension: A Systematic Review and Meta-Analysis

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Background: Post-exercise hypotension (PEH) can be an important non-pharmacological strategy in the treatment of arterial hypertension. Both aerobic and resistance exercises produce PEH, but it is not clear if the exercise environment can lead to a higher PEH.

Objective: This meta-analysis investigated whether a session of aquatic exercise (AE) induces PEH in comparison with control conditions such as land exercise (LE) or rest in hypertensive subjects.

Methods: The present systematic review and meta-analysis was conducted using the following electronic databases: PubMed, Google Scholar, and EMBASE. Ambulatory blood pressure measurements made in randomized clinical trials were pooled to compare PEH induced by AE with LE and rest conditions in hypertensive subjects.

Results: Data from four trials were included, which comprised 127 participants (94 women and 33 men). A 24-h analysis did not detect significant differences between AE and LE or rest for either systolic blood pressure (SBP) or diastolic blood pressure (DBP). Monitoring during the night showed that AE induced significant PEH in comparison with LE for SBP [−8.6 (−15.0 to −1.5) mmHg ($p = 0.01$)]. For DBP, the AE had pronounced PEH during the night in comparison with LE [−3.7 (−4.7 to −2.8) mmHg, $p = 0.000$] and rest [−1.7 (−1.9 to −0.8) mmHg, $p = 0.000$]. There were no differences in daytime values.

Conclusion: AE showed a higher PEH effect than LE sessions and rest conditions. PEH was observed in both SBP and DBP during the night. The number of studies was low, but all studies included in this meta-analysis used 24-h monitoring. The understanding of clinical relevance of AE, inducing a higher PEH, depends on a standardization of exercise protocols plus a rigorous monitoring of blood pressure.

Systematic Review Registration: PROSPERO registration: CRD42021271928.

Keywords: post-exercise hypotension, aquatic exercise, water-based exercise, exercise, ambulatory blood pressure, systematic review and meta-analysis

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INTRODUCTION

Recent publications in the American Heart Association (AHA) and the American College of Cardiology (ACC) recommend lifestyle approaches and physical activity as the first line of therapy for elevated blood pressure (Barone Gibbs et al., 2021). The guidelines for hypertension treatment recommend 90–150 min per week of moderate-to-vigorous intensity aerobic exercise and 90–150 min per week (6 exercises × 3 sets × 10 repetitions) of dynamic resistance exercise (Whelton et al., 2018).

An important phenomenon that occurs after exercise is post-exercise hypotension (PEH). PEH is characterized by a reduction in systolic and/or diastolic blood pressure (BP) below the control level after a single bout of exercise. PEH has been analyzed as a reduction in BP below the values immediately prior to the exercise session or in comparison with a control condition (without exercise) (Kenney and Seals, 1993). A meta-analysis that included 65 studies showed a reduction in systolic (SBP) and diastolic pressure (DBP) after exercise in pre-hypertensives (−6 mmHg) and hypertensives (−8 mmHg). Both aerobic and resistance exercises reduce SBP/DBP (6/4 mmHg) and (3/3 mmHg), respectively (Carpio-Rivera et al., 2016).

Aquatic exercise (AE) has several benefits in comparison with land exercise (LE) on account of water properties such as its density and hydrostatic pressure, which contribute to lower cardiovascular demand (Yoo et al., 2014; Chien et al., 2015) and orthopedic injury. This suggests the possibility of AE serving several individuals of different ages (Torres-Ronda and Del Alcázar, 2014).

Water-based and aquatic exercises promote several cardiovascular alterations in healthy and cardiac patients. There is a greater increase in cardiac output and pulse pressure (PP) during water immersion exercises than those performed on land. These alterations are observed at rest and during exercise (Christie et al., 1990; Gabrielsen et al., 2000; Schega et al., 2007; Schmid et al., 2007; Mourot et al., 2008). In addition, there is a reduction in the vascular tone and peripheral vascular resistance (Schega et al., 2007; Mourot et al., 2008).

A recent meta-analysis reported that AE improved vascular function, which is an important aspect of AE in reducing BP in hypertensive subjects (Igarashi et al., 2017). Considering the relevance of PEH in hypertension treatment and the differential effects of water-based/aquatic exercise on the cardiovascular system, the purpose of this meta-analysis was to evaluate whether water-based/aquatic exercise results in higher PEH than exercise on land or rest.

METHODS

This systematic review and meta-analysis followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Liberati et al., 2009). The study protocol was registered with the PRISMA statement PROSPERO (CRD42021271928).

TABLE 1 | Search strategy demonstration.

Population	+	Independent variable	+	Dependent variable
("Hypertension"[Mesh] OR "High Blood Pressure")	AND	("Aquatic Therapy"[Mesh] OR "aquatic exercise" "water-based exercise" "water aerobics exercise" OR "Exercise"[Mesh] OR "Physical Activity" OR "Physical Activities" OR "Physical Exercise" OR "Acute Exercise" OR "Aerobic Exercise" OR "Exercise Training")	AND	("Hypotension"[Mesh] OR "Post-Exercise Hypotension"[Mesh] OR "Acute exercise response" OR "blood pressure response" OR "Postexercise Hypotension")

Research Strategy

The present systematic review was conducted using data from the following electronic databases: PubMed, Google Scholar, and EMBASE. The search terms included a combination of the following key concepts: "hypertension," "hypotension," "post-exercise hypotension," "aquatic exercise," "hypotension," and "water-based exercise." No language restrictions were imposed.

Two authors (C.O.T. and L.K.B.) independently conducted a systematic search. The search strategy was performed using the combination of Mesh terms and other important descriptors, as shown in the **Table 1**.

The combination of terms defined for "population," "independent variable," and "dependent variable" were performed using Boolean operators. In this sense, below is an example of the command line applied to search in PubMed. ("Hypertension"[Mesh] OR "High Blood Pressure") AND ("Aquatic Therapy"[Mesh] OR "aquatic exercise" "water-based exercise" "water aerobics exercise" OR "Exercise"[Mesh] OR "Physical Activity" OR "Physical Activities" OR "Physical Exercise" OR "Acute Exercise" OR "Aerobic Exercise" OR "Exercise Training") AND ("Hypotension"[Mesh] OR "Post-Exercise Hypotension"[Mesh] OR "Acute exercise response" OR "blood pressure response" OR "Post-exercise Hypotension").

Eligibility Criteria

The criteria for the included studies were based on a checklist that considered the following characteristics: randomized control trial studies that were performed in pre-hypertensive humans (≥18 years of age), all participants were hypertensive, and the intensity and method of blood pressure measurement were described in detail. The trials compared the effect of a single session of land-based vs. water-based exercise and rest conditions, and the office and/or ambulatory BP were measured at least 15 min following the exercise bouts. The extracted data were full-text

TABLE 2 | Criteria for inclusion and exclusion of studies selected for review.

		Inclusion criteria	Exclusion criteria
P	Population	Hypertensive adult humans	Musculoskeletal disorders, other chronic diseases and under 18 years old
I	Intervention	A bout of water-based/aquatic exercise	Other types of exercise and chronic interventions
C	Comparison	1) Land exercise and 2) Rest control	-
O	Outcome	Blood pressure response	Blood pressure follow-up for <60 min
S	Study type	Randomized control trial	Systematic review, cross-sectional, quasi-experimental study, case reports, observational study, review, protocol study, qualitative study

peer-reviewed. Exclusion criteria included any study that did not meet all the above inclusion criteria. The eligibility for selecting the studies was determined through the PICOS process (**Table 2**).

Study Selection and Quality

Two reviewers (C.O.T and L.K.B.) independently examined the titles and abstracts of all studies for eligibility. Then, the full texts of all studies that met the inclusion criteria and those in which there were some uncertainties were retrieved and reviewed by both reviewers. To reach a consensus, disagreements between reviewers were discussed with a third researcher (E.C.O). Reviewers were not blinded to the journal or authors. The rationale for deleting any full-text article was also documented.

In addition, the procedural quality of the studies was assessed using the *Tool for the assEssment of Study qualiTy and reporting in Exercise*—TESTEX (Smart et al., 2015), which is a study quality assessment and reporting tool designed specifically for use in exercise training studies. All selected studies (Terblanche and Millen, 2012; Sosner et al., 2016; Cunha et al., 2018; Júnior et al., 2019) were analyzed using the TESTEX scale. Two studies (Cunha et al., 2018; Júnior et al., 2019) scored 09, while one study (Terblanche and Millen, 2012) scored 10 and another study (Sosner et al., 2016) scored 11, which indicates high quality. These studies failed to score items 3 (allocation concealment) and 5 (supervisor blindness) concerning study quality. And in items 6a (outcome measures assessed in 85% of patients, in which more than 85% were completed), 6c (if attendance per year is reported), item 8b (if statistical comparisons between groups are reported for by minus one secondary measure) and item 10 (activity monitoring in control groups) referring to the study report. The study with score 10 (Terblanche and Millen, 2012) scored item 6a because it kept the sample at more than 85% and the study with score 11 (Sosner et al., 2016) scored item 5 because it was stated that the measure of the primary outcome evaluator was blind.

Therefore, eligible studies (Terblanche and Millen, 2012; Sosner et al., 2016; Cunha et al., 2018; Júnior et al., 2019) were classified as high quality through the quality analysis of the TESTEX scale for intervention studies. **Table 3** illustrates the criteria awarded for each study.

Data Extraction

A specific data extraction file was created and used by the authors. The following study information was extracted: authors, publication year, study design, sample size, participant characteristics (sex, mean age, hypertension status), exercise protocol (intensity, duration, mode), level of water immersion (pool depth), water temperature, the method of measuring BP, and BP measurement time (**Table 4**).

Statistical Analyses

Analyses were performed using Comprehensive Meta-Analysis software (CMA, version 2.2.064, Biostat, NJ, USA). Two-sided statistical significance was set at $p < 0.05$. The primary outcome measure was an effect on blood pressure response. Descriptive data of treatment groups and participants are reported as the mean ± SD. Study data were pooled using a random-effects model. Inconsistencies were estimated using the I^2 statistic. Additionally, we evaluated an additional hypothesis that there might be differences in the effects of AE on post-exercise hypotension accordingly to the comparison type (land exercise or rest control). Differences between subgroups were analyzed by means of an analysis of variance (*Q*-test-based ANOVA). Additionally, the Duval and Tweedie (2000) trim and fill computation were used to estimate the effect of publication bias on the results.

RESULTS

A PRISMA flow diagram of the literature search and selection process is shown in **Figure 1**. The priori search identified 2,450 articles involving PEH. After the screening process, 141 abstracts were read, 99 articles were excluded for duplicates or other reasons, 39 articles were selected as potential studies for evaluation, 32 full-text reports were excluded, seven reports were assessed for eligibility, and after analyses, three reports were excluded due to insufficient blood pressure monitoring time. Only four articles were selected, finally (Terblanche and Millen, 2012; Sosner et al., 2016; Cunha et al., 2018; Júnior et al., 2019). These studies were included in the final meta-analysis because they were conducted in hypertensive volunteers and because PEH was recorded 24-h after aquatic, land, or rest conditions.

Risk of Bias Within and Across Studies

The TESTEX scale uses 12 criteria, with some criteria scoring more than one possible point, for a maximum score of 15 points. The overall quality of the included studies was of high quality, all studies scored above 09. Weaknesses in the studies were: allocation concealment, whether attendance per year is reported, whether statistical comparisons between groups are reported for at least one secondary measure, and activity monitoring in

TABLE 3 | Analysis of the methodological quality of the included studies.

References	Study quality					Partial	Study reporting										Partial	Total
	1	2	3	4	5	(1–5)	6a	6b	6c	7	8a	8b	9	10	11	12	(1–10)	(0–15)
Júnior et al. (2019)	1	1	0	1	0	3	0	1	0	1	1	0	1	0	1	1	6	09
Cunha et al. (2018)	1	1	0	1	0	3	0	1	0	1	1	0	1	0	1	1	6	09
Terblanche and Millen (2012)	1	1	0	1	0	3	1	1	0	1	1	0	1	0	1	1	7	10
Sosner et al. (2016)	1	1	0	1	1	4	1	1	0	1	1	0	1	0	1	1	7	11

Tool for the assEssment of Study quality and reporting in Exercise (TESTEX) (15) criteria: (Study quality) 1—Eligibility criteria specified; 2—Randomization specified; 3—Allocation concealment; 4—Groups similar at baseline; 5—Blinding of assessor; (Study reporting); 6—Outcome measures assessed in 85% of patients (6a = 1 point if more than 85% were completed, 6b = 1 point if adverse events were reported, 6c = if attendance to the year is reported); 7—Intention-to-treat analysis; 8—Between-group statistical comparisons reported (8a = 1 point if between-group comparisons are reported for the primary outcome variable of interest; 8b = 1 point whether statistical comparisons between groups are reported for at least one secondary measure); 9—Point measures and measures of variability for all reported outcome measures; 10—Activity monitoring in control groups; 11—Relative exercise intensity remained constant; 12—Exercise volume and energy expenditure.

control groups (Terblanche and Millen, 2012; Sosner et al., 2016; Cunha et al., 2018; Júnior et al., 2019).

The kappa correlation showed high overall agreement between the researchers [k = 0.93; 0.73–1.00 (95% CI)—$p < 0.001$].

The Duval and Tweedie (2000) correction model was applied to the AE study groups for PEH. No trimmed studies could be identified. The consistency of studies was analyzed using I^2 as a test of heterogeneity for subgroup analyses (**Table 5**).

Study Characteristics

Table 4 shows the characteristics of these studies. The characteristics of the sample included (Terblanche and Millen, 2012; Sosner et al., 2016; Cunha et al., 2018; Júnior et al., 2019) in the trials were as follows: 33 men and 94 women, a water group (n = 46) (Sosner et al., 2016; Cunha et al., 2018; Júnior et al., 2019), land group (n = 34) (Sosner et al., 2016; Júnior et al., 2019), and a rest or control group (n = 12) (Cunha et al., 2018); one study (Terblanche and Millen, 2012) (n = 21) in which the participants performed one land and one water exercise session in random order, as well as a control session with no exercise. Two studies (Terblanche and Millen, 2012; Cunha et al., 2018) were crossover-type studies, one study (Júnior et al., 2019) was a controlled clinical trial, and the other (Sosner et al., 2016) was a parallel study. In one study (Sosner et al., 2016), the volunteers were allocated to two groups: high-intensity dry land or high intensity in immersed condition, and in another (Terblanche and Millen, 2012; Cunha et al., 2018; Júnior et al., 2019), the volunteers were allocated to aquatic and land groups using a stratified randomization method. The mean ages of the participants in the studies were 53–65 years. All studies (Terblanche and Millen, 2012; Sosner et al., 2016; Cunha et al., 2018; Júnior et al., 2019) reported that the subjects were hypertensive; only one study included high blood pressure (systolic ≥ 130 mmHg and diastolic ≥ 85 mmHg) and hypertensive subjects. Exercise intensity was expressed as heart rate reserve (75%) (Júnior et al., 2019). One study (Sosner et al., 2016) expressed exercise intensity using the percentage of maximal grade test (60–80%), and one study (Terblanche and Millen, 2012) used the VO_2 maximal percentage (60–80%). Only two studies (Terblanche and Millen, 2012; Sosner et al., 2016) reported the depth of water and temperature. Four studies (Terblanche and Millen, 2012; Sosner et al., 2016; Cunha et al., 2018; Júnior et al., 2019) used automatic ambulatory BP monitors for 24 h. **Supplementary Material** shows the office SBP and DPB and more details of exercise prescription parameters.

Main Outcomes

Systolic Blood Pressure

The 24-h analysis did not identify PEH for AE compared to LE [−7.3 mmHg (−14.9 to −0.2 mmHg), I^2 = 93%, p = 0.057] or rest [−6.0 mmHg (−12.0 to −1.4 mmHg), I^2 = 0%, p = 0.1] conditions. Monitoring during the night showed a significant PEH for AE compared to LE [−8.6 mmHg (−15.0 to −1.5 mmHg), I^2 = 88%, p = 0.01] and no significant favorable effect in relation to control rest [−5.4 mmHg (−12.8 to 1.5 mmHg), I^2 = 0%, p = 0.12]. Daytime analysis did not identify significant PEH in favor to AE compared to LE [−10.2 mmHg (−22.5 to 2.1 mmHg), I^2 = 96%, p = 0.105] or control rest [−6.4 mmHg (−18.7 to 5.8 mmHg), I^2 = 0%, p = 0.306] (**Figure 2**).

Diastolic Blood Pressure

The 24-h analysis did not identify differences in favor to AE in comparison to LE [−4.1 mmHg (−8.8 to 0.4 mmHg), I^2 = 88%, p = 0.07] or rest [−1.9 mmHg (−6.0 to −2.4 mmHg), I^2 = 0%, p = 0.06] control conditions. The AE had favorable PEH during the night in comparison with LE [−3.7 mmHg (−4.7 to −2.8 mmHg), I^2 = 23%, p = 0.000] and rest [−1.7 mmHg (−1.9 to −0.8 mmHg), I^2 = 0%, p = 0.000] control conditions. There were no differences in the daytime values in comparison to LE [−5.2 mmHg (−10.7 to 0.1 mmHg), I^2 = 93%, p = 0.057] and rest [−2.0 mmHg (−7.5 to 3.4 mmHg), I^2 = 0%, p = 0.461] control conditions (**Figure 3**).

The mean effects were similar for "control conditions" (LE vs. rest), except for DBP during the nighttime period of blood pressure monitoring, where the magnitude of blood pressure reduction was greater in relation to LE (p = 0.000; Q-test-based ANOVA).

TABLE 4 | Overview of the general characteristics of the study and participants.

