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REVIEW ARTICLE

Evidence for the Role of Isometric Exercise Training in Reducing Blood Pressure: Potential Mechanisms and Future Directions

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Abstract Hypertension, or the chronic elevation in resting arterial blood pressure (BP), is a significant risk factor for cardiovascular disease and estimated to affect ~1 billion adults worldwide. The goals of treatment are to lower BP through lifestyle modifications (smoking cessation, weight loss, exercise training, healthy eating and reduced sodium intake), and if not solely effective, the addition of antihypertensive medications. In particular, increased physical exercise and decreased sedentarism are important strategies in the prevention and management of hypertension. Current guidelines recommend both aerobic and dynamic resistance exercise training modalities to reduce BP. Mounting prospective evidence suggests that isometric exercise training in normotensive and hypertensive (medicated and non-medicated) cohorts of young and old participants may produce similar, if not greater, reductions in BP, with meta-analyses reporting mean reductions of between 10 and 13 mmHg systolic, and 6 and 8 mmHg diastolic. Isometric exercise training protocols typically consist of four sets of 2-min handgrip or leg contractions sustained at 20–50 % of maximal voluntary contraction, with each set separated by a rest period of 1–4 min. Training is usually completed three to five times per week for 4–10 weeks. Although the mechanisms responsible for these adaptations remain to be fully clarified, improvements in conduit and resistance vessel endothelium-dependent dilation, oxidative stress, and autonomic regulation of heart rate and BP have been reported. The clinical significance of isometric exercise training, as a time-efficient and effective training modality to reduce BP, warrants further study. This evidence-based review aims to summarize the current state of knowledge regarding the effects of isometric exercise training on resting BP.

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1 Introduction

Hypertension or the chronic elevation of resting arterial blood pressure (BP) is estimated to affect 1 billion people worldwide (approximately one in seven) and remains one of the most significant modifiable risk factors for cardiovascular disease (CVD; e.g. coronary artery disease, stroke, heart failure) [1, 2]. Hypertension is directly responsible for as many as 7 million global deaths annually [3, 4], representing a significant societal and economic burden [4, 5]. The traditional objective of clinical practice has been to achieve a resting BP target of ≤140/90 mmHg [1, 6, 7]. However, as higher than normal resting BP ((Pre-hypertension; 120–140/80–90 mmHg) also increases the risk of CVD [8–10] guidelines are proposing lower optimal BP targets to maximize reductions in morbidity and mortality,

particularly in patients with other co-morbidities such as renal disease and diabetes [1, 6, 7].

Current national and international treatment guidelines for primary and secondary prevention of hypertension universally recommend non-pharmacological lifestyle changes (smoking cessation, weight loss, exercise training, healthy eating and reduced sodium intake) as the first-line of therapy [1, 7]. These lifestyle changes are to be continued even in the case of a need to start antihypertensive pharmacologic treatment [1, 7]. Substantial evidence supports the benefits of these lifestyle modifications on reducing resting BP [11], with reduced sedentarism and increased regular physical exercise being particularly effective [1, 12]. As a result, it is recommended that individuals participate in aerobic exercise training of at least moderate intensity for ≥30 min on most (preferably all) days of the week, to reduce the risk of developing hypertension or to manage high BP [1, 7, 13]. Dynamic resistance training (i.e. weightlifting) has also been advocated, but because of a smaller body of evidence, especially in hypertensive populations, is considered to be a secondary adjunct exercise modality [1, 13–15].

These collective recommendations are reinforced by meta-analytic evidence demonstrating small, but significant, mean reductions in resting BP following aerobic exercise training (Δ 2–4/1–3 mmHg; class I, level of evidence A) [16–21], and dynamic resistance training (Δ 3–5/3–4 mmHg; class IIA, level of evidence B) [20–25]. The largest reductions in BP are observed following aerobic exercise training in participants with hypertension [Δ 6–7/5 mmHg (means)] [17, 19, 20]. To date, relatively little attention has been paid to the effects of isometric exercise training on resting BP.

Over the last 20 years, a number of randomized, controlled and uncontrolled, proof-of-concept studies have investigated a role for isometric hand and leg exercise training to reduce BP in individuals with and without hypertension. In comparison to aerobic and dynamic resistance exercise training, meta-analytic evidence suggests that isometric exercise training may produce larger mean reductions in resting BP (Δ 10–14/6–8 mmHg), although overall sample sizes remain small [20, 25–27]. In the most recent scientific statement on alternative (non-pharmacological) approaches to lowering BP by the American Heart Association, isometric exercise training is given a class IIB level of evidence C recommendation, demonstrating the emergence of this modality as a potential treatment strategy for individuals with hypertension and the need for additional investigations [21].