References	Design	Subjects analyzed	Age* (Yrs)	BP category	Land exercise/rest	Aquatic exercise	Pool depth	Water temperature	BP measurements (device)	Time point BP measurements
Júnior et al. (2019)	Controlled clinical trial	40F	(LE-PEH) 67 ± 3 (AE-PEH) 64 ± 3 (LE) 65 ± 3 (AE) 70 ± 2	Hypertensive	Exercise session consisted of aerobic collective gymnastics (50 m: including 5 m of warm-up; 20 m of aerobic exercises at 75% of reserve heart rate; 20 m of resistance exercises; and 5m of stretching)	Exercise session consisted of a combined aerobic and resistance exercises at 75% of reserve heart rate	-	-	Heart rate monitor (POLAR® RS800) and Ambulatory Blood Pressure Monitoring (ABPM)	Over 24-h post-exercise
Cunha et al. (2018)	Crossover	24F	70.0 ± 3.9	Hypertensive	The control session was a 45 m session with no exercise. During this session, participants remained seated or standing as desired. They read, talked, and drank water, but did nothing else	Exercise intensities were 55–60% of maximum heart rate (HRmax) during warm-up; 70–75% of HRmax during active exercise; and 55–60% of HRmax during cooldown.	-	-	Heart rate monitor (POLAR® RS800) and ABPM	21-h post-exercise
Terblanche and Millen (2012)	Crossover	11M 10F	50 ± 12 M 54 ±10 F	Hypertensive	Exercise sessions were between 60 and 80% of peak VO_2. Exercises included 30 m of resistance exercises followed by 25 m of aerobic exercises	Exercise sessions were between 60 and 80% of peak VO_2 and consisted of combined aerobic and resistance exercises	The depth at the shallowest point of the pool was 2.1 meters	27°C	Automated ambulatory air bladder-containing cuff (Ergoline Ergoscan 2008, Germany)	24-h post-exercise
Sosner et al. (2016)	Parallel	22M 20F	(MICE) 65 ± 6 (HIIE-D) 65 ± 8 (HIIE-I) 63 ± 9	Hypertensive	On an electromagnetically braked cycle ergometer, each exercise session was preceded by a 5 m of warm-up consisting in pedaling at 60 W with a cadence of 80 revolutions per min (rpm) and followed by a 5 m of recovery period in a sitting position that began immediately after exercise cessation. The intensity was determinate based in Maximal Continuous Graded Exercise Test potency	On a mechanically braked cycle ergometer, each exercise session was preceded by a 5 m of warm-up consisting in pedaling at 40 rpm and followed by a 5 m of passive recovery period in a sitting position that began immediately after exercise cessation. The intensity was determinate based in Maximal Continuous Graded Exercise Test potency	Saddle and handlebar height as well as forward placement were adjusted to determine optimal position. Immersed cycling (up-to-the-chest)	30°C	Ambulatory BP (Mobil-O-Graph PWA)	24-h post-exercise

*ABPM, Ambulatory Blood Pressure Monitoring; BP, Blood Pressure; HRmax, maximum heart rate; M, male; F, female; W, watts; RPM, revolutions per minute; m, minutes; s, seconds; *Mean ± SD; Yrs, years; AE-PEH, aquatic exercise post-exercise hypotension; LE-PEH, land exercise post-exercise hypotension; AE, aquatic exercise; LE, land exercise; MICE, moderate-intensity continuous exercise; HIIE-D, high-intensity interval exercise dryland; HIIE-I, high-intensity interval exercise immersed.*

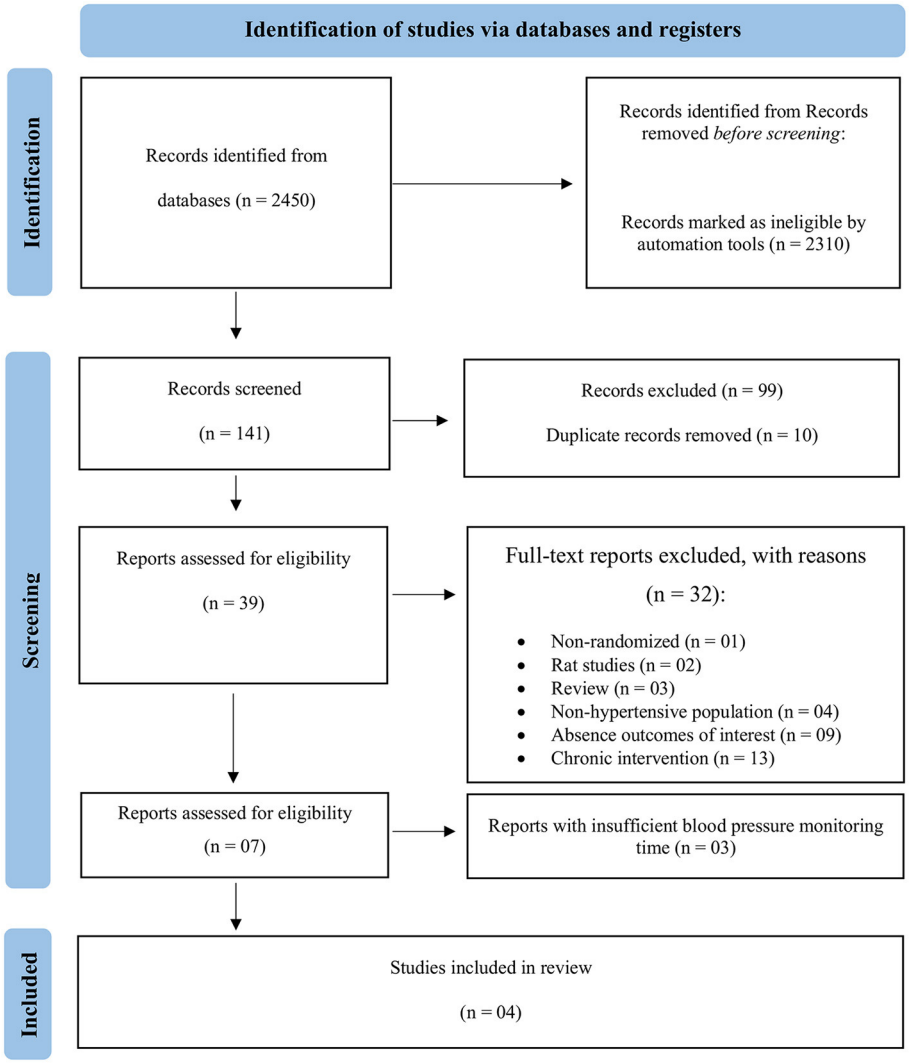


FIGURE 1 | PRISMA flow diagram showing the selection process of eligible articles.

DISCUSSION

The purpose of the present systematic review and meta-analysis was to determine whether AE induces significant PEH compared to LE and rest conditions. The pooled results suggest that a single session of AE induced a statistically significant PEH during the night for both SBP and DPB; for DBP, the AE led to different results between land and rest.

An interesting recent review (Zhou et al., 2021) examined AE for health promotion during a 31-year bibliometric analysis. The results suggest that research on this topic has been constantly increasing over the past 30 years, and trends have focused on improving cardiovascular health with AE.

One meta-analysis that investigated the chronic effects of AE on BP showed a significant decrease in BP; the SBP was estimated to be −8.4 mmHg while the change in DBP was estimated to be −3.3 mmHg (Igarashi and Nogami, 2017). These reductions are higher than those observed in other exercise modalities: regular endurance exercise led to a decrease of approximately −3.5 mmHg (SBP) and −1.8 mmHg (DBP) (Cornelissen and Smart, 2013); resistance exercises led to a decrease of −3.9 mmHg (SBP) and −3.6 mmHg (DBP) (Cornelissen et al., 2011); and yoga exercise training led to a decrease of −5.2 mmHg (SBP) and −5.0 mmHg (DBP) (Chu et al., 2014).

The mechanisms by which aquatic/water-based exercise reduces BP must be further investigated. Currently, research shows that these exercises result in a reduction in peripheral vascular resistance (Pendergast et al., 2015), suppression of the renin-angiotensin system, and cardiopulmonary and baroreflex activation (Gabrielsen et al., 1996; Reilly et al., 2003) that lead to a marked reduction in renal sympathetic nerve activity and increased urine flow and sodium excretion (Larochelle et al., 1994). These alterations are mediated by hydrostatic effects of immersion in water, which redirects ∼700 mL of blood flow from

TABLE 5 | Heterogeneity of studies.

		Heterogeneity test		
Control	***n***	***Q***	***p***	I^2
Systolic blood pressure–24 h				
Land exercise	3	32.9	0.000	93.9
Rest	3	1.7	0.413	0.0
Overall	6	34.7	0.000	85.6
Systolic blood pressure—daytime				
Land exercise	3	63.0	0.000	96.8
Rest	3	0.7	0.671	0.0
Overall	6	156.7	0.000	96.8
Systolic blood pressure—nighttime				
Land exercise	3	17.5	0.000	88.6
Rest	3	1.0	0.599	0.0
Overall	6	78.7	0.000	93.6
Diastolic blood pressure–24 h				
Land exercise	3	18.0	0.000	88.9
Rest	3	0.6	0.713	0.0
Overall	6	20.3	0.001	75.4
Diastolic blood pressure—daytime				
Land exercise	3	28.7	0.000	93.0
Rest	3	1.1	0.569	0.0
Overall	6	81,0	0.000	93.8
Diastolic blood pressure—nighttime				
Land exercise	3	2.6	0.269	23.8
Rest	3	0.6	0.728	0.0
Overall	6	22.4	0.000	77.7

N, number of trials; Q, observed variation; I^2, ratio of true heterogeneity to the total variation in observed effects.

the extremities (increased venous return) to the thorax (Sik Park et al., 1999; Meredith-Jones et al., 2011).

Another important point that must be observed in further works is the standardization of participants' physical activity level. Only two studies included in this review describe the physical level of voluntaries. In one of them (Júnior et al., 2019), the hypertensive subjects were trained in AE or land exercise at least for 6-months before the experiment. Another study described that the voluntaries were trained only in land (Cunha et al., 2018). The forest plot showed that the AE trained group (6-months) had higher PEH than the land trained group. However, both groups of hypertensive subjects showed significant PEH in favor of AE compared to land or rest. On the other hand, in two articles (Terblanche and Millen, 2012; Sosner et al., 2016) that do not describe if the participants were physically active, AE was not better, with an exception for SBP (Terblanche and Millen, 2012). These results can indicate that participants' physical activity level can impact PEH.

The pooled net change contained significant heterogeneity, but the reason for this could not be determined. Probably the active level of participants can be one reason. Physically active individuals achieved higher PEH after the exercise session. This seems to support the theory proposed by some authors (Hamer, 2006). Some physiological mechanisms produced by the chronic effect of exercise that reduce BP also play a role in PEH onset. For example, exercise training has been shown to lead to important adaptations and better arterial vessel compliance that may facilitate the decrease in peripheral resistance following an exercise session (Thijssen et al., 2013). It has been also demonstrated that trained hypertensive patients presented lower values of SBP and DBP than the sedentary participants after a single bout of continuous aerobic exercise (Imazu et al., 2017).

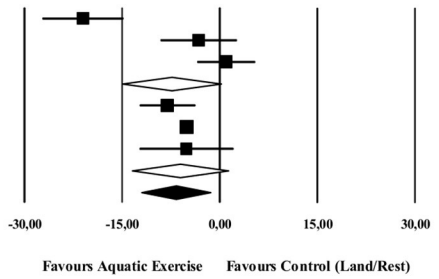
The adaptations to AE can collaborate with PEH. Training seems to generate neurohumoral adaptations that are important for BP control, and chronic AE (12-weeks) in resistant hypertensive subjects showed a significant decrease in 24-h SBD and DBP in the clinic; concomitantly, nitric oxide levels increased, and endothelin-1, renin, and norepinephrine levels showed significant reductions (de Cruz et al., 2017). The confirmation of these effects must justify the further clinical use of AE training for treatment of hypertensive subjects.

Another important question is the modality and/or way the exercise was performed. Three studies included in this meta-analysis used a combination of aerobic and resistance exercise in water or land; one used only aerobic exercise, and the last used High Intensive Interval Exercise (HIIE). A recent meta-analysis showed that land HIIE promoted a larger PEH than moderate-intensity continuous exercise on ambulatory daytime blood pressure (Marçal et al., 2021). Another meta-analysis showed that several types of regular AE as swimming, deep water, circuits, resistance, and others, significantly reduce the blood pressure in hypertensive subjects. The pooled net results of the present work showed significant PEH, especially during the nighttime, so it seems that the AE, independently of how it is done, leads to significant PEH (Igarashi and Nogami, 2017) characterizes one more area for future studies.

One study (Júnior et al., 2019) included in this meta-analysis shows that PEH is higher for the AE group only in the 12th hour after exercise session compared to the land group. This point of ambulatory blood pressure measurement is characterized as nighttime evaluation. Another study (Cunha et al., 2018) finds more points of differences between AE and rest for DBP in 4th, 11th, 12th, and 13th h after exercise session, showing the predominance of differences in nighttime period. The exact underlying mechanisms by which exercise improves nighttime PEH are not clear. One possible mechanism involved can be the effects of AE in autonomic control. The blood pressure and heart rate are modulating by autonomous nervous system, which exhibits a predominant vagal tone in most species, including humans. Bocalini et al. (2017) measured the heart rate variability (HRV) which indicated the predominance of sympathetic (Low Frequency—LF) and vagal modulation (High Frequency—HF), 90-min after land and AE session. After both land and AE, the HF was significantly greater than that assessed at rest condition, suggesting that more than just a parasympathetic reactivation in PEH occurs. In addition, the increase in HF and the reduction in LF and LF/HF ratio during recovery were also significantly greater in the AE than in the land-based exercise, reinforcing the effectiveness of exercise under immersion, especially for hypertensive patients. During nighttime there is a prevalence of

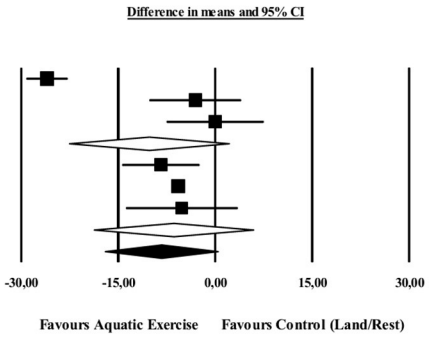
A

Group by Comparison	Study name	Comparison	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Land	Junior et al., 2019	Land	-21,000	3,162	10,000	-27,198	-14,802	-6,641	0,000
Land	Sosner et al., 2016b	Land	-3,215	2,970	8,823	-9,037	2,607	-1,082	0,279
Land	Terblanche & Millen, 2012b	Land	1,000	2,253	5,075	-3,415	5,415	0,444	0,657
Land			-7,377	3,875	15,018	-14,973	0,218	-1,904	0,057
Rest	Terblanche & Millen, 2012a	Rest	-8,000	2,162	4,675	-12,238	-3,762	-3,700	0,000
Rest	Cunha et al., 2018a	Rest	-5,100	0,289	0,083	-5,666	-4,534	-17,667	0,000
Rest	Sosner et al., 2016a	Rest	-5,072	3,666	13,436	-12,256	2,112	-1,384	0,166
Rest			-6,075	3,767	14,190	-13,458	1,308	-1,613	0,107
Overall			-6,708	2,701	7,296	-12,002	-1,414	-2,483	0,013



B

Group by Comparison	Study name	Comparison	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Land	Junior et al., 2019a	Land	-26,000	1,612	2,600	-29,160	-22,840	-16,125	0,000
Land	Sosner et al., 2016d	Land	-3,071	3,611	13,038	-10,148	4,006	-0,850	0,395
Land	Terblanche & Millen, 2012d	Land	0,000	3,818	14,580	-7,484	7,484	0,000	1,000
Land			-10,223	6,302	39,721	-22,576	2,129	-1,622	0,105
Rest	Terblanche & Millen, 2012c	Rest	-8,400	3,038	9,231	-14,355	-2,445	-2,765	0,006
Rest	Cunha et al., 2018b	Rest	-5,700	0,318	0,101	-6,322	-5,078	-17,950	0,000
Rest	Sosner et al., 2016c	Rest	-5,143	4,393	19,300	-13,753	3,467	-1,171	0,242
Rest			-6,428	6,281	39,454	-18,739	5,883	-1,023	0,306
Overall			-8,319	4,449	19,793	-17,039	0,401	-1,870	0,062



C

Group by Comparison	Study name	Comparison	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Land	Junior et al., 2019b	Land	-16,000	1,304	1,700	-18,555	-13,445	-12,271	0,000
Land	Sosner et al., 2016f	Land	-5,000	3,105	9,640	-11,085	1,085	-1,610	0,107
Land	Terblanche & Millen, 2012f	Land	-1,000	4,944	24,442	-10,690	8,690	-0,202	0,840
Land			-8,663	3,615	13,068	-15,748	-1,578	-2,396	0,017
Rest	Terblanche & Millen, 2012e	Rest	-9,000	4,531	20,528	-17,880	-0,120	-1,986	0,047
Rest	Cunha et al., 2018c	Rest	-4,500	0,115	0,013	-4,726	-4,274	-38,971	0,000
Rest	Sosner et al., 2016e	Rest	-3,786	3,574	12,773	-10,791	3,219	-1,059	0,289
Rest			-5,441	3,582	12,833	-12,462	1,580	-1,519	0,129
Overall			-7,037	2,545	6,475	-12,024	-2,050	-2,766	0,006

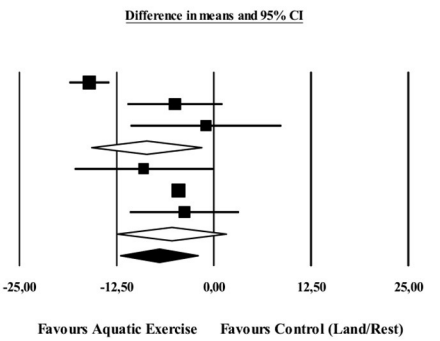
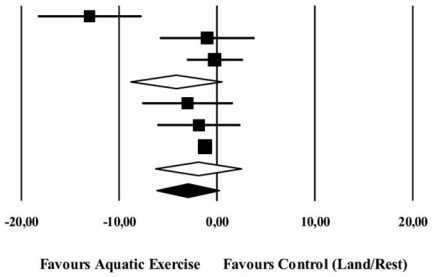


FIGURE 2 | Systolic blood pressure post-exercise hypotension effect. Comparison between water exercise (aquatic) with land exercise or rest condition. **(A)** 24 h, **(B)** Daytime, **(C)** Nighttime.

vagal tone (Furlan et al., 1990), the AE can contribute to increased vagal modulation by alterations in the ratio of sympathetic/vagal tone once the decrease in sympathetic activity is a mechanism described for AE (Schmid et al., 2007).

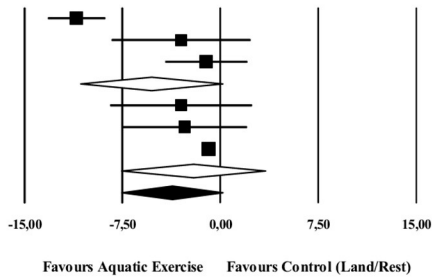
A

Group by Comparison	Study name	Comparison	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Land	Junior et al., 2019a	Land	-13,000	2,693	7,250	-18,277	-7,723	-4,828	0,000
Land	Terblanche & Millen, 2012b	Land	-1,000	2,455	6,025	-5,811	3,811	-0,407	0,684
Land	Sosner et al., 2016b	Land	-0,214	1,449	2,100	-3,055	2,627	-0,148	0,883
Land			-4,185	2,373	5,633	-8,837	0,466	-1,763	0,078
Rest	Terblanche & Millen, 2012a	Rest	-3,000	2,353	5,535	-7,611	1,611	-1,275	0,202
Rest	Sosner et al., 2016a	Rest	-1,857	2,156	4,646	-6,082	2,368	-0,862	0,389
Rest	Cunha et al., 2018a	Rest	-1,200	0,087	0,008	-1,370	-1,030	-13,856	0,000
Rest			-1,910	2,240	5,017	-6,300	2,480	-0,853	0,394
Overall			-2,982	1,629	2,653	-6,174	0,211	-1,830	0,067



B

Group by Comparison	Study name	Comparison	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Land	Junior et al., 2019b	Land	-11,000	1,118	1,250	-13,191	-8,809	-9,839	0,000
Land	Terblanche & Millen, 2012d	Land	-3,000	2,706	7,320	-8,303	2,303	-1,109	0,268
Land	Sosner et al., 2016d	Land	-1,072	1,594	2,542	-4,197	2,053	-0,672	0,501
Land			-5,277	2,773	7,688	-10,711	0,158	-1,903	0,057
Rest	Terblanche & Millen, 2012c	Rest	-3,000	2,764	7,640	-8,418	2,418	-1,085	0,278
Rest	Sosner et al., 2016c	Rest	-2,715	2,422	5,864	-7,461	2,031	-1,121	0,262
Rest	Cunha et al., 2018b	Rest	-0,900	0,173	0,030	-1,239	-0,561	-5,196	0,000
Rest			-2,069	2,809	7,890	-7,575	3,436	-0,737	0,461
Overall			-3,694	1,973	3,894	-7,561	0,174	-1,872	0,061



C

Group by Comparison	Study name	Comparison	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Land	Junior et al., 2019c	Land	-4,000	0,500	0,250	-4,980	-3,020	-8,000	0,000
Land	Terblanche & Millen, 2012f	Land	-3,000	3,484	12,140	-9,829	3,829	-0,861	0,389
Land	Sosner et al., 2016f	Land	-0,714	1,986	3,945	-4,607	3,179	-0,359	0,719
Land			-3,789	0,480	0,231	-4,730	-2,848	-7,889	0,000
Rest	Terblanche & Millen, 2012e	Rest	-4,000	3,922	15,385	-11,688	3,688	-1,020	0,308
Rest	Cunha et al., 2018c	Rest	-1,400	0,260	0,068	-1,909	-0,891	-5,389	0,000
Rest	Sosner et al., 2016e	Rest	-0,286	2,515	6,325	-5,215	4,643	-0,114	0,909
Rest			-1,400	0,258	0,066	-1,905	-0,894	-5,427	0,000
Overall			-2,560	1,194	1,426	-4,900	-0,219	-2,144	0,032

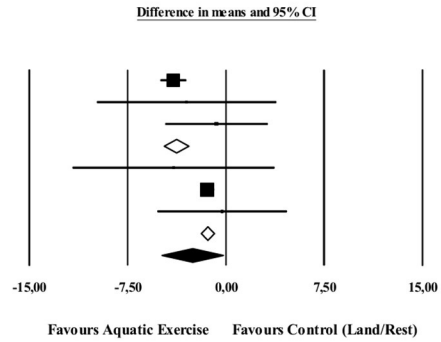


FIGURE 3 | Diastolic blood pressure post-exercise hypotension effect. Comparison between water exercise (aquatic) with land exercise or rest condition. **(A)** 24 h, **(B)** Daytime, **(C)** Nighttime.

There are very few studies that have compared the chronic effects of AE and LE on blood pressure (BP) control. Júnior et al. (2019) observed that elderly hypertensive individuals trained in an aquatic setting had lower baseline BP during the daytime; Arca et al. (2013) and Ruangthai et al. (2020) showed the same effect for BP, but a study in patients with peripheral artery disease

revealed that although land-based exercise therapy is effective in reducing arterial stiffness, heated-water exercise demonstrates greater benefits on vascular function (Park et al., 2020).

Interestingly, recent data (Ruangthai et al., 2020) showed a better lipid profile for AE compared to LE, suggesting that the improvement in blood lipid levels and body fat after aquatic training programs might result from the influence of water temperature. Studies have shown a positive effect of AE on blood lipids and body composition (Takeshima et al., 2002), temperatures of 28–30°C for 60 min, indicating that temperature can influence metabolic rate. This response is due to the increased activity of the sympathetic nervous system (Daanen and Van Marken Lichtenbelt, 2016).

A study examining patients with stable chronic heart failure showed that AE has additional benefits to endothelial function because this type of exercise effectively increases the basal level of plasma nitrates (Mourot et al., 2009). Water immersion decreases the vascular tone and total peripheral resistance (Mourot et al., 2008). A study conducted on a dog model showed an increase in skeletal muscle blood flow in the forelimbs and hindlimbs during immersion, suggesting an increased peripheral blood flow (Hajduczok et al., 1987). The aquatic immersion effect led to increased shear stress on vessel walls, increasing nitric oxide bioavailability (Niebauer and Cooke, 1996; Green et al., 2004). Thus, water/aquatic-based exercises may have different effects on vessel responses compared to LE, and further studies are required to investigate these effects.

The practical clinical importance of AE is the possibility of adherence to an exercise program. The water proprieties enable the participation of several people, for example, elderly subjects, patients who cannot support their weight, or have poor balance. Another important point with great clinical relevance is a cardiovascular response in AE, the SBP, DBP, and HR gradually increased during the underwater treadmill walking, but their mean maximum increases were significantly smaller than those of the land treadmill walking, underwater treadmill walking can better help relieve the cardiovascular workload compared to the land treadmill walking in stroke patients (Yoo et al., 2014). Additionally, AE allows the combination of aerobic and resistance exercises due to the buoyancy effect, which may potentiate the effects of exercise as well-known effects of exercise, such as autonomic activity modulation, better baroreceptor reflex sensitivity, and endothelium-dependent vasodilatation (Fadel, 2008).

The clinical relevance of AE in PEH must be more evident after the elucidation of magnitude and duration time of the PEH, so, at the end of this discussion, some future perspectives will be indicated. In these meta-analyses was evident that AMBP monitoring is scarce. The use of ABPM has limitations due to the adherence of the equipment in arms for 24-h. In addition, the equipment is expensive. One alternative is the home blood pressure monitoring, at least 2 or 3-times at nighttime. Another important question is the standardization of participants' activity level, as well the monitoring of the daily life activities during the intervention period of the experiment. Investigators can use a step counter or another device for these monitoring. Another gap that needs investigation is the autonomic control during and after AE. In these perspectives, a simple and applicable methodology of measuring heart rate variability can be used. Baroreflex sensibility is another parameter that demands more investigation, considering the importance of neural mechanisms involved in blood pressure control. This measurement presents more limitations, but several no invasive methods can be applied: Valsalva maneuver, which produces a natural challenge for the baroreceptors by voluntarily increasing intrathoracic and abdominal pressure through straining; the neck chamber technique, which allows a selective activation/deactivation of carotid baroreceptors by application of negative/positive pressure to the neck region and spontaneous oscillations of systolic arterial pressure and RR interval.

CONCLUSION

AE is effective in promoting PEH during the night for SBP in comparison with LE and for SBP and DPB in comparison with the rest condition. The 24-h analysis did not show any significant differences. The number of studies describing a 24-h measure was low, and further studies are required, including different physical conditions (active or sedentary) and the type of exercise enrolled (aquatic or land). Additionally, the nighttime results draw attention to possible aquatic and water-based effects in autonomic control of BP. The benefits provided by this type of exercise warrant for this research topic to be further explored.

LIMITATIONS

The current meta-analysis has several limitations. The pooled net change for land comparisons contained significant heterogeneity, but the reason for this heterogeneity could not be determined. Several important questions need to be addressed: the physical level of volunteers was described in only two papers, and in one of them (Cunha et al., 2018) the subjects were physically active on land but not in water; in another study (Júnior et al., 2019), the study population consisted of elderly hypertensive individuals, of which 20 trained in land-based exercises and 20 in aquatic-based exercises. The participants were enrolled in recurrent physical exercise for at least 6 months before evaluation for a minimum of two sessions a week.

Another important point that can contribute to high heterogeneity to land exercise is the standardization of exercise session between studies, one study was made in cycle ergometer (Sosner et al., 2016) and other 3 studies made through dynamic whole-body exercise (Terblanche and Millen, 2012; Cunha et al., 2018; Júnior et al., 2019), in addition, the intensity of exercise is controlled by different methods: HR reserve, HR maximal, VO_2 maximal and RPM. More studies with similar protocols are necessary to evaluate the aquatic vs. land exercise effect in blood pressure.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

CT, LB, JC, and EO contributed to the conception and design of the manuscript. CT and LB performed the data search and data extraction. JC performed the data analysis. CT, EO, and DC drafted the manuscript. JC, LB, and DC performed critical revisions of the manuscript. All authors contributed to the manuscript and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2022.834812/full#supplementary-material

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Skeletal Muscle Hyperemia: A Potential Bridge Between Post-exercise Hypotension and Glucose Regulation

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For both healthy individuals and patients with type 2 diabetes (T2D), the hemodynamic response to regular physical activity is important for regulating blood glucose, protecting vascular function, and reducing the risk of cardiovascular disease. In addition to these benefits of regular physical activity, evidence suggests even a single bout of dynamic exercise promotes increased insulin-mediated glucose uptake and insulin sensitivity during the acute recovery period. Importantly, post-exercise hypotension (PEH), which is defined as a sustained reduction in arterial pressure following a single bout of exercise, appears to be blunted in those with T2D compared to their non-diabetic counterparts. In this short review, we describe research that suggests the sustained post-exercise vasodilation often observed in PEH may sub-serve glycemic regulation following exercise in both healthy individuals and those with T2D. Furthermore, we discuss the interplay of enhanced perfusion, both macrovascular and microvascular, and glucose flux following exercise. Finally, we propose future research directions to enhance our understanding of the relationship between post-exercise hemodynamics and glucose regulation in healthy individuals and in those with T2D.

Keywords: glucose delivery, blood pressure, vasodilation, recovery, type 2 diabetes, histamine receptors

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INTRODUCTION

As with healthy individuals, in patients with type 2 diabetes (T2D), regular physical activity offers numerous benefits, including improved blood glucose regulation (reduced HbA1c) (Boulé et al., 2001; Umpierre et al., 2011) increased insulin sensitivity (Winnick et al., 2008), improved clinical symptoms (Wojtaszewski and Richter, 2006) and the delay or prevention of developing cardiovascular disease (Balducci et al., 2012). In addition to these benefits of regular exercise, evidence suggests even one bout of dynamic exercise stimulates increased insulin-mediated glucose uptake (Usui et al., 1998; Oguri et al., 2009) and insulin sensitivity (Devlin et al., 1987; Perseghin et al., 1996; Bordenave et al., 2008) in patients with T2D during post-exercise recovery. These findings highlight the importance of the post-exercise period in optimizing glycemic regulation in this population. In this mini review, we provide a brief overview of the phenomenon known as post-exercise hypotension (PEH) and how the sustained vasodilation that is frequently associated with PEH may affect glucose regulation in both healthy individuals and in people with T2D.

In doing so, we focus on the significance of post-exercise blood flow, both macrovascular and microvascular, in the delivery, transport and metabolism of glucose. Finally, we suggest future research directions to advance our understanding of how post-exercise hemodynamics affect glucose regulation in both healthy individuals and those with T2D.

OVERVIEW OF POST-EXERCISE HYPOTENSION

During recovery from an acute bout of dynamic exercise, humans experience PEH, which features a sustained reduction in arterial pressure compared to pre-exercise control levels (Kenney and Seals, 1993). In most circumstances, PEH is associated with post-exercise skeletal muscle vasodilation that is not completely off-set by a still elevated cardiac output (Halliwill et al., 2013). However, occasionally (e.g., in some hypertensive subjects) it has corresponded with a decreased cardiac output accompanied by an increase in systemic vascular resistance (Brito et al., 2014). Numerous mechanisms appear to be responsible for PEH and the sustained post-exercise vasodilation often observed in the previously active skeletal muscle vascular beds. The baroreflex is reset to defend a lower pressure following exercise (Halliwill et al., 1996), which is sometimes associated with a decrease in post-exercise muscle sympathetic outflow (Halliwill et al., 1996) and/or an increase in parasympathetic activity concomitant to the PEH (Park et al., 2006). However, other investigations have found no changes in autonomic modulation (Park et al., 2008; Anunciação et al., 2016) or have observed increased sympathetic activity (Teixeira et al., 2011; Cunha et al., 2016) post-exercise, which suggests that variations in autonomic control may reflect a physiological response to compensate for the fall in blood pressure via the downward resetting of the arterial baroreflex following exercise (Farinatti et al., 2021). For a given level of sympathetic nerve activity, reduced vascular resistance has been observed in the previously active skeletal muscle vascular beds after exercise (Halliwill et al., 2003). Importantly, post-exercise skeletal muscle vasodilation is facilitated locally by activation of both the histamine H_1 and H_2 receptors, as combined H_1 and H_2-receptor antagonism attenuates PEH by ∼65% and post-exercise vasodilation by ∼80% following 60 min of moderate-intensity dynamic exercise (Halliwill et al., 2013).

PEH has been observed in men and women (Senitko et al., 2002) and in both sedentary and endurance-trained individuals (Senitko et al., 2002; Lockwood et al., 2005; McCord et al., 2006; McCord and Halliwill, 2006). Numerous modes of aerobic exercise may evoke PEH (MacDonald, 2002) and although most investigations have employed large muscle dynamic exercise (e.g., cycle ergometer), PEH and post-exercise vasodilation have also been induced by single-leg dynamic knee extension exercise (Barrett-O'Keefe et al., 2013). In normotensive and hypertensive individuals, in both laboratory and ambulatory studies, PEH has been provoked by varying doses of exercise (MacDonald et al., 2000; Pescatello et al., 2004; Eicher et al., 2010), although the magnitude and duration of PEH are somewhat dose-dependent with regards to exercise intensity (Forjaz et al., 2004; Smelker et al., 2004) and duration (Forjaz et al., 1998; Mach et al., 2005).

POST-EXERCISE GLUCOSE REGULATION IN HEALTHY INDIVIDUALS

Skeletal muscle glucose uptake is dependent on several determinants that can be sequentially categorized into either glucose delivery, transport, or metabolism (Wasserman and Ayala, 2005). Delivery of glucose to the interstitial space is determined by arterial glucose concentration, skeletal muscle blood flow, capillary perfusion, and endothelial permeability (Jensen and Richter, 2012). Depending on acute (e.g., physical activity level) or chronic conditions (e.g., disease), any of these steps can be rate-limiting.

During the first 90 min post-exercise, skeletal muscle glucose uptake is enhanced in an insulin-independent manner (Richter et al., 2001; Henriksen, 2002). This elevated muscle glucose uptake corresponds with the peak glycogen synthesis rate in the previously exercised skeletal muscle (Price et al., 1994; Casey et al., 2000), thereby promoting post-exercise glycogen repletion.

Research on both rodents (Schultz et al., 1977; Hespel et al., 1995) and humans (Hickner et al., 1991; Baron et al., 1994; Durham et al., 2003) suggest augmented limb blood flow promotes skeletal muscle glucose uptake, even independent of the vasodilatory influence of insulin. In examining the influence of exercise on this relationship, Hamrin et al. (2011) observed, via skeletal muscle microdialysis, that increased tissue perfusion was associated with enhanced glucose uptake 12 h after the completion of a 2-h bout of moderate-intensity one-legged cycling. Notably, this response was independent of enhancement of insulin responses, as they found similar increases in skeletal muscle glucose uptake in the post-exercising and post-resting legs in response to a hyperinsulinemic-euglycemic clamp.