In this review, we aim to summarize (i) the available literature on the effects of isometric exercise training on resting BP; (ii) the current evidence for specific isometric training protocols; (iii) issues of safety; (iv) potential mechanisms that may be responsible for these training adaptations; and (v) general recommendations for future studies.

1.1 Literature Search

Studies for this review were identified in PubMed using an advanced search with the combined keywords: 'training', 'exercise', 'isometric' and 'blood pressure'. All identified articles were reviewed and excluded if they (i) were not related to the specific topic; (ii) did not involve humans; or (iii) did not perform >3 weeks of isometric exercise training.

2 Isometric Exercise and Blood Pressure (BP) Reductions Following Training

2.1 Isometric Exercise Training

An isometric or static contraction is defined as a sustained muscle contraction (i.e. increase in tension) with no change in length of the involved muscle group [28]. Although pure static contractions are observed only with in vitro models, for the purposes of this review an isometric contraction will be considered a sustained contraction with minimal change in muscle length.

The most widely studied isometric training protocols consist of four sets of 2-min handgrip or leg contractions at 30–50 % maximal voluntary contraction (MVC) or an equivalent electromyographic value, with each set separated by a timed rest period that ranges from 1 to 4 min, performed three to five times per week for 4–10 weeks [29, 31–35, 37, 38, 43, 44]. Similar protocols with shorter (45 s) [29, 36] or longer (3 min) [30] contraction lengths and reduced intensities (≤20 % MVC) [39–42] have also been studied (Tables 1, 2). In general, a systematic evaluation of isometric exercise protocols has not been completed and continued use of individual protocols appears to persist based largely on past success in eliciting training adaptations [30]. It should be appreciated from this brief description that isometric exercise training involves a markedly smaller time commitment (11–20 min/session), compared with traditional aerobic exercise training recommendations of ≥30 min/day [13].

2.2 Effects of Isometric Exercise Training on Resting BP

We identified 16 prospective trials investigating the effects of isometric exercise training on resting BP [29–44]. These studies involved both normotensive (Table 1) and pre-hypertensive and hypertensive (medicated and

Table 1 Prospective studies examining the effects of isometric exercise training on resting blood pressure in normotensive subjects

Reference (year)	Study design	Participants (*n*)	Age (years; range or mean ± SD)	Initial BP status	Exercise mode and intensity	Intervention (frequency; duration)	Major findings
Wiley et al. (1992) [29]	Cohort	Ex: 10	29–52	Normotensive	Alternating unilateral IHG[a] 4 × 45 s, 1-min rest periods, 50 % MVC	5×/week; 5 weeks	↓ in SBP 10 mmHg ↓ in DBP 9 mmHg
Ray and Carrasco (2000) [30]	Cohort controlled	Ex: 9 Sham: 7 Con: 8	19–35	Normotensive	Unilateral IHG 4 × 3 min, 5-min rest periods, 30 % MVC	4×/week; 5 weeks	↓ in DBP 5 mmHg ↓ in MAP 4 mmHg ↔ in MSNA
Howden et al. (2002) [31]	Cohort controlled	Ex: 8 Con: 8	21 ± 1	Normotensive	Bilateral arm flexion 4 × 2 min, 3-min rest periods, 30 % MVC	3×/week; 5 weeks	↓ in SBP 12 mmHg
		Ex: 10 Con: 8		Normotensive	Bilateral leg extension 4 × 2 min, 3-min rest periods, 20 % MVC	3×/week; 5 weeks	↓ in SBP 10 mmHg
McGowan et al. (2007) [35]	Cohort	Ex: 11	28 ± 14	Normotensive	Unilateral IHG 4 × 2 min, 4-min rest periods, 30 % MVC	3×/week; 8 weeks	↓ in SBP 5 mmHg ↔ BMAD or BABF
Millar et al. (2008) [37]	RCT	Ex: 25 Con: 24	66 ± 6	Normotensive	Alternating unilateral IHG[a] 4 × 2 min, 1-min rest periods, 30–40 % MVC	3×/week; 8 weeks	↓ in SBP 10 mmHg ↓ in DBP 3 mmHg
Wiles et al. (2010) [39]	RCT	Ex: 11 Con: 11	18–34	Normotensive	Bilateral leg extension 4 × 2 min, 2-min rest periods, 75 % HR_{peak} (∼10 % MVC)	3×/week; 8 weeks	↓ in SBP 4 mmHg ↓ in DBP 3 mmHg ↓ in MAP 3 mmHg
		Ex: 11		Normotensive	Bilateral leg extension 4 × 2 min, 2-min rest periods, 95 % HR_{peak} (∼20 % MVC)	3×/week; 8 weeks	↓ in SBP 5 mmHg ↓ in DBP 3 mmHg ↓ in MAP 3 mmHg
Devereux et al. (2010) [40]	Crossover	$n = 13$	21 ± 2	Normotensive	Bilateral leg extension 4 × 2 min, 2-min rest periods, 95 % HR_{peak} (∼20 % MVC)	3×/week; 4 weeks	↓ in SBP 5 mmHg ↓ in DBP 3 mmHg ↓ in MAP 3 mmHg
Badrov et al. (2013) [44]	RCT	Ex: 12 Con: 9	19–45	Normotensive	Alternating unilateral IHG[a] 4 × 2 min, 1-min rest periods, 30 % MVC	3×/week; 8 weeks	↓ in SBP 6 mmHg ↑ in RV endothelial function by 42 %
		Ex: 11		Normotensive	Alternating unilateral IHG[a] 4 × 2 min, 1-min rest periods, 30 % MVC	5×/week; 8 weeks	↓ in SBP 6 mmHg ↑ in RV endothelial function by 57 %