Role of Histamine Receptor-Mediated Vasodilation

Several studies employing histamine-receptor blockade have lent support to the notion that sustained skeletal muscle vasodilation following exercise aids in the movement of glucose from the central circulation to skeletal muscles. Pellinger et al. (2010) utilized skeletal muscle microdialysis following 60 min of moderate-intensity cycling exercise to demonstrate that glucose delivery to previously active skeletal muscle is supported by post-exercise vasodilation, as interstitial glucose concentration was reduced when post-exercise hyperemia was blunted by local H_1- and H_2-receptor blockade. Subsequently, Emhoff et al. (2011) found that oral H_1- and H_2-receptor antagonism reduced both femoral vascular conductance and leg glucose delivery after 60 min of cycling exercise. Interestingly, due to high interindividual variability, skeletal muscle glucose uptake was not universally decreased by the histamine receptor blockade in this study. However, they noted that histamine receptor blockade blunted glucose uptake in subjects who obtained higher absolute oxygen consumptions, suggesting a potential histaminergic impact on glucose uptake and glycogen repletion in individuals

who exercise at high workloads. Furthermore, Pellinger et al. (2013) observed that oral H_1- and H_2-receptor antagonism reduced whole body insulin sensitivity by 25% in healthy individuals following 60 min of moderate-intensity cycling exercise. This finding suggests that if histaminergic skeletal muscle vasodilation is blunted, so too is delivery of glucose and insulin to skeletal muscle cells, likely attenuating insulin-mediated vasodilation and capillary recruitment. Under these circumstances, greater secretion of insulin would be required in response to a sustained elevation of blood glucose (Pellinger et al., 2013). Taken together, these investigations suggest the importance of histamine-receptor-mediated elevations in skeletal muscle blood flow in glucose regulation following exercise.

Post-exercise Microvascular Perfusion and Membrane Permeability

To determine the impact of prior acute exercise on insulin-mediated skeletal muscle microvascular blood flow, Sjøberg et al. (2017) employed a euglycemic-hyperinsulinemic clamp 4 h after single-legged exercise by young, healthy males. They found microvascular perfusion was greater 4 h post-exercise and increased 40% more in the previously exercised leg than in the rested leg, in response to insulin stimulation. Furthermore, after insulin stimulation, leg glucose uptake increased 50% more in the previously exercised leg than in the rested leg. Importantly, arterial infusion of the nitric oxide synthase (NOS) inhibitor (L-NMMA) reversed the insulin-induced rise in arterial and microvascular blood flow in both legs and abolished the greater glucose uptake found in the previously exercised leg. Interestingly, the previously exercised muscle had higher insulin signaling at the level of the protein coding gene TBC1D4 (which mediates both exercise and insulin-stimulated GLUT4 translocation) and glycogen synthase activity and this was largely unaffected by L-NMMA. These findings indicate that acute exercise increases skeletal muscle insulin sensitivity via coordinated increases in both microvascular perfusion and insulin signaling (Sjøberg et al., 2017).

Recently, Parker et al. (2021) provided further evidence of elevated microvascular perfusion well after the cessation of dynamic exercise. Utilizing a randomized cross-over design, they investigated the effect of 60 min of moderate-intensity cycling exercise on postprandial skeletal muscle microvascular blood flow responses to a high-glucose mixed nutrient meal consumed 3 h post-exercise. The exercise bout enhanced both femoral artery and muscle microvascular blood flow for up to at least 3 h post-exercise. Moreover, although the high-glucose meal evoked microvascular impairments in each condition, muscle microvascular blood flow remained almost twice that of the non-exercise control condition during the 2 h following the meal consumed post-exercise. These findings are promising regarding the impact of dynamic exercise on individuals with microvascular dysfunction or impairments in glucose regulation.

Both exercise (Kennedy et al., 1999; Flores-Opazo et al., 2020) and insulin-induced (Ryder et al., 2000; Koistinen et al., 2003) GLUT4 translocation to the skeletal muscle membrane promote glucose uptake. However, research indicates that increases in insulin-stimulated GLUT4 translocation are significantly less than the increases in glucose transport (Thorell et al., 1999). In an effort to clarify this discrepancy, McConell et al. (2020) used measurements of leg glucose uptake and skeletal muscle interstitial glucose concentrations to estimate insulin-stimulated muscle membrane permeability in healthy young men 4 h after performing 60 min of 1-legged knee-extensor exercise during a submaximal euglycemic-hyperinsulinemic clamp. Using this novel technique, they found that during insulin stimulation, muscle membrane permeability to glucose and glucose uptake increased roughly twice as much in the previously exercised leg than in the rested leg. In addition, although muscle membrane permeability to glucose did not change in either leg with ATP (an endothelium-dependent vasodilator) infusion, this caused both leg blood flow and glucose uptake to rise substantially, with the greater increases found in the previously exercised leg. These findings reinforce the possible role of increased post-exercise blood flow to support sufficient glucose uptake during recovery from exercise. **Figure 1** provides an overview of the relationship between PEH, post-exercise blood flow, and glucose delivery to the skeletal muscle cell for uptake.

POST-EXERCISE HEMODYNAMICS AND GLUCOSE REGULATION IN INDIVIDUALS WITH TYPE 2 DIABETES

While the aforementioned studies were conducted on healthy, non-diabetic subjects, their findings highlight the importance of understanding the complex interactions amongst post-exercise hemodynamic and glucose regulation mechanisms in patients with T2D, who may engage in regular exercise to help manage their blood glucose levels. Sustained post-exercise vasodilation likely increases delivery of insulin to the microvasculature, where it has been shown to enhance capillary recruitment (Coggins et al., 2001; Vincent et al., 2004; Sjøberg et al., 2017) and may increase nutritive blood flow in patients with T2D (Clark, 2008), thus potentially circumventing insulin resistance in this population.

Effects of Exercise on Glycemia in Patients With Type 2 Diabetes

It has been established that a single bout of dynamic exercise immediately confers beneficial post-exercise effects on glycemia in patients with T2D (Asano et al., 2014), thus serving as an effective strategy to help improve glycemic control in this population through repeated bouts of exercise (Way et al., 2016; Grace et al., 2017; Wake, 2020). The attenuation of hyperglycemia is primarily due to the enhanced uptake of glucose from the circulation, as shown in studies utilizing stable isotope tracers to assess glucose flux in patients with T2D (Borghouts et al., 2002; Boon et al., 2007). In this context, Boon et al. (2007) reported a significant decline in plasma glucose concentration in long-term-diagnosed T2D patients following 60 min of cycling exercise at 50% of W_{max}. Comparisons in isotopic enrichments found that even though the plasma glucose rate of appearance

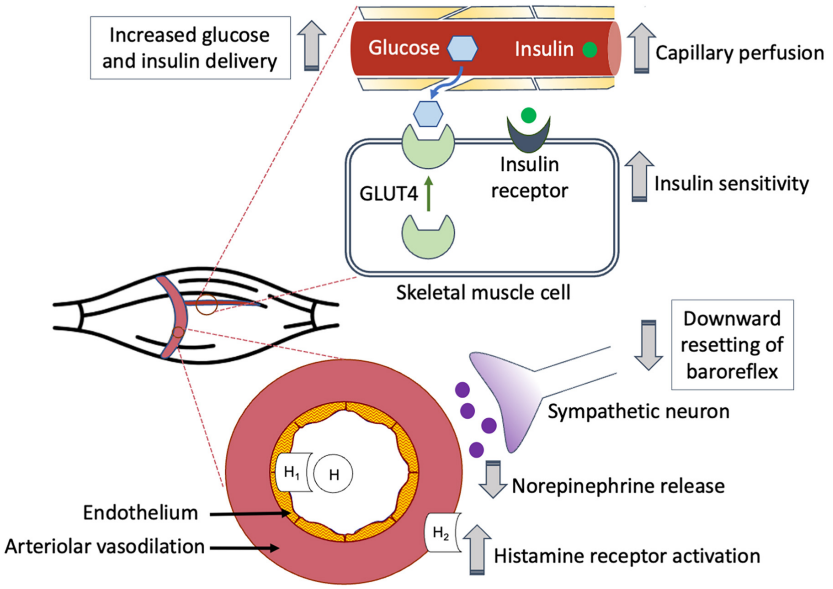

FIGURE 1 | Post-exercise hyperemia facilitates glucose delivery to previously active skeletal muscle.

(Ra) remained higher in T2D at rest and during post-exercise recovery, a significantly greater percentage of plasma glucose Ra was taken up and disappeared during and following exercise in the T2D patients compared to normoglycemic controls. Similarly, Borghouts et al. (2002) found that compared to non-diabetic control subjects, patients with T2D had greater reliance on plasma glucose oxidation vs. muscle glycogen oxidation for energy expenditure during 60 min of cycling exercise at 40% of VO_{2peak}. These results support the notion that the exercise-induced decline in blood glucose concentration in patients with T2D is attributed to an acute increase in glucose uptake.

Effects of Exercise on Endothelial Function in Patients With Type 2 Diabetes

Individuals with T2D often express early signs of cardiovascular co-morbidities, including endothelial dysfunction and arterial stiffness (Guerci et al., 2001; Frontoni et al., 2005), which may interfere with exercise-induced vasodilation following exercise. To determine whether exercise improves vasodilatory function in patients with T2D, Simões et al. (2013) compared post-exercise responses in patients with T2D to non-diabetics during a 20-min constant load exercise corresponding to 90% of LT, followed by a 45-min recovery period. The non-diabetic group showed slightly higher plasma kallikrein activity, bradykinin concentration, and nitric oxide (NO) concentration after exercise, all indicative of endothelium-dependent vasodilatory responses. To examine whether the release of these vasodilator substances is associated with the occurrence of PEH, the authors further reported that both groups did experience PEH, although it was more pronounced in the non-diabetic group compared to their counterparts with T2D. Moreover, as discussed below, these findings suggest that the bioavailability of NO released during exercise may be dependent on the intensity of the exercise bout.

Dose-Dependent Effects of Exercise in Patients With Type 2 Diabetes

Several studies have suggested, given that patients can sustain it, higher intensity or longer duration exercise confers greater benefits to T2D management (Lima et al., 2008; Pellinger et al., 2017; Liu et al., 2019; Mendes et al., 2019; de Mello et al., 2021). The occurrence of PEH in T2D patients has been observed in a dose-dependent manner, such that a significant reduction in systolic blood pressure (SBP) occurred following 20 min of exercise at 90% of anaerobic threshold (AT), whereas diastolic blood pressure and mean arterial pressure were also reduced when the exercise intensity reached 110% of AT (Lima et al., 2008). Similarly, the increased concentration of exercise-induced NO was greater and the reduction in SBP was more pronounced when an exercise bout consisting of 20 min of cycling was conducted at 120% of LT, compared to 80% of LT (Asano et al., 2013). A recent study by Mendes et al. (2019) compared treadmill walking protocols for T2D patients involving either moderate-intensity steady exercise for 30 min at 50% of heart rate reserve (HRR) or high-intensity interval exercise (five sets of 3-min bouts at 70% of HRR interspersed by 3-min bouts at 30% of HRR). Including warm-up and cool-down, both protocols consisted of 40 min of exercise, followed by a 50-min recovery period. Acute effects during and following exercise showed that the high-intensity interval exercise reduced blood glucose to a greater extent compared to the moderate-intensity steady exercise.

Recent findings by Pellinger et al. (2017) suggest that in addition to intensity, exercise duration may also affect acute post-exercise femoral blood flow and vascular conductance in patients with T2D in a dose-dependent manner. In this

study, individuals with well-controlled T2D participated in four different combinations of cycling exercise: 30 min at 40% VO_{2peak}, 30 min at 60% VO_{2peak}, 60 min at 40% VO_{2peak}, and 60 min at 60% VO_{2peak}. Sustained post-exercise hyperemia and reductions in SBP were observed in the latter three exercise protocols, suggesting that exercise must be at least moderate in intensity and/or prolonged in duration to evoke these acute hemodynamic responses in patients with T2D. Taken together, these findings suggest that higher intensity and/or longer duration exercise may promote PEH and improved glucose regulation in patients with T2D, at least in part due to enhanced post-exercise skeletal muscle blood flow.

DISCUSSION: FUTURE DIRECTIONS

Additional research is needed to further elucidate the complex relationship between PEH, post-exercise skeletal muscle blood flow and glucose regulation. Although the aforementioned research examining the potential relationship between post-exercise vasodilation and glucose regulation is compelling, most of the data derived from these investigations are associative. Therefore, more studies employing experimental manipulations designed to determine if there is a cause and effect relationship between these post-exercise phenomena are necessary.

Much of the research on healthy individuals may be extended to patients with T2D. For example, it is unclear if the histamine receptor-mediated post-exercise vasodilation that appears to subserve glucose regulation in healthy subjects (Pellinger et al., 2010, 2013; Emhoff et al., 2011) has the same effect in patients with T2D. In addition, the ability to estimate skeletal muscle membrane permeability (McConell et al., 2020) will allow investigations designed to better understand the interactions between glucose delivery, transport, and metabolism, in both healthy individuals and those with T2D.

In addition to investigations examining the acute effects of post-exercise vasodilation on glucose regulation, future investigations are needed to examine emerging interactions between vascular and metabolic adaptions to exercise. Along those lines, Van der Stede et al. (2021) observed that histamine receptor blockade blunted post-exercise muscle perfusion and increases in whole body insulin sensitivity in response to 6 weeks of high-intensity interval training in healthy males. Importantly, they also found that several histamine receptor-mediated adaptations were interrelated, as increases in VO_{2max} were related to changes in vascular function and whole-body insulin sensitivity. Moreover, a correlation was found between changes in capillary-fiber ratio and whole-body insulin sensitivity (Van der Stede et al., 2021). These findings are consistent with recent research suggesting that the post-exercise activation of H_1- and H_2-receptors upregulate several related pathways, including those related to metabolism, endothelial and vascular function (Romero et al., 2016), thereby highlighting important histaminergic adaptations to exercise that potentially impact both post-exercise blood flow and metabolic regulation.

In conclusion, recent investigations suggest that the post-exercise vasodilation that is often observed with PEH may aid in glucose regulation, via increased macrovascular and microvascular perfusion. Additional research is needed to further elucidate the relationship between post-exercise hemodynamics and glucose regulation in humans.

AUTHOR CONTRIBUTIONS

TP and C-AE wrote and revised the manuscript. Both authors contributed to the article and approved the submitted version.

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Postexercise Hypotension Is Delayed in Men With Obesity and Hypertension

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Background: Postexercise hypotension (PEH) can play a major role in the daily blood pressure management among individuals with hypertension. However, there are limited data on PEH in persons with obesity and hypertension, and no PEH data in this population beyond 90 min postexercise.

Purpose: The purpose of this study was to determine if PEH could be elicited in men with obesity and hypertension during a 4-h postexercise measurement period.

Methods: Seven men [age = 28 ± 4 years; body mass index = 34.6 ± 4.8 kg/m^2; brachial systolic blood pressure (SBP): 138 ± 4 mmHg; brachial diastolic BP (DBP): 80 ± 5 mmHg; central SBP: 125 ± 4 mmHg; central DBP: 81 ± 8 mmHg] performed two exercise sessions on a cycle ergometer, each on a separate day, for 45 min at ∼65% VO_{2max}. One exercise session was performed at a cadence of 45 RPM and one at 90 RPM. Blood pressure was monitored with a SunTech Oscar2 ambulatory blood pressure monitor for 4 h after both exercise sessions, and during a time-matched control condition.

Results: Both brachial and central SBP were not changed during the first h postexercise but were reduced by ∼5–11 mmHg between 2 and 4 h postexercise ($p < 0.05$) after both exercise sessions. Brachial and central DBP were elevated by ∼5 mmHg at 1 h postexercise ($p < 0.05$) but were ∼2–3 mmHg lower compared to control at 4 h postexercise, and ∼2–4 mmHg lower at 3 h postexercise compared to baseline. Mean arterial pressure (MAP) was elevated compared to control at 1 h postexercise after both exercise sessions, but was ∼2–3 mmHg lower compared to control at 2, 3, and 4 h postexercise, and ∼4–7 mmHg lower at 3 h postexercise compared to baseline.

Conclusion: Despite the small sample size and preliminary nature of our results, we conclude that PEH is delayed in men with obesity and hypertension, but the magnitude and duration of PEH up to 4 h postexercise is similar to that reported in the literature for men without obesity and hypertension. The PEH is most pronounced for brachial and central SBP and MAP. The virtually identical pattern of PEH after both exercise trials indicates that the delayed PEH is a reproducible finding in men with obesity and hypertension.

Keywords: blood pressure, exercise, body mass index, obese, overweight

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INTRODUCTION

Hypertension is a leading risk factor for cardiovascular disease (Whelton et al., 2018), and physical activity can lower blood pressure and reduce the rate of conversion from elevated blood pressure (BP) to hypertension (Faselis et al., 2012; Diaz and Shimbo, 2013; Pescatello et al., 2015). A single bout of exercise has been shown to lower blood pressure for at least 12 h (Pescatello and Kulikowich, 2001; Pescatello et al., 2004), and this postexercise hypotension (PEH) is thought to play an important role in the antihypertensive effects of exercise (Hamer, 2006; Brito et al., 2018).

Although PEH has been well-established in normal weight and overweight individuals, whether obesity influences the PEH response is unclear. This is mainly due to a limited number of publications on PEH in persons with obesity (Figueroa et al., 2007; Zeigler et al., 2018; Bunsawat et al., 2021). One meta-analyses reported that PEH was inversely related to body mass index [BMI (Body Mass Index); kg/m^2], with a regression line that predicted no PEH above a BMI of approximately 31 (Carpio-Rivera et al., 2016). This meta-analysis included only one study that reported postexercise BP responses in persons with obesity. In that study, which included obese women with and without type 2 diabetes, 20 min of exercise at 65% of maximal oxygen uptake (VO_{2max}) reduced systolic BP (SBP) at 10 and 20 min postexercise, but PEH was no longer evident at 30 min postexercise, which was the last measurement time (Figueroa et al., 2007). It was recently reported that 1 h of exercise at 60% of VO_{2max} produced a modest PEH of ∼2–4 mmHg in adults with obesity (Bunsawat et al., 2021). In that study, the PEH observed at 30 and 60 min postexercise was no longer present at 90 min. We previously reported that PEH was not observed in 8 men with obesity after a 40-min exercise bout at 65–70% of heart rate maximum (Zeigler et al., 2018). However, we measured blood pressure for only 1 h postexercise. Despite the lack of PEH during the 1-h postexercise measurement period, there was a clear trend for declining BP between the first 30 min postexercise and the last 30 min postexercise. This was evident for SBP, diastolic BP (DBP) and mean arterial pressure (MAP). But because BP was elevated immediately postexercise, despite the trend for decreasing BP during the 60-min postexercise measurement period, PEH relative to baseline BP was not observed. Thus, a PEH may have been observed if the postexercise measurement period been extended beyond 1 h. Because PEH can be observed for several hours after exercise (Pescatello and Kulikowich, 2001; Pescatello et al., 2004; Angadi et al., 2015), it is possible that PEH is delayed in obese individuals. In the few prior studies published on PEH in adults with obesity (Figueroa et al., 2007; Zeigler et al., 2018; Bunsawat et al., 2021), postexercise BP measurements did not extend beyond 90 min.

Another limitation of the studies on PEH in obesity is that the subject populations had relatively normal blood pressures, with mean SBP of 110 ± 10 mmHg (Bunsawat et al., 2021), 122 ± 6 mmHg (Figueroa et al., 2007), and 126 ± 7 mmHg (Zeigler et al., 2018). The magnitude of PEH is positively related to the baseline BP prior to exercise (Brito et al., 2018). Indeed, PEH has been repeatedly demonstrated in hypertensive populations (Legramante et al., 2002; Melo et al., 2006; Brito et al., 2011; Dos Santos et al., 2014; Cunha et al., 2016; Cunha et al., 2017; Ferrari et al., 2017; Imazu et al., 2017; Cunha et al., 2018; Goessler et al., 2018; de Freitas Brito et al., 2019; Pires et al., 2020; Iellamo et al., 2021). However, in virtually all of these studies the hypertensive populations included individuals with and without obesity, with mean BMI < 30 kg/m^2 in most instances. One study reported PEH in 8 hypertensive women, all with BMI > 30 kg/m^2 (Cunha et al., 2018), but the results may have limited applicability due to the nature of the experimental design. The exercise involved 45 min of water aerobics, and it has been demonstrated that water immersion induces significant hemodynamic changes even without exercise (Sramek et al., 2000; Stocks et al., 2004). This is especially relevant because the control condition included no water immersion and the postexercise measurement period lasted only 30 min. Consequently, a research gap exists with regard to PEH in adults with both obesity and hypertension. Thus, the purpose of this study was to determine whether PEH is observed during a postexercise period lasting 4 h in adult men with obesity and hypertension. Based on results from our previous study described above (Zeigler et al., 2018), we hypothesized that PEH would be delayed, with significantly reduced brachial and central BPs observed only after the first 1 h postexercise.

MATERIALS AND METHODS

Participants

Seven physically inactive men (age 28 ± 4 years; BMI 34.6 ± 4.8 kg/m^2) participated in this study. Subject characteristics are provided in **Table 1**. Physical activity levels were ascertained with the International Physical Activity Questionnaire (Hagstromer et al., 2006). Subjects were not currently participating in any structured exercise program or adhering to any specific diet or weight loss program. Those with known cardiovascular, pulmonary, and renal or metabolic diseases, current smokers, or those on vasoactive medications for the treatment of blood pressure, were excluded. The study was approved by the Arizona State University Institutional Review Board and was conducted in a manner consistent with the Declaration of Helsinki. Written and informed consent was obtained from each subject prior to enrollment.

The seven subjects included in this study were part of a larger study in which glucose tolerance was the primary outcome, with the goal of determining whether muscle contraction frequency (defined by different pedaling cadences, described below) during an aerobic exercise session affected postexercise glucose tolerance (unpublished data not shown). Postexercise blood pressure was a secondary outcome in this study. Although blood pressure was not one of the inclusion/exclusion criteria, all seven men had resting SBP > 130 mmHg (see **Table 1**), thus meeting the definition of hypertension (Whelton et al., 2018). One of the subjects had a BMI of 28.9 kg/m^2. However, results were essentially the same with and without including this subject in the statistical analyses (see Section "Results").

TABLE 1 | Participant characteristics.

	Mean ± SD	Range
N	7	
Age (year)	28 ± 4	20–35
Height (cm)	175.1 ± 7.4	165.0–187.5
Weight (kg)	105.8 ± 15.4	91.7–137.9
BMI (kg/m^2)	34.6 ± 4.8	28.9–43.2
Body fat (%)	37.1 ± 4.4	31.3–43.0
Visceral fat (g)	1,398 ± 707	506–2,559
Systolic blood pressure (mmHg)	138 ± 4	131–145
Diastolic blood pressure (mmHg)	80 ± 5	70–87
VO_{2max} (ml/kg/min)	28.7 ± 6.1	18.7–36.3

BMI, Body Mass Index; VO_{2max}, maximal oxygen uptake.

VO_{2max} Assessment

Prior to the PEH protocol (described below) each participant performed a ramp-style maximal exercise test on a cycle ergometer (Viasprint 150P; Ergoline, Bitz, Germany) for determination of VO_{2max}. Pulmonary ventilation and gas exchange were measured continuously with a Parvo Medics TrueOne 2400 (Parvo Medics, Sandy, UT, United States). Standard three-point calibration was performed before each test. Heart rate was measured with a Polar heart rate monitor (Polar, Lake Success, NY, United States). After a 5-min warm-up phase at 50 W, power was increased by 30 W/min until exhaustion. Participants were provided with verbal encouragement throughout the test. After a cool-down period of 5–10 min, in which subjects pedaled at the warm-up work rate, each subject performed a verification phase test at a constant power of 100% of the peak power attained during the ramp test (Sawyer et al., 2015). The mean of the two highest consecutive 15-s VO_2 averages during the ramp or verification phase tests was taken as VO_{2max}. All subjects achieved a maximum respiratory exchange ratio > 1.10 on the ramp test and a heart rate > 90% of age-predicted maximum on either the ramp test or the verification phase test.

Body Composition

Participants' heights and weights were measured on a standard scale (Seca274, Medical Measuring Systems, Chino, CA, United States). Body composition was assessed *via* Dual-energy X-ray Absorptiometry (DEXA) (Lunar iDXA, GE Healthcare, Madison, WI, United States).

Experimental Protocol for Determination of Postexercise Hypotension

All subjects underwent three experimental conditions in a randomized cross-over design. The conditions consisted of a non-exercise control day and two exercise conditions on a cycle ergometer at different pedaling frequencies (45 and 90 RPM). As stated above, the rationale for the two pedaling frequencies pertained to the primary outcome measure of glucose tolerance. There was no *a priori* reason for expecting cycling cadence to influence PEH. However, the two exercise trials allowed for an assessment of the reproducibility of the postexercise blood pressure responses to aerobic exercise in men with obesity. Only one study has reported information on PEH reproducibility (Fecchio et al., 2017), and that study only measured PEH at 45 min after exercise cessation.

Subjects reported to the laboratory at 7:00 a.m. for each visit, 1 h after consuming a standardized breakfast meal at home. The breakfast meal consisted of a bagel, cream cheese, and chocolate milk (630 kcal; 104 g carbohydrate; 10 g fat; 30 g protein). The same meal was consumed prior to each visit. The breakfast meal was provided to subjects the day before each laboratory visit. In addition, gift cards to a local restaurant were provided to each subject for purchasing lunch and dinner on the day before each laboratory visit. Subjects were instructed to consume the same lunch and dinner meals on the day before each laboratory visit. An ambulatory blood pressure monitor was placed on the right arm of the participant. After 15 min of seated rest, resting blood pressures were recorded. Resting blood pressure data obtained for each trial were averaged over the three trials. The average resting brachial blood pressures are presented in **Table 1**, and reflect the average of 5–13 total recordings taken during these baseline assessment periods for each subject. After resting blood pressure was taken, the blood pressure monitor was then set to record automatically every 15 min for 4 h during the control trial and after exercise for the two exercise trials. For exercise study visits, the monitor was removed during cycling and replaced following the cool-down. All visits were separated by at least 1 week, and this procedure was completed for all study visits.

Aerobic Exercise

Participants performed two cycle ergometer exercise sessions on separate occasions, using the same ergometer as used for determination of VO_{2max}. These exercise sessions were randomized for sequence. During one exercise session subjects maintained a cadence of 45 RPM and during the other exercise session maintained a cadence of 90 RPM. Each exercise session began with a 5-min warm-up during which time power was gradually increased so that VO_2 was ∼65% VO_{2max} by the end of the fifth min. Subjects then exercised at this intensity for 45 min. Heart rate and VO_2 were monitored continuously throughout each exercise session, and power was adjusted to maintain VO_2 at ∼65% VO_{2max}. Each exercise session concluded with a 5-min cool-down at 25–50 W.

Postexercise Measurement of Blood Pressure

Blood pressure was monitored by a SunTech Oscar2, Model 250 (Sun Tech Medical, Morrisville, NC, United States) ambulatory blood pressure monitor. The Oscar 2 device has embedded, automated technology (SphygmoCor Inside^{TM}, ATCOR, Naperville, IL, United States) that allows for the estimation of central aortic systolic and diastolic pressures (Pauca et al., 2001). During the 4 h of BP measurements in the control condition and after both exercise sessions, subjects spent the entire time in a private office room adjacent to the laboratory. During this time the subjects spent most of their time seated at a desk where they were allowed to use their laptop computer

or phone, or to read. The only time they were allowed to leave the private office space was to use the restroom. Participants were instructed to remain still and not talk while the device was inflating. During the 4-h postexercise period, the majority of measurements were taken while participants were seated quietly. If they were walking or standing when a measurement started (e.g., walking to the restroom) they were instructed to stand quietly until the measurement was completed. Blood pressure data were downloaded using AccuWin Pro v4.0.

Statistical Methods

Blood pressure data were pooled into hourly averages. All statistical procedures were performed using SPSS (SPSS 23, IBM Corporation, Armonk, NY, United States). Values were tested for normality and homogeneity. One-way analysis of variance was used to test for differences in baseline values between the three trials for all blood pressures. Paired-samples *t*-tests were used detect differences in work rate, VO_2 and heart rate responses to the two RPM conditions. Linear mixed models were used to detect differences for hourly differences for BP variables with both fixed and random effects explored. Baseline BP was included as a covariate in the linear models analysis. Pairwise comparisons were also used to determine within-condition differences in BP at each postexercise time point compared with pre-exercise baseline BP. The Bonferroni adjustment was used for multiple comparisons when appropriate. The mixed model estimated marginal means (EMM) are shown in all figures. A p-value < 0.05 was considered statistically significant.

RESULTS

The mean VO_2 (45 RPM = 1.93 ± 0.30 L/min; 90 RPM = 1.97 ± 0.33 L/min), and heart rate (45 RPM = 147 ± 12 beats/min; 90 RPM = 152 ± 17 beats/min) were not different between exercise conditions. However, the power output during exercise at 45 RPM (106 ± 27 W) was significantly greater ($p < 0.001$) than that during exercise at 90 RPM (90 ± 30 W). The lower power output during exercise at the faster cadence was necessary due to the effect of pedaling frequency on VO_2 (Gaesser and Brooks, 1975).

There were no differences in baseline blood pressures for the three conditions. All blood pressures remained unchanged during the non-exercise control trial. Brachial and central SBPs were unchanged during the first h postexercise. Compared to corresponding control values, brachial SBP was ∼5–8 mmHg lower at 2 and 4 h postexercise, and central SBP was ∼5–7 mmHg lower at 2, 3, and 4 h postexercise ($p < 0.05$; **Figures 1**, **2**). Compared to baseline, brachial SBP was reduced by ∼8–11 mmHg at 2, 3, and 4 h postexercise, and central SBP was reduced by 5–10 mmHg at 2 and 3 h postexercise ($p < 0.05$).

During the first h postexercise, brachial DBP was ∼5 mmHg higher, and central DBP ∼6–8 mmHg higher, compared to the corresponding control value ($p < 0.05$; **Figures 3**, **4**). Thereafter, the only significant difference in DBP was a lower brachial and central DBP at 4 h postexercise compared to the control trial. Compared to baseline, both brachial and central DBP were reduced by ∼2–4 mmHg only at 3 h postexercise ($p < 0.05$).

Compared to the control trial, mean arterial pressure was elevated at 1 h postexercise after both exercise sessions but was ∼2–3 mmHg lower compared to control at 2, 3, and 4 h postexercise ($p < 0.05$; **Figure 5**). Compared to baseline, MAP was reduced by ∼4–7 mmHg at 2 and 3 h postexercise ($p < 0.05$).

Removal of the subject with a BMI of 28.9 kg/m^2 did not materially affect the results. Brachial SBP was also significantly lower at 3 h postexercise for both 45 and 90 RPM, whereas it was not with $n = 7$. With $n = 6$, brachial and central DBP were significantly lower at 3 h postexercise, but no longer significant at 4 h postexercise. Results for MAP were unchanged with $n = 6$.

DISCUSSION

The main finding of this study was that PEH is observed in obese men, but the blood pressure-lowering effect of exercise is not observed until after the first h postexercise. Furthermore, due to the fact that the PEH response in our subjects was observed after both exercise trials that differed only in terms of cycling cadence, our results demonstrate that the delayed PEH response in men with obesity is reproducible.

Although PEH has been consistently reported in non-obese populations (Pescatello and Kulikowich, 2001; MacDonald, 2002; Forjaz et al., 2004; Jones et al., 2008; Angadi et al., 2010; Liu et al., 2012; Terblanche and Millen, 2012; Halliwill et al., 2013; Hecksteden et al., 2013; Brito et al., 2014; Angadi et al., 2015; Carpio-Rivera et al., 2016; Fecchio et al., 2017; Brito et al., 2018; Zeigler et al., 2018), there are limited data published on individuals with obesity (Figueroa et al., 2007; Zeigler et al., 2018; Bunsawat et al., 2021). Although it has been reported that PEH is not associated with BMI (Hamer and Boutcher, 2006), that study only included men identified as normal weight (BMI = 23.0 ± 1.7 kg/m^2) or overweight (BMI = 27.5 ± 1.4 kg/m^2). A meta-analysis reported a significant correlation between BMI and PEH ($r = 0.26$, $p < 0.001$), with a regression line predicting no PEH for individuals with BMI greater than ∼31 kg/m^2 (Carpio-Rivera et al., 2016). Our data are not consistent with that prediction, as a significant PEH was evident for 2–4 h postexercise in our subjects. To our knowledge, this is the first time a PEH has been reported in individuals with obesity during this postexercise time period.

In an earlier study of 12 subjects with BMI 25–35 kg/m^2 (mean = 29 ± 4 kg/m^2), a PEH was observed 1 h after a maximal exercise test (Hecksteden et al., 2013). SBP was reduced from 134 ± 18 to 125 ± 13 mmHg, and DBP reduced from 88 ± 10 to 84 ± 7 mmHg 1 h after the maximal exercise test. Information on the number of participants with BMI > 30 kg/m^2 was not provided. In a recent study of young adults with and without obesity, it was reported that 1 h of moderate-intensity cycling at 60% VO_{2peak} reduced brachial SBP by ∼2 mmHg and central SBP by ∼3–4 mmHg, with no differences between subjects with BMI < 25 kg/m^2 and subjects with BMI > 30 kg/m^2 (Bunsawat et al., 2021). In that study, PEH was significant at 30 and 60 min postexercise but was not evident by 90 min postexercise. Because

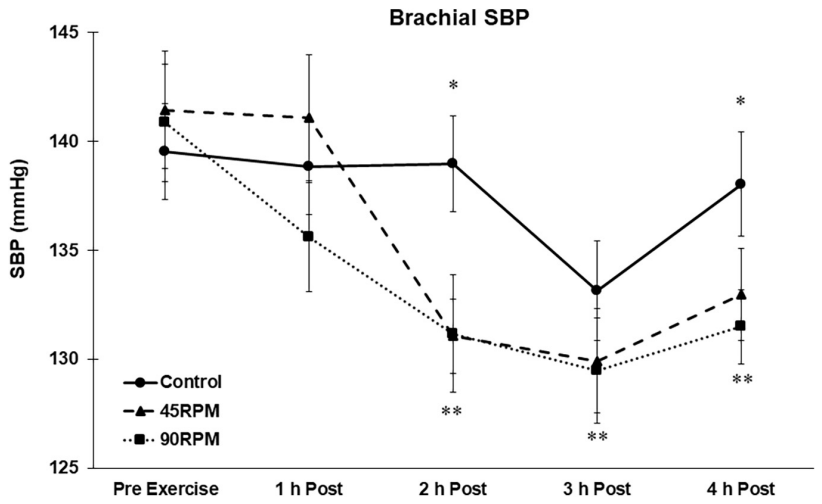

FIGURE 1 | Brachial systolic blood pressure (SBP) postexercise with time matched control. Data presented as Estimated Marginal Means ± SE; $N = 7$. *Significant difference between control and exercise conditions $p < 0.05$. **Significantly different from baseline for both exercise conditions $p < 0.05$.