All blood pressure values are reported as means

BABF brachial artery blood flow, *BMAD* brachial mean artery diameter, *BP* blood pressure, *Con* control, *DBP* diastolic blood pressure, *Ex* exercise, HR_{peak} peak heart rate, *IHG* isometric handgrip, *MAP* mean arterial pressure, *MSNA* muscle sympathetic nerve activity, *MVC* maximal voluntary contraction, *n* number of subjects, *RCT* randomized controlled trial, *RV* resistance vessel, *SBP* systolic blood pressure, *SD* standard deviation, ↓ indicates reduction, ↑ indicates increase, ↔ indicates no change

[a] Changing hands with each contraction

Table 2 Prospective studies examining the effects of isometric exercise training on resting blood pressure in pre-hypertensive and hypertensive subjects

Reference (year)	Study design	Participants (*n*)	Age (years; range or mean ± SD)	Initial BP status	Exercise mode and intensity	Intervention (frequency; duration)	Major findings
Wiley et al. (1992) [29]	RCT	Ex: 8 Con: 10	20–35	Pre-hypertensive	Unilateral IHG 4 × 2 min, 3-min rest periods, 30 % MVC	3×/week; 8 weeks	↓ in SBP 13 mmHg ↓ in DBP 15 mmHg
Taylor et al. (2003) [32]	RCT	Ex: 9 Con: 8	69 ± 6	Medicated hypertensive	Alternating unilateral IHG[a] 4 × 2 min, 1-min rest periods, 30 % MVC	3×/week; 10 weeks	↓ in SBP 19 mmHg ↓ in MAP 11 mmHg
McGowan et al. (2006) [33]	Cohort	Ex: 17	67 ± 6	Medicated hypertensive	Unilateral IHG 4 × 2 min, 4-min rest periods, 30 % MVC	3×/week; 8 weeks	↑ in BA FMD by 61 % ↔ in MAP
McGowan et al. (2007) [34]	Cohort	Ex: 7	62 ± 11	Medicated hypertensive	Alternating unilateral IHG[a] 4 × 2 min, 1-min rest periods, 30 % MVC	3×/week; 8 weeks	↓ in SBP 15 mmHg
		Ex: 9	66 ± 19	Medicated hypertensive	Unilateral IHG 4 × 2 min, 4-min rest periods, 30 % MVC	3×/week; 8 weeks	↓ in SBP 9 mmHg
Peters et al. (2006) [36]	Cohort	Ex: 10	52 ± 5	Hypertensive	Alternating unilateral IHG[a] 4 × 45 s, 1-min rest periods, 50 % MVC	3×/week; 6 weeks	↓ in SBP 13 mmHg ↓ in DBP 2 mmHg
Millar et al. (2013) [38]	Cohort controlled	Ex: 13 Con: 10	66 ± 6	Medicated hypertensive	Unilateral IHG 4 × 2 min, 4-min rest periods, 30 % MVC	3×/week; 8 weeks	↓ in SBP 5 mmHg ↓ in MAP 3 mmHg
Stiller-Moldovan et al. (2012) [42]	RCT	Ex: 11 Con: 9	60 ± 9	Medicated hypertensive	Alternating unilateral IHG[a] 4 × 2 min, 1-min rest periods, 30 % MVC	3×/week; 8 weeks	↔ in resting or 24-h ambulatory BP
Baross et al. (2012) [41]	RCT	Ex: 10 Con: 10	55 ± 5	Pre-hypertensive and hypertensive	Bilateral leg extension 4 × 2 min, 2-min rest periods, 85 % HR_{peak} (~14 % MVC)	3×/week; 8 weeks	↓ in SBP 11 mmHg ↓ in MAP 5 mmHg ↓ HR
		Ex: 10		Pre-hypertensive and hypertensive	Bilateral leg extension 4 × 2 min, 2-min rest periods, 70 % HR_{peak} (~8 % MVC)	3×/week; 8 weeks	↔ in resting BP
Badrov et al. (2013) [43]	RCT	Ex: 12 Con:12	51–74	Medicated hypertensive	Alternating unilateral IHG[a] 4 × 2 min, 1-min rest periods, 30 % MVC	3×/week; 10 weeks	↓ in SBP 8 mmHg ↓ in DBP 5 mmHg ↓ in MAP 6 mmHg ↓ in PP 4 mmHg