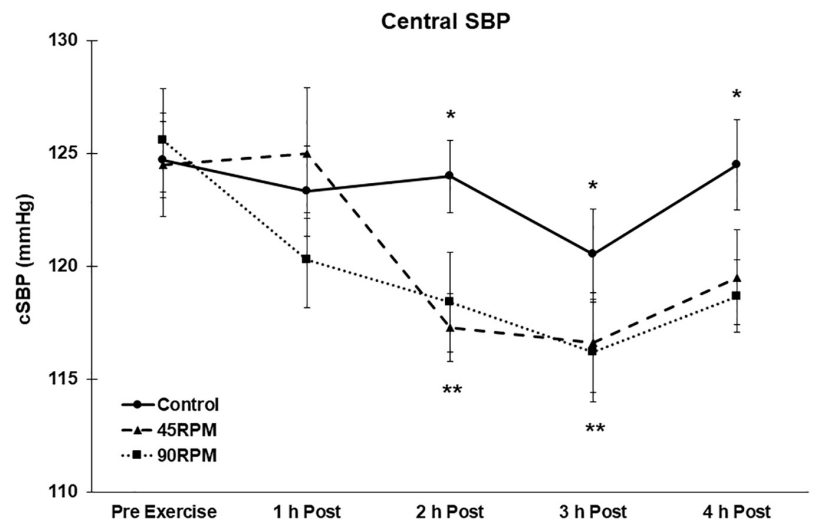

FIGURE 2 | Central systolic blood pressure (cSBP) postexercise with time matched control. Data presented as Estimated Marginal Means ± SE; $N = 7$. *Significant difference between control and exercise conditions $p < 0.05$. **Significantly different from baseline for both exercise conditions $p < 0.05$.

this study did not include a control condition, PEH was assessed relative to pre-exercise baseline blood pressure. Even if diurnal variation in blood pressure could be expected to be minimal over the 90-min postexercise period, this could still have influenced the interpretation of PEH effect of exercise due to the small PEH observed (e.g., ∼2 mmHg PEH for brachial SBP). Including a non-exercise control trial for PEH assessment is essential for determination of the true impact of exercise on PEH due to the inherent fluctuations in resting BP over several h (see **Figures 1**– **4**).

Body mass index has been reported to be unrelated to PEH (Hamer and Boutcher, 2006), and also inversely related to PEH (Carpio-Rivera et al., 2016). However, there were virtually no subjects with BMI > 30 in these studies. In a previous manuscript we reported that PEH was not observed in obese men (Zeigler et al., 2018). However, postexercise BP was only measured for 1 h. Furthermore, in our previous study it was evident that the pattern of BP responses during the 1 h postexercise was such that a PEH might have eventually been observed with a longer postexercise measurement period. Our current postexercise data are consistent with that finding because postexercise BP was also not observed during the first hour after exercise, but a significant PEH was observed between 2 and 4 h postexercise. The magnitude of the PEH for SBP in our subjects, ∼5–8 mmHg at 2 and 4 h postexercise compared to control and ∼5–11 mmHg at 2–4 h postexercise compared to pre-exercise baseline values, is at least as great as that observed in non-obese individuals during this same time period (Angadi et al., 2015). The transient

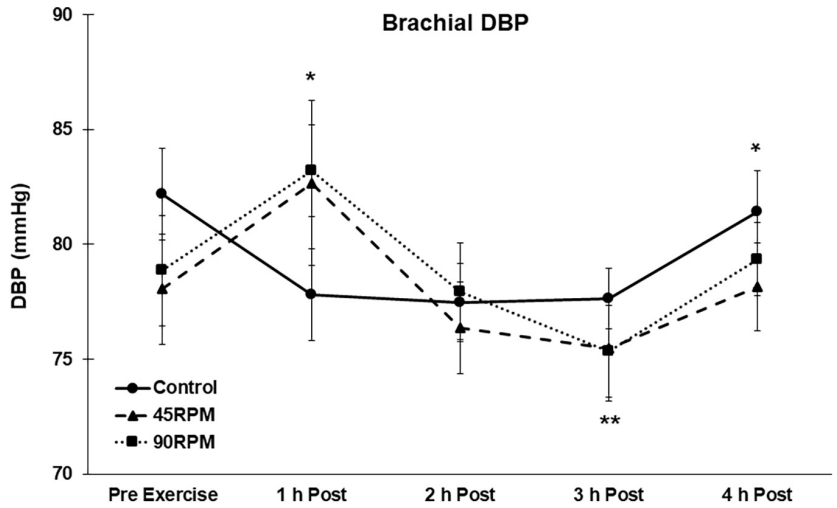

FIGURE 3 | Brachial diastolic blood pressure (DBP) postexercise with time matched control. Data presented as Estimated Marginal Means ± SE; *N* = 7. *Significant difference between control and exercise conditions $p < 0.05$. **Significantly different from baseline for both exercise conditions $p < 0.05$.

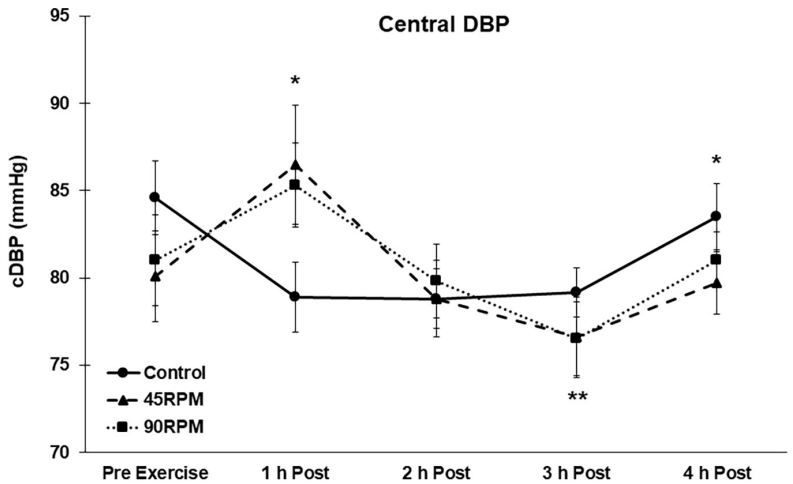

FIGURE 4 | Central diastolic blood pressure (cDBP) postexercise with time matched control. Data presented as Estimated Marginal Means ± SE; *N* = 7. *Significant difference between control and exercise conditions $p < 0.05$. **Significantly different from baseline for both exercise conditions $p < 0.05$.

increase in brachial and central DBP at 1 h was not expected. To our knowledge, this is the first time that a significant increase in brachial and central DBPs have been reported after aerobic exercise. The fact that DBP was significantly elevated at 1 h postexercise after both exercise trials suggests that this was not a spurious finding.

The reductions in postexercise central blood pressures may be of particular clinical significance because data from the Conduit Artery Function Evaluation study demonstrated significant and divergent effects of central vs. brachial blood pressure lowering (Williams et al., 2006). Specifically, a reduced central aortic SBP of ∼4 mmHg was associated with significantly lower total cardiovascular events and/or procedures as well as development of renal impairment. Further, it is important to note that reductions in central blood pressures are superior to reductions in brachial blood pressures with regard to predicting improved subclinical outcomes such as left ventricular hypertrophy, carotid IMT, and urinary albumin secretion (Kollias et al., 2016). We acknowledge that these reports on the significance of central BP reflect measurements under resting conditions, but PEH may contribute to the overall antihypertensive effects of exercise (Hamer, 2006; Brito et al., 2018).

Most studies of PEH have reported measurements only for the initial hour after exercise (Marcal et al., 2021). Thus it is difficult to compare our subjects' PEH responses over longer postexercise periods with published data. We previously reported brachial blood pressures during a 3-h postexercise period after continuous and interval exercise in young, non-obese adults (Angadi et al., 2015). The greatest PEH was observed during the first h postexercise, and averaged ∼4–6 mmHg. However,

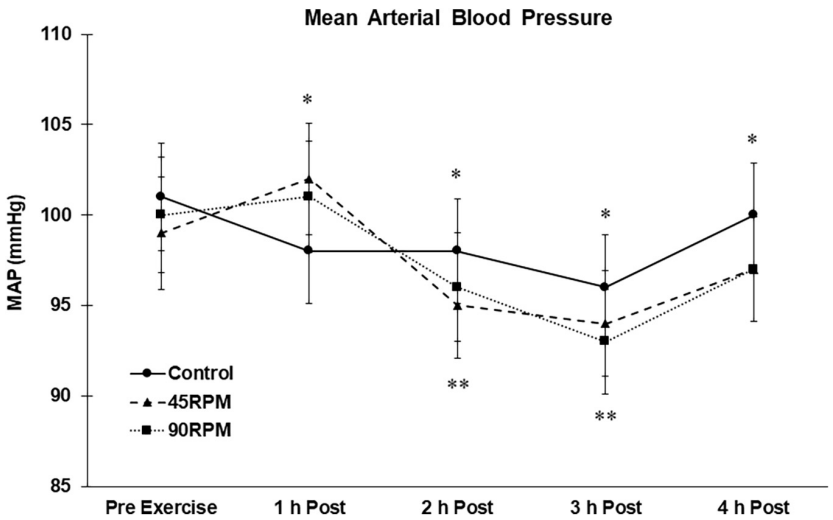

FIGURE 5 | Mean arterial blood pressure (MAP) postexercise with time matched control. Data presented as Estimated Marginal Means ± SE; $N = 7$. *Significant difference between control and exercise conditions $p < 0.05$. **Significantly different from baseline for both exercise conditions $p < 0.05$.

the PEH was no longer evident by the third hour postexercise after the steady-state continuous bout of exercise, which was comparable to the exercise bouts in the present study. By contrast, in the current study both brachial and central SBP and DBP were significantly lower than the corresponding control values 4 h after exercise. This 4-h PEH was observed for both exercise trials (**Figures 1–4**). In fact, the peak PEH occurred at approximately 3 h postexercise, at a time when PEH was no longer evident after a similar continuous exercise session in subjects without obesity (Angadi et al., 2015). One difference is that the exercise duration in the current study was 45 min, compared to 30 min for our previous study. Although some studies have shown that exercise duration had no effect on PEH (MacDonald et al., 2000; Guidry et al., 2006), a more recent meta-analysis reported that exercise duration was inversely correlated ($r = -0.19$; $P = 0.01$) with the change in postexercise SBP (Carpio-Rivera et al., 2016). The fact that a pronounced PEH was still apparent 4 h postexercise in the current study suggests that PEH, although delayed, may extend for a longer period of time in adult men with both obesity and hypertension.

Strengths and Weaknesses

One important strength of our study is the fact that the PEH was essentially identical after both exercise sessions. Our study was designed primarily to determine whether exercise of the same intensity and duration, but differing in muscle contraction rate, would differentially affect postexercise glucose tolerance. Blood pressure responses were a secondary outcome. By having two exercise sessions that were the same in intensity and duration, the second exercise session served as a *de facto* reliability test. The observation that postexercise BP responses were the same for both exercise tests indicates that our PEH findings in men with obesity and hypertension are reproducible.

One weakness is that our sample size is relatively small, and included only men. The magnitude of PEH has been reported to be greater in men compared to women (Carpio-Rivera et al., 2016). However, despite the small sample size, due to the consistent PEH for both exercise conditions, our results strongly suggest that the delayed PEH in men with obesity and hypertension is not a spurious finding.

Our subjects were not taking anti-hypertensive medications, whereas most studies of PEH in hypertensive individuals have included subjects on blood pressure medications (Melo et al., 2006; Brito et al., 2011; Cunha et al., 2016; Cunha et al., 2017; Ferrari et al., 2017; Imazu et al., 2017; Cunha et al., 2018; Goessler et al., 2018; de Freitas Brito et al., 2019; Costa et al., 2020; Pires et al., 2020). Thus, our results may not be applicable to those taking anti-hypertensive medications. Also, our subjects were physically inactive, and it has been documented that exercise training status affects PEH in older hypertensive adults on medication (Imazu et al., 2017; Iellamo et al., 2021). Whether training status affects PEH in younger adults with obesity and hypertension has not been evaluated.

One of our subjects had a BMI of <30 kg/m^2. However, even when restricting our analyses to those subjects with BMI > 30 kg/m^2, the results were essentially unchanged.

CONCLUSION

Due to the small sample size our results must be viewed as preliminary. Nevertheless, they strongly suggest that PEH occurs in men with obesity and hypertension, but that the blood pressure-lowering effect of a single bout of aerobic exercise is delayed until after the first h postexercise. The PEH is most pronounced for brachial and central SBP and MAP. The magnitude of the PEH is at least as great as that observed in non-obese subjects, and may last for a longer duration.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Arizona State University Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CJ performed the experiments. CJ and SA performed the statistical analyses. CJ and GG wrote the initial draft of the manuscript. All authors contributed to conception and design of the study, critically revised the manuscript, and approved the final version of the manuscript.

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Evaluating the Methodological Quality of Postexercise Hypotension Aerobic Exercise Interventions

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Background: Postexercise hypotension (PEH) is the immediate reduction in blood pressure (BP) of 5–8 mmHg that occurs after a single bout of aerobic exercise among adults with hypertension. Across PEH studies, there are variations in the level of rigor of the study designs and methods that limit the conclusions that can be made about PEH.

Objective: To develop and then apply a methodological study quality evaluation checklist to aerobic exercise PEH studies to provide methodological guidance.

Methods: We developed a PEH checklist (PEH$\surd$list) based upon contemporary methodological study quality standards. The PEH$\surd$list contains 38 items divided into three categories: sample (n = 10 items), study (n = 23 items), and intervention characteristics (n = 5 items). We then systematically searched six databases to January 2019 to identify and then evaluate studies that: (1) enrolled adults ≥18 years with hypertension and without other chronic diseases or conditions; (2) included a bout of aerobic exercise and a non-exercise control session; and (3) were published in English.

Results: Of 17,149 potential studies, 64 qualified. Participants (N = 1,489) were middle-aged (38.6 ± 15.6 year), overweight (26.1 ± 2.5 kg/m^2) mostly men (64.4%) with elevated BP (systolic BP 129.5 ± 15.2/diastolic BP 81.0 ± 10.1 mmHg). Overall, the qualifying studies satisfactorily reported 53.9 ± 13.3% (24.2–82.8%) of the relevant items on the PEH$\surd$list. Of note, only 20.3% of the studies disclosed BP was measured following professional guidelines, 18.8% reported BP was taken by the same assessor pre- and post-intervention, and 35.5% stated participants abstained from caffeine, alcohol, and physical activity prior to testing. Half (51.5%) indicated they statistically controlled for pre-exercise/baseline BP. Meanwhile, 100% of the studies reported the setting in which the BP measurements were taken, time from the end of the exercise to the start of the BP measurements, and if relevant, the length of the ambulatory BP monitoring period.

Conclusion: Overall, the PEH$\surd$list items were not well satisfied; especially items with potential confounding effects on PEH. We contend the PEH$\surd$list provides guidance to investigators on the important methodological study considerations in PEH aerobic exercise studies that should be attended to in the future.

Systematic Review Registration: [https://www.crd.york.ac.uk/PROSPERO/], identifier [#CRD42020221996].

Keywords: blood pressure, cardiovascular disease, hypertension, physical activity, systematic review

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INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in the United States and the world, accounting for approximately one in three deaths annually (Virani et al., 2021). Hypertension is the most common, costly, and preventable CVD risk factor affecting nearly 50% of adults in the United States. The total United States health care expenditures attributed to hypertension in 2016 were $79 billion dollars (Virani et al., 2021) and are projected to be $153.7 billion dollars in 2035 (Nelson et al., 2016) underscoring the public health burden hypertension places on our society.

Professional organizations throughout the world recommend exercise as first-line lifestyle therapy to lower blood pressure (BP; Pescatello et al., 2015a; Whelton et al., 2018). *Postexercise hypotension* (PEH) is the immediate reduction in BP of 5–8 mmHg that occurs after a single bout of aerobic exercise and persists for up to 24 h. PEH is clinically important because: (1) PEH occurs immediately (Fitzgerald, 1981; Pescatello et al., 1991; Kenney and Seals, 1993); (2) PEH reduces BP throughout the day when BP is typically at its highest levels (Pescatello et al., 2004); (3) an individual does not have to be physically fit to experience PEH (Pescatello et al., 2003, 2007, 2017; Ash et al., 2017; Zaleski et al., 2019); and (4) PEH can be used as a behavioral self-regulation strategy to increase exercise adherence (Zaleski et al., 2019). Also, there is evidence that PEH is correlated with the BP response to the exercise training effect (Pescatello et al., 2015a,b; Wegmann et al., 2018).

Within the PEH literature, there is a wide range of variations in the study designs. Some of the variations include: (1) PEH studies may or may not include a control comparison (de Brito et al., 2019); (2) PEH studies may or may not disclose baseline/pre-exercise BP levels (de Brito et al., 2019); (3) PEH studies include different intensities, modalities, and durations of exercise (Pescatello et al., 2015a; US Department of Health and Human Services, 2018); (4) PEH studies involve samples with an admixture of BP status, ranging from normal to stage 2 hypertension (Chobanian et al., 2003; Pescatello et al., 2015a); and (5) BP monitoring occurs in different settings, notably in the laboratory or under ambulatory conditions (Pescatello et al., 2015a; de Brito et al., 2019). Due to the variance in the exercise protocols between studies, it is important for studies to clearly report the intensity, time, and type of the exercise intervention so that the exercise dose that elicits PEH can be more clearly defined (MacDonald, 2002; Pescatello et al., 2015a; de Brito et al., 2019; Fecchio et al., 2020). For example, studies including participants with normal BP will underestimate the magnitude of PEH, as consistent with the law of initial values, those with the highest resting BP will experience the greatest BP reductions resulting from exercise (Wilder, 1965; Eicher et al., 2010; Pescatello et al., 2019; Hanssen et al., 2021). As a result, the 2018 Physical Activity Guidelines Advisory Committee called for additional well-controlled studies to better understand PEH (Pescatello et al., 2015a; US Department of Health and Human Services, 2018).

To the best of our knowledge, there is no existing easy-to-use checklist or scale that researchers can follow when designing, implementing, or reporting PEH studies. Therefore, we have developed a 38-item evaluation instrument named, the *Evaluation Tool for Studies Examining Postexercise Hypotension* or the PEH$\surd$list. We then performed a high-quality systematic review to evaluate studies examining the BP response to acute aerobic exercise. Based on our findings, our intent was also to provide methodological guidance to investigators studying PEH.

METHODS

Development of the PEH$\surd$list and Selection of Core Items

We developed an evaluation instrument named, *Evaluation Tool for Studies Examining Postexercise Hypotension* (the PEH$\surd$list), consisting of three categories: sample, study, and intervention characteristics. See **Supplementary Material A** for a complete copy of the PEH$\surd$list. We identified the items on the PEH$\surd$list based upon our extensive experience conducting PEH studies (Downs and Black, 1998; Higgins et al., 2011; Ash et al., 2013; Johnson et al., 2014; Hacke et al., 2018; de Brito et al., 2019). We also consulted articles regarding general methodological study quality standards for randomized controlled trials that included the Cochrane tool for assessing risk of bias (Higgins et al., 2011) and the Downs and Black checklist for methodological quality (Downs and Black, 1998). We included the specifics of the intervention characteristics such as reporting the frequency, intensity, time, and type of the exercise intervention (Johnson et al., 2014). Last, we also included, methods papers commenting on unique aspects of PEH studies such as de Brito et al. (2019), commented on the different statistical approaches for calculating PEH (Ash et al., 2013; Hacke et al., 2018).

The PEH$\surd$list consists of three sections with a total of 38 items: (1) sample characteristics (10 items); (2) study characteristics (23 items); and (3) intervention characteristics (5 items). The total number of relevant items evaluated in the PEH$\surd$list for a study was dependent on the method used for measuring BP (i.e., resting BP, ambulatory BP, or both). Accordingly, a total of 38 PEH$\surd$list items pertained to a study if both resting BP and ambulatory BP measurements were reported, 29 PEH$\surd$list items pertained to a study if only resting BP was reported, and 33 PEH$\surd$list items pertained to a study if only ambulatory BP was reported. In addition, we have selected 13 core items that are shaded in gray in **Tables 1–3** that we contend are fundamental considerations in designing, implementing, and reporting findings from PEH studies to ensure transparent replication of the methods and trustworthiness of the findings (Guadagnoli and Velicer, 1988; Downs and Black, 1998; Whelton et al., 2018; Flack and Adekola, 2020).

Literature Search and Study Screening

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Higgins et al., 2011). The protocol was registered at PROSPERO (#CRD42020221996). Qualifying articles were retrieved from electronic databases (PubMed, Scopus, Sport Discuss, CINAHL, Cochrane, and Web of Science) from inception until January 2019, with key words related to

TABLE 1 | PEH$\surd$list part one participant characteristics.

Items	*k*	Reporting rates	
1. Age (year)	61	95.3%	38.6 ± 15.7
2. Ethnicity/race	8	12.5%	–
3. Gender/sex	60	93.8%	Male (*n* = 960, 66.9%) Female (*n* = 476, 33.1%)
4. BP classification scheme used	36	56.3%	
4a. Followed professional guidelines	11	30.6%	American College of Sports Medicine (*k* = 1) Brazilian Guidelines for Hypertension (*k* = 2) World Health Organization (*k* = 2) American Heart Association (*k* = 3) 7th Joint National Committee (*k* = 3)
Values at Baseline			
5. BP (mmHg)	41	64.1%	129.5 ± 15.2/81.0 ± 10.1
6. Physical activity level	45	70.3%	Active (46.7%, *k* = 21) Inactive/Sedentary (48.9%, *k* = 22) Mixture Active and Inactive (4.4%, *k* = 2)
7. Cardiorespiratory fitness level (mL/kg.min^{-1})	37	57.8%	35.3 ± 9.9
8. Body mass index (kg/m^2)	57	89.1%	26.1 ± 2.5
9. Waist circumference (cm)	10	15.6%	86.7 ± 27.9
10. Medication use	53	82.8%	
10a. Reported the type and/or dosage of medication*	39	75.0%	–
10b. Reported the length of the washout or run-in period* (weeks)	11	21.2%	1–6

BP, Blood Pressure. Items shaded in gray are the core items.
**k values and percentage is based on the main question.*

TABLE 2 | PEH$\surd$list part two study characteristics.

Items	*k*	Reporting %	
11. Performed sample size estimation analysis based on BP as the primary outcome	16	25.0%	–
12. The allocation sequence	61	95.3%	Randomized
13a. Disclosed the procedure used*	5	7.8%	Table with random number (*k* = 1) Used Randomizer.org (*k* = 4)
13. The investigator who performed the BP measurements	5	7.8%	i.e., trained investigator
14. The same investigator performed all BP measurements	12	18.8%	–
15. The model of the BP device	62	96.9%	Ambulatory (*k* = 25, 40.3%), e.g., Accutracker II Automated (*k* = 23, 37.1%), e.g., Microlife Baroreflex Responses (*k* = 1, 1.6%) Finapres (*k* = 5, 8.1%), e.g., Ohmeda Finapres Manuel (*k* = 8, 12.9%), e.g., Mercury Sphygmomanometer
15a. The same BP device used through the study for a participant*	4	6.6%	–
16. Participant abstained from caffeine prior to intervention	40	62.5%	–
16a. Hours participant abstained from caffeine*	29	72.5%	15.6 ± 11.8
17. Participant abstained from alcohol prior to intervention	27	42.2%	–
17a. Hours participant abstained from alcohol*	20	74.1%	21.4 ± 21.2
18. Participant abstained form physical activity prior to intervention	33	51.6%	–
18a. Hours participant abstained form physical activity*	31	93.9%	28.5 ± 12.8
Was The BP Response to Exercise Controlled for By Pre-Exercise BP			
19a. Reported Average = (Average BP post-exercise) minus (Average BP post-control) with baseline/pre-exercise BP as a covariate	10	15.6%	–
19b. Reported Change from baseline/pre-exercise BP = (Average BP post- minus pre-exercise) minus (Average BP post- minus pre-control) with or without baseline/pre-exercise BP as a covariate	23	35.9%	–
Resting Blood Pressure Measurement Protocol	41		
20. Location/environment	41	100%	Aquatic Center (*k* = 1) Lab and Workplace (*k* = 2) Lab and Outdoors (*k* = 1) Lab (*k* = 37)

(Continued)

aerobic exercise and BP. Studies qualified if they: (1) were peer-reviewed and published in English; (2) involved healthy adults ≥18 years; (3) included an acute bout of aerobic exercise; and (4) included a non-exercise control session to control for the circadian variation in BP (de Brito et al., 2019). The potentially relevant studies were screened by two trained coders (CD, YW); first by title and abstract, and then by full text. See **Figure 1** for the flow diagram and **Supplementary Material B** for references of included PEH intervention studies. All disagreements were resolved through discussion by two independent reviewers (CD, YW). When an agreement could not be reached, a third party was consulted (LSP).

Data Extraction and Study Evaluation

Data were extracted using a standardized coding form and coder manual we adapted for PEH studies (Johnson et al., 2014). Coders extracted and entered information regarding the study (e.g., publication year, number of participants, and location), participant (e.g., age, gender, and body mass index), intervention (e.g., exercise intensity, exercise type, and time of day when sessions began) characteristics, and methodological study quality. The risk of bias was assessed in accordance with the Revised Cochrane Risk-of-Bias Tool for Randomized Trials (Higgins et al., 2011). The five domains evaluated for

TABLE 2 | (Continued)

Items	*k*	Reporting %	
21. Followed professional guidelines during BP measurements	7	17.1%	5th Brazilian Guidelines for Hypertension (*k* = 2) 7th Joint National Committee (*k* = 2) American Heart Associations (*k* = 1) Brazilian Society of Cardiology (*k* = 1) International Protocol of the European Society of Hypertension (*k* = 1)
22. Participant's position	40	97.6%	Seated (*k* = 25) Supine (*k* = 14) Semi recumbent (*k* = 1)
23. Time Lapse from the end of exercise and start of the BP measurements (minutes)	41	100%	12.6 ± 11.0 (2–45)
24. Total time of the BP monitoring (minutes)	38	92.7%	142.1 ± 247.3 (5–1,440)
Ambulatory Blood Pressure Measurement Protocol	27		
25. Followed professional guidelines during BP measurements	6	22.2%	American Heart Association (*k* = 2) British Hypertension Society (*k* = 1) European Society of Hypertension (*k* = 1) 5th Brazilian Guidelines for Hypertension (*k* = 1) Brazilian Guidelines for Ambulatory BP Monitoring (*k* = 1)
26. Performed a calibration check	9	33.3%	Calibrated against mercury sphygmomanometer (*k* = 9)
27. Including participant familiarization to wearing the ambulatory BP monitor	6	22.2%	–
28. Participants were given instruction while wearing the BP monitor	22	81.5%	Keep similar routine/No physical activity (*k* = 5) Instructed to keep arm still during measurements (*k* = 17) Instructed to keep an activity log (*k* = 11)
29. Time-lapse from the end of exercise and start of BP measurements (minutes)	24	88.9%	27.1 ± 17.8 (2–100)
30. Location/environment	27	100%	Free-Living Conditions (*k* = 24) Lab and Free-Living Conditions (*k* = 2) Lab (*k* = 1)
31. Disclosed when ABP monitor was attached during the day	7	25.9%	–
32. Total time of the BP monitoring (minutes)	27	100%	1,206 ± 366 (120–1,440)
33. Specified acceptable level of missing data for ambulatory BP analysis	17	63.0%	79.40% ± 14.2 (25–95.6%)

BP, Blood Pressure. Items shaded in gray are the core items.
**k values and percentage is based on the main question.*

TABLE 3 | PEH$_\surd$/list part three intervention characteristics.

Items	*k*	Reporting %	
34. The time of day the exercise and control sessions began	34	53.1%	Morning 7:00 am–12:00 pm (*k* = 27) Afternoon 12:00 pm–5:00 pm (*k* = 2) Evening 5:00 pm–7:00 pm (*k* = 3) Both morning and evening times (*k* = 2)
34a. The start of exercise and control sessions were conducted within 3–4 h of one another*	37	97.4%	
35. The location of exercise	50	78.1%	Workplace (*k* = 1, 2.0%) Thermal Bath (*k* = 1, 2.0%) Laboratory and Outdoors (*k* = 1, 2.0%) Chamber (*k* = 1, 2.0%) Aquatic (*k* = 2, 4.0%) Laboratory (*k* = 44, 88%)
36. The temperature that participants exercised in	25	39.1%	15–36 Celsius
37. The time, intensity, and type of the exercise intervention[a]	58	90.6%	*Time* 41 ± 22.3 min *Intensity* VO_2peak 56 ± 0.16% (*k* = 37, 37.4%) VO_2max 61 ± 0.09% (*k* = 20, 20.2%) ml/kg.min 22.815 ± 10.13 (*k* = 10, 10.1%) Heart Rate Max 74.83 ± 0.12% (*k* = 7, 7.1%) Ventilatory Threshold 80% (*k* = 4, 4.0%) Heart Rate Peak 75 ± 0.17% (*k* = 4, 4.0%) Heart Rate Max Age 59 ± 0.02% (*k* = 3, 3.0%) Anaerobic Threshold 100 ± 0.21% (*k* = 2, 2.0%) Rate of Perceived Exertion 15.25 ± 3.18 (*k* = 2, 2.0%) *Type* Cycle Ergometer (*k* = 61, 61.6%) Treadmill (*k* = 32, 32.3%) Aquatic (*k* = 2, 2.0%) Other (*k* = 4, 4.0%)
38. The content of the sham control session[b]	49	76.6%	*Time* 48.3 ± 58.6 min *Position* Seated Rest (*k* = 55, 93.2%) Option to Stand or Sit (*k* = 2, 3.3%) Standing (*k* = 1, 1.6%) Supine Rest (*k* = 3, 4.9%)

**k values are percentage is based on the main question.*
[a] The percentage is based on the 99 total exercise arms.
[b] The percentage is based on the 61 total control arms.
VO_2peak, peak oxygen uptake; VO_2max, maximum oxygen consumption. Items shaded in gray are the core items.

risk of bias were: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result in each included study. Studies were rated as low, some concern, or high risk of bias. Methodological study quality was assessed using an augmented version of Downs and Black Checklist

(Downs and Black, 1998). Methodological study quality was reported as the percentage of items satisfied out of a possible 29 items. The overall methodological quality was classified as: low (<50%), moderate (50–79%), and high (≥80%). We conducted a preliminary correlation analysis which showed the PEH✓list study score is correlated with the Downs and Black Checklist score. Therefore, we used the cutoffs in Downs and Black Checklist to define the PEH✓list study scores as low (<50%), moderate (50–79%), and high (≥80%). All disagreements were resolved through discussion by two independent reviewers (CD, YW). When an agreement could not be reached a third party was consulted (LSP).

Statistical Analysis

Descriptive statistics were calculated for the baseline characteristics of the sample in the qualifying studies. For each of the PEH✓list items, the reporting rate was calculated as (the number of studies satisfactorily reporting this item/the number of studies to which this item was deemed relevant) × 100%. For each of the studies included, the PEH✓list study score was calculated as (the number of items reported/by the number of relevant items) × 100%. We also compared the PEH✓list study scores against a validated study quality scale score, the Downs and Black Checklist (Pescatello et al., 2019), by performing a Pearson Correlation test. All analyses were performed using IBM SPSS Statistics for Windows, Version 26.0.

RESULTS

The initial search resulted in 27,921 potentially qualifying studies. An additional 34 records were identified through manual searches. After triaging, 64 studies qualified. See **Figure 1** for the PRISMA flow diagram. The average reporting rate for PEH✓list items was 61.8 ± 31.7%.

PEH✓list Part 1: Sample Characteristics

The reporting rate for each of the items in the PEH✓list Part 1 is listed in **Table 1**. The sample (n = 1,511) consisted of young to middle-aged (38.6 ± 15.7 years) healthy adults who on average, were overweight (body mass index 26.1 ± 2.5 kg/m^2) and had no chronic conditions other than hypertension (129.5 ± 15.2/81.0 ± 10.1 mmHg). Over half of the participants were men (66.9%, n = 960), and nearly half were physically inactive (48.9%, k = 22). In addition, only 12.5% of the studies (k = 8) reported the ethnicity/race of the participants. A majority (82.8%, k = 53) of the studies controlled for the potential influence of medications that could impact the BP response to exercise. Of these studies, less than half excluded participants if they were taking various medications. Among the studies excluded participants due to medication use, more than half (k = 12, 46.2%) excluded participants if they were taking antihypertensive medications; a few (k = 4, 15.4%) excluded participants if they were taking antihypertensive medication or oral contraceptive (k = 1) and lipid medication (k = 3); one study (0.04%) excluded participants who were taking any medication; and the rest (k = 9, 34.6%) excluded participants who were taking medications that can alter lipid profile (k = 4), metabolism (k = 2), heart rate (k = 2), and the renin–angiotensin system (k = 1). For the remainder of the 53 studies, participants: (1) remained on the same medication throughout the study (11%, k = 7); (2) were not taking any medication (12.5%, k = 8); or (3) stopped taking medication by going through a washout period of 1–6 weeks before the study started (17.5%, k = 11). Of note, only 45.3% (k = 29) of the studies identified their participants had hypertension, however, only 30.6% (k = 11) of the studies reported following professional guidelines to classify the subjects as having hypertension.

PEH✓ Part 2: Study Characteristics

The reporting rate for each of the items in the PEH✓list Part 2 is listed in **Table 2**. The included studies were mostly randomized controlled trials (95.3%, k = 61) published between 1987 and 2018 (2006 ± 8) and conducted in North America (35.9%, k = 23), South America (32.8%, k = 21), Europe (26.6%, k = 17), Asia (3.1%, k = 2), and Australia (1.6%, k = 1). Studies included 6–109 participants (24 ± 20), and more than half contained multiple exercise arms (64%, k = 41), while 15.6% (k = 10) contained multiple control arms. Of note, only 25% (k = 16) of the studies reported they performed a sample size estimation based on BP as the primary outcome, and only six studies (9.8%) reported the procedure used for randomization.

When calculating PEH more than half (51.6%, k = 33) of the studies reported controlling for baseline/pre-exercise BP by including baseline/pre-exercise BP as a covariate in the statistical models comparing: (1) average BP post-exercise versus average BP post-control (15.6%, k = 10); or (2) the change of BP due to exercise (i.e., post-exercise BP – pre-exercise BP) versus the change of BP due to control (i.e., post-control BP – pre-control BP) (35.9%, k = 23).

Regarding the measurement of BP, 64.1% of the studies (k = 41) measured resting BP, 42.2% measured ambulatory BP (k = 27), or 6.3% measured both (k = 4). Among the 41 studies measuring resting BP, most were measured in the seated position (62.5%, k = 25) in the laboratory (90.2%, k = 37) starting 12.6 ± 11 min after the end of the exercise session and continued for 142.1 ± 247.3 min thereafter. Of the 27 studies assessing ambulatory BP, most occurred under free-living conditions (88.9%, k = 24) starting 27.1 ± 17.8 min after the end of the exercise sessions and continued for 20.1 ± 6.1 h. Of note, most studies (96.9%, k = 62) reported the model of the BP device used to measure BP. However, studies rarely disclosed they followed protocols recommended by professional guidelines when measuring resting BP (only 17.1% did, k = 7) or ambulatory BP (only 22.2% did, k = 6). The studies assessing ambulatory BP rarely (only 22.2% did, k = 6) disclosed whether a familiarization session was performed prior to the start of experiments, or a calibration check was performed (only 33.3% did, k = 9). In addition, only 31.3% (k = 20) of the 64 studies assessing resting and/or ambulatory BP asked participants to abstain from physical activity, alcohol, and caffeine prior to experiments.