All blood pressure values are reported as means

BA FMD brachial artery flow mediated dilation, *BP* blood pressure, *Con* control, *DBP* diastolic blood pressure, *Ex* exercise, *HR* heart rate, HR_{peak} peak heart rate, *IHG* isometric handgrip, *MAP* mean arterial pressure, *MVC* maximal voluntary contraction, *n* number of subjects, *PP* pulse pressure, *RCT* randomized controlled trial, *SBP* systolic blood pressure, *SD* standard deviation, ↓ indicates reduction, ↑ indicates increase, ↔ indicates no change

[a] Changing hands with each contraction

unmedicated) populations (Table 2), and employed either isometric handgrip or leg exercise training protocols. The results of these small-scale (<50 participants) studies are not uniform, with mean reductions in systolic and diastolic BP ranging between 0 and 19, and 0 and 15 mmHg, respectively. Unfortunately, only ~50 % of these trials employed randomized controlled trial (RCT) [29, 32, 37, 39, 41–44] or crossover [40] designs, increasing the risk of a type I error. In those studies employing a control group, only one employed an active sham-training control [30]. Furthermore, in all trials the exercisers and investigators have not been blinded, preventing the exclusion of both a placebo effect and investigator bias on outcomes. Finally, although most studies have determined BP as the average of multiple measurements taken using an automated oscillatory device after a rest period (as opposed to manual auscultatory methods [29, 32, 36]) [30, 31, 33–35, 37–44], the length of time between measurement and the last exercise session does not appear to be standardized, with the majority describing that measurements were taken between 2 and 7 days following training [29, 31, 33, 35, 37–40, 42–44].

No prospective studies directly compared the effects of isometric exercise training on BP against dynamic aerobic or resistance exercise training adaptations or antihypertensive medications. However, a number of studies report reductions in resting BP within participants already engaged in regular dynamic aerobic and resistance training [32, 34, 35, 37, 39, 40]. These observations may suggest an independent mechanism of action and the potential for additional incremental benefits of combining exercise modalities. The prospective observations of reduced resting BP have been confirmed in four meta-analyses of either RCT data [21, 25, 26] or RCT and cohort-controlled data [27]. However, each of these analyses included ≤5 studies and <125 total participants (exercisers plus controls) (Table 3), and did not comment on issues of exercise safety, isometric exercise protocols, or potential mechanisms responsible for the reductions in resting BP. Overall, these results highlight the need for future investigations to corroborate reductions in BP in a large-scale RCT with an intention-to-treat analysis against established hypertensive treatments.

Similar to aerobic exercise training, the largest isometric training reductions in resting BP have been demonstrated in hypertensive patients [29, 32, 36]. A strong correlation has been reported between the magnitude of change following isometric exercise training and baseline BP, such that the reductions are greatest in those with higher pre-training BP [41, 44, 45]. Even so, significant reductions in BP have been found in young normotensive females, using an RCT design, suggesting a robust stimulus for adaptation [44]. An important limitation given the small individual study sample sizes and widespread use of non-randomized designs, is the potential that the observed findings represent a 'regression to the mean'. While this possibility should not be discounted, the risk appears mitigated by the increasing RCT evidence and the observation that the majority of studies report run-in or familiarization procedures [29, 30, 34–44] and multiple measurements of BP at each time point [29–32, 34–44].