PEH✓ Part 3: Intervention Characteristics

The reporting rate for each of the items in the PEH✓list Part 3 is listed in **Table 3**. Over half of the studies (53.1%, k = 34) reported

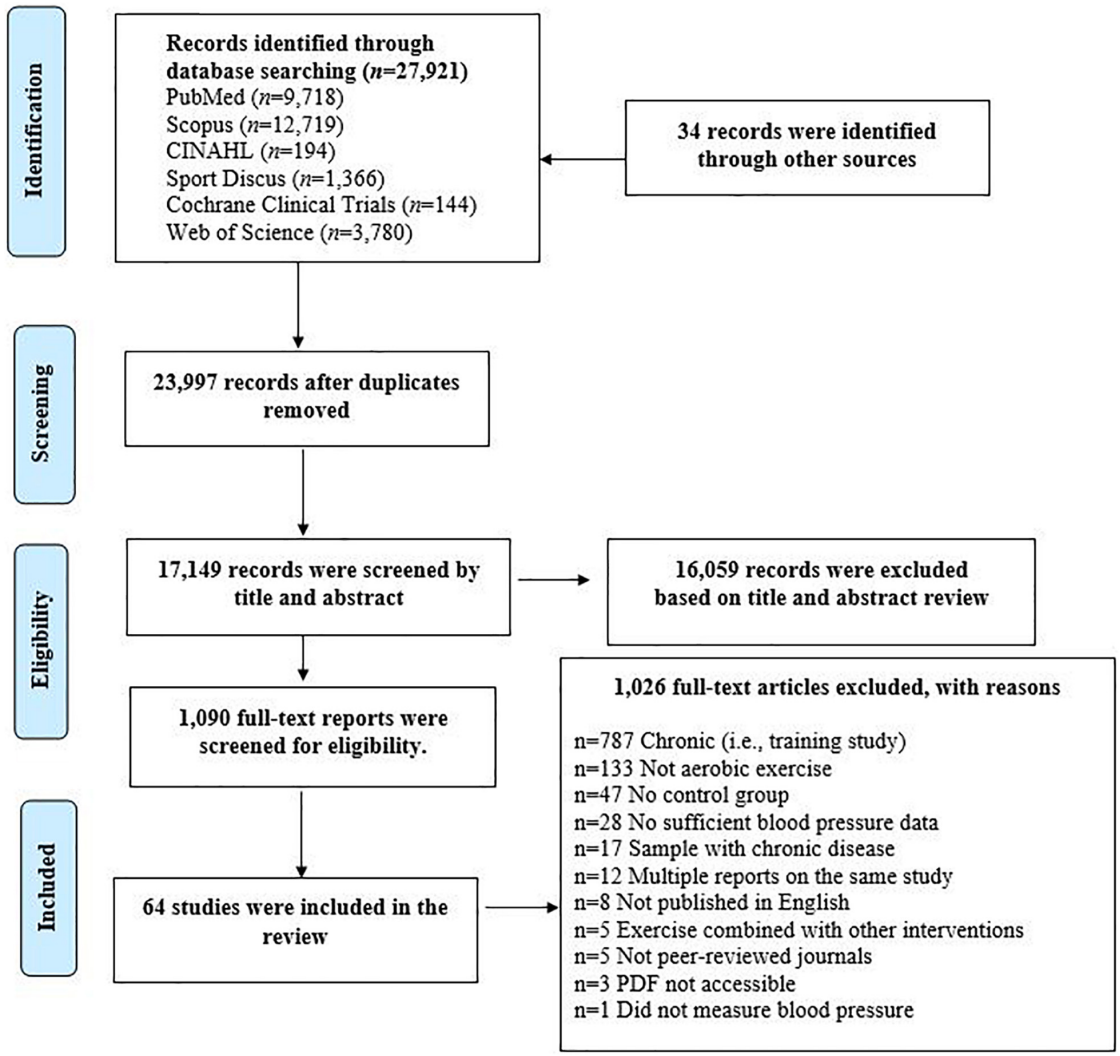

FIGURE 1 | Preferred reporting items for systematic reviews and meta-analyses flow chart detailing the systematic search of potential intervention studies.

the time of day of the exercise and control sessions, with most of the sessions occurring in the morning between 7:00 am and 12:00 pm (42.2%, k = 27). There were 99 exercise arms in the included studies. The majority of exercises were performed in a laboratory setting (k = 44, 88.0%), two studies (4.0%) performed exercises in aquatic setting, and others were in workplace (k = 1, 2.0%), thermal bath (k = 1, 2.0%), and a combination of laboratory and outdoors (k = 1, 2.0%). There were 25 studies (39.1%) that reported the temperature that the participants exercised in with the lowest temperature range being 15–22°C in Casonatto et al. (2011), and the highest temperature range being ≤36.0°C in Matzer et al. (2017). The exercise sessions on average lasted 41.0 ± 22.3 min at moderate (82.8%, k = 82) and vigorous (17.2%, k = 17) intensity measured by various methods such as peak oxygen uptake, maximal oxygen uptake, and heart rate maximum (see **Table 3** for a complete list of intensity methods). Most of the studies were performed on a cycle ergometer (61.6%, k = 61) or treadmill (32.3%, k = 32). Among the 61 control arms, control sessions on average lasted 48.3 ± 58.6 min with seated rest being the most common (93.2%, k = 55) (see more details in **Table 3**).

Evaluations of Studies Included

For the determination of the overall risk of bias using the Revised Cochrane Risk-of-Bias Tool for Randomized Trial (Higgins et al., 2011), eight studies (12.9%) were of low risk, 39 studies (62.9%) had some concerns, and 17 studies (24.2%) were of high risk. In the *Domain of Bias Arising from the Randomization Process*, 17.2% (k = 11) of the studies were of low risk, 75% (k = 48) had some concerns, and 7.8% (k = 5) were of high risk. In the *Domain of Bias Arising from the Deviations from Intended Interventions,* 64.1% (k = 41) of the studies were of low risk, 21.9% (k = 14) had some scored some concern, and 14.1% (k = 9) were of high risk. In the *Domain of Bias Due to Missing Outcome Data*, 93.8% (k = 60) were of low risk, 6.2% of the studies (k = 4) had some concerns, and no studies were of high risk. In the *Domain of Bias in Measurement of The Outcome*,

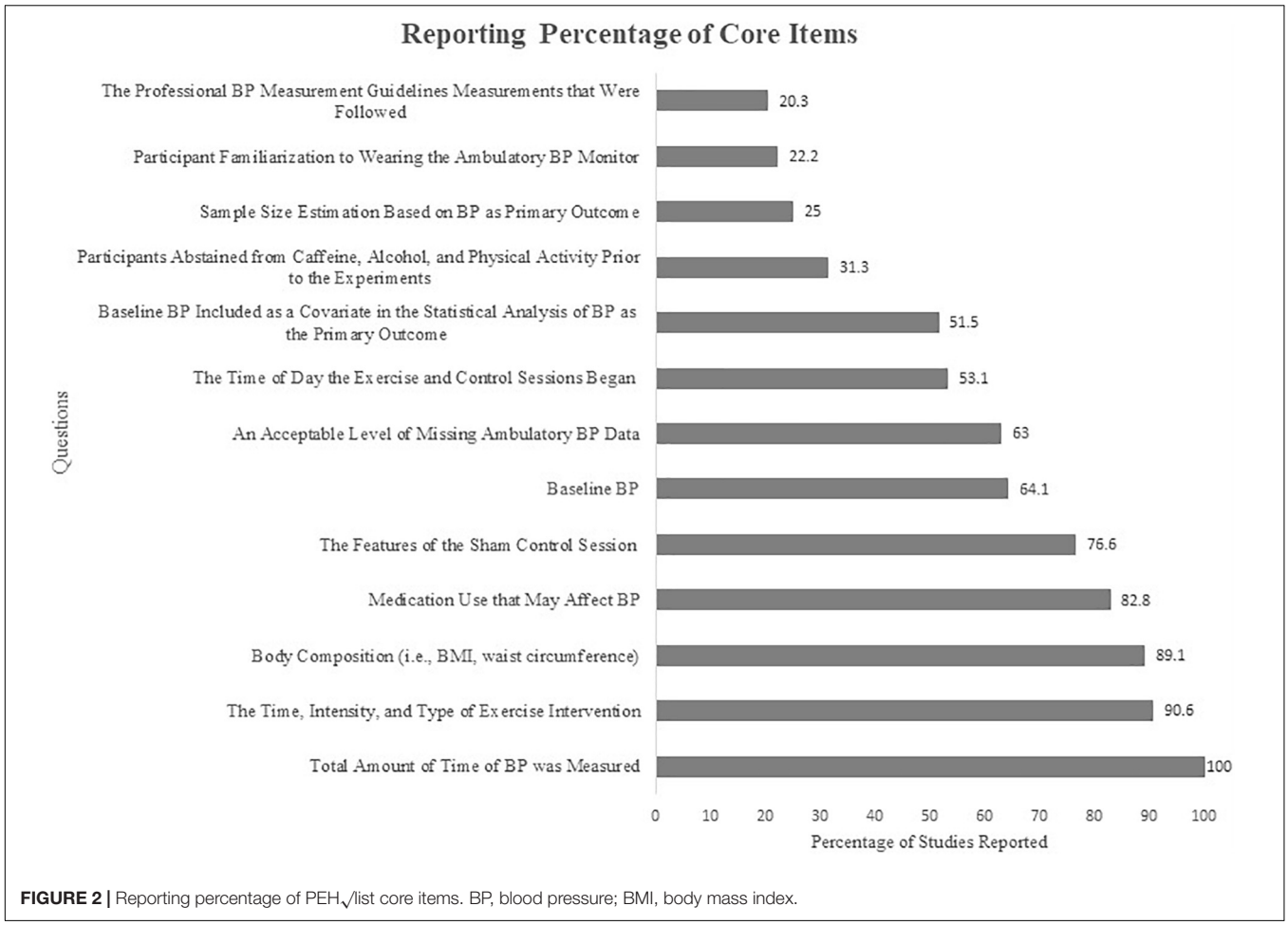

FIGURE 2 | Reporting percentage of PEH√list core items. BP, blood pressure; BMI, body mass index.

85.5% of the studies (k = 55) were of low risk, 14.5% (k = 9) had some concerns, and no studies were of high risk. In the *Domain of Bias in Selection of The Reported Result*, 96.8% of the studies (k = 62) were of low risk, 3.2% (k = 2) of the studies had some concerns, and no studies were high risk. Please see **Supplementary Material C** for the Risk of Bias scores of qualifying studies.

On the Downs and Black checklist, studies scored averaged 55.6 ± 10 (37.9–79.3%). Of these, 31.3% (k = 20) exhibited low methodological quality, most of the studies (68.8%, k = 44) exhibited moderate methodological quality (k = 44), and no study scored high methodological quality. Meanwhile the average PEH√list study score was 53.9 ± 13.3%. Among the 64 studies, two reached a high checklist study score (81.0 ± 0.02%), 36 reached a moderate checklist study score (62.1 ± 0.08%), and 26 had low study scores (41.2 ± 0.06%). Please see **Supplementary Material C** for the studies respective PEH√list study score. Based on the Pearson correlation analysis, there was a positive relationship between the Downs and Black checklist score and the PEH√list study score with a Pearson correlation coefficient of 0.325 (p = 0.009). Please see **Supplementary Material C** for the Downs and Black scores of qualifying studies.

DISCUSSION

The clinical utility of PEH as an antihypertensive lifestyle therapy needs to be better understood partially due to the variations in PEH study designs (MacDonald, 2002; Pescatello et al., 2015a; US Department of Health and Human Services, 2018; de Brito et al., 2019; Fecchio et al., 2020). We developed a 38-item evaluation instrument, the PEH√list, based upon our laboratory (Downs and Black, 1998; Higgins et al., 2011; Ash et al., 2013; Johnson et al., 2014; Hacke et al., 2018; de Brito et al., 2019) and others' (Hacke et al., 2018; de Brito et al., 2019) experience of performing PEH studies adhering to the contemporary methodological study quality standards of the Cochrane risk of bias tool (Higgins et al., 2011) and Downs and Black checklist for methodological quality (Downs and Black, 1998). We then performed a high-quality systematic review adhering to contemporary standards (Moher et al., 2009) to evaluate qualifying PEH studies with the PEH√list that examined the BP response to acute aerobic exercise.

The average PEH√list study score was 53.94 ± 13.3%. Two studies reached a high checklist study score (81.0 ± 0.02%), 36 reached a moderate checklist study score (62.1 ± 0.08%), and 26 reached a low checklist study scored (41.2 ± 0.06%). Of the three sections of PEH√list, Part 3-Intervention Characteristics

(**Table 3**) had the highest reporting rate of 67.5%, followed by Part 1-Sample Characteristics at 63.6% (**Table 1**), and Part 2-Study Characteristics at 51.1%. Therefore, Part 2-Study Characteristics (e.g., following professional protocols for the measurement of BP, participant instruction abstaining from caffeine, alcohol, and physical activity) had the most room for improvement.

The average reporting rates of all PEH$\surd$list items were 61.8 ± 31.7%. However, we acknowledge for various reasons it may not be feasible to integrate all the items on the PEH$\surd$list into the study protocol. For example, having the same investigator take all BP measurements could be challenging for studies with larger sample sizes. If the accessors are well-trained and follow the same protocol the potential bias for methodological bias would be reduced. Therefore, after careful deliberations, we have identified 13 core items that are fundamental and practical to be controlled for within studies. The PEH$\surd$list core items had a reporting rate from 20.3 to 100% with an average rate of 59.2 + 27.9%. These reporting rates are present in **Figure 2**. The five core items (n = 13) that were reported ∼<50% of the time relevant to a given study were: (1) 20% followed standard protocols for measuring BP, such as the American College of Cardiology and American Heart Association guidelines, to ensure the accuracy of BP measurements (Flack and Adekola, 2020); (2) 22% provided an ambulatory BP familiarization session which should be integrated to avoid an alerting reaction to initially wearing the monitor (Thomas et al., 2006; Ash et al., 2013); (3) 25% reported performing a sample size estimation based on the primary BP outcome suggesting many of the qualifying studies may have been underpowered (Guadagnoli and Velicer, 1988); (4) 31% of the studies reported having their participants abstain from caffeine, alcohol, and physical activity that are common PEH confounders (Downs and Black, 1998; Whelton et al., 2018); and (5) 52% of the studies reported they controlled for baseline/pre-exercise BP in their statistical analyses (Eicher et al., 2010). Clearly, the lack of disclosure of these five PEH$\surd$list core items and the others shown in **Figure 2** indicate a need for improvement in the rigor of PEH studies.

There are some limitations to the current study. First, our review only involved aerobic exercise PEH studies (Johnson et al., 2014; Pescatello et al., 2015a). However, the items within PEH$\surd$list are not applicable to only aerobic exercise but to other types of exercise as well. Second, our evaluation of PEH aerobic exercise studies was based on what was reported and may not completely reflect the rigor of the study protocols due to the journal word limitations and the feasibility of implementing certain procedures due to funding limitations, among other reasons. We acknowledge the PEH$\surd$list has not been validated; however, the PEH$\surd$list and Downs and Black checklist scores had a positive correlation coefficient of 0.325 (p = 0.009), indicating the PEH$\surd$list can be used as a methodological study quality evaluation tool specifically designed for PEH studies.

Despite these limitations, our study has several strengths. To the best of our knowledge, our study is the first to systematically review the aerobic exercise PEH study methodology. We systematically searched six different databases following PRISMA guidelines. The development of the PEH$\surd$list is based on our (Pescatello et al., 1991, 2004, 2007, 2016; Keese et al., 2011; Ash et al., 2013; Headley et al., 2017; Cordeiro et al., 2018; Cilhoroz et al., 2019; Zaleski et al., 2019; Babcock et al., 2020; Farinatti et al., 2021) and others (Hacke et al., 2018; de Brito et al., 2019) long history of performing well-controlled PEH studies (Guadagnoli and Velicer, 1988; Pescatello et al., 1991, 2003, 2004, 2015a, 2017, 2019; Thomas et al., 2006; Moher et al., 2009; Casonatto et al., 2011; Johnson et al., 2014; Matzer et al., 2017) as well as the methodological study quality standards of the Cochrane risk of bias tool (Higgins et al., 2011) and Downs and Black checklist for methodological quality (Downs and Black, 1998). The PEH$\surd$list is comprehensive addressing essential study design considerations. Accordingly, investigators even with no prior experience can use our checklist as a template to design their PEH studies.

In conclusion, founded upon a high-quality, contemporary systematic review, we have stringently evaluated aerobic exercise PEH studies with the PEH$\surd$list and identified fundamental study design considerations that need improvement. Future researchers should consider using our PEH$\surd$list, or at minimum the core items, in conjunction with methodological study quality standards when designing and implementing PEH studies as well as reporting their results.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

CD participated in the design of the study, data extraction, and interpretation of details, performed the statistical analysis, and drafted and revised the manuscript critically for important intellectual content. YW participated in the design of the study, data extraction, and interpretation of details and revised the manuscript critically for important intellectual content. LP participated in the design of the study and revised the manuscript critically for important intellectual content and final approval of the version to be published. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2022.851950/full#supplementary-material

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