An important consideration not detailed when reporting simple mean group reductions, a practice common in the literature to date, is the overall inter-individual response rates. Thus, while the available evidence appears to demonstrate a high consistency in producing post-training reductions in mean group resting BP, it should be noted that a high inter-individual variability does exist, whereby

Table 3 Meta-analytic data on the effects of isometric exercise training on resting blood pressure

Reference (year)	Included studies	Participants (*n*)	Major findings
Kelley and Kelley (2010) [26]	Wiley et al. [29]	Ex: 42	↓ in SBP of 13 mmHg
	Taylor et al. [32]	Con: 39	↓ in DBP of 6–8 mmHg[a]
	Millar et al. [37]		
Owen et al. (2010) [27]	Wiley et al. [29]	Ex: 64	↓ in SBP of 10 mmHg
	Howden et al. [31]	Con: 58	↓ in DBP of 7 mmHg
	Taylor et al. [32]		
	Millar et al. [37]		
	Wiles et al. [39]		
Cornelissen et al. (2011) [25]	Wiley et al. [29]	Ex: 42	↓ in SBP of 13 mmHg
	Taylor et al. [32]	Con: 39	↓ in DBP of 6–8 mmHg[a]
	Millar et al. [37]		
Cornelissen and Smart (2013) [20]	Wiley et al. [29]	Ex: 64	↓ in SBP of 11 mmHg
	Taylor et al. [32]	Con: 50	↓ in DBP of 6 mmHg
	Millar et al. [37]		
	Wiles et al. [39]		

All blood pressure values reported as means

Con control, *DBP* diastolic blood pressure, *Ex* exercise, *n* number of subjects, *SBP* systolic blood pressure, ↓ indicates reduction

[a] Range dependent on random- or fixed-effect model

some participants respond to isometric exercise training, while others do not [33, 42, 45]. In general, a reduction in resting systolic or diastolic BP of ≥2 mmHg has been considered to be clinically relevant [1, 13]. Published and unpublished response rates based on this criterion are estimated to be between 50 and 83 % in medicated (i.e. antihypertensive drug treated) hypertensive patients [33, 34, 42, 43, 45] and between 60 and 96 % in unmedicated normotensive and hypertensive patients [35–37]; however, the majority of studies have failed to publish this statistic.

We identified two published neutral studies, both involving individuals medicated for hypertension [33, 42]. Specifically, one of these studies may have been limited by its cohort design without the use of a control group [33], while the other was an RCT that failed to detect statistically significant reductions in resting BP yet reported clinically meaningful reductions in mean ambulatory 24-h systolic BP and night-time systolic BP [~3–4 mmHg (means)] [42]. The reason for the lower response rate in individuals receiving pharmacotherapy to treat their hypertension is unknown, but may involve overlap between the mechanisms mediating the isometric training response and specific classes of antihypertensive drug therapies. Unfortunately, participant stratification based on medication class has not been completed, likely as a result of the small sample of medicated hypertensives and overlapping drug therapies needed to control BP in many patients [43]. Additional investigation is warranted to determine if the medicated hypertensive population requires a greater exposure to the isometric training stimulus (e.g. increased frequency of training, increased intervention length) to elicit adaptations. Although not detected in recent funnel plots [20, 27] or Egger regression [20] analyses, a potential publication bias against negative studies should not be overlooked and further strengthens the need for a large-scale RCT.

2.3 Effects of Isometric Training Protocol Variables on Resting BP

As mentioned, a systematic evaluation of the variables involved in the training protocol (intensity, frequency, duration) has not been undertaken, and current isometric exercise protocols appear to be based primarily on continued success [31]. The following sections expand on the impact of the individual components of the isometric exercise training protocol on resulting adaptations.

2.3.1 Contraction Intensity

Two RCT studies have directly compared the effects of isometric bilateral leg extension (four sets of 2-min contractions) at a lower (~10 % MVC) and higher (~20 % MVC) intensity, demonstrating that the magnitude and rate (i.e. speed) at which resting BP was reduced is greater in the higher intensity training group [39, 41]. A possible threshold for adaptations was also observed as training at ~8 % MVC did not produce reductions in BP [41]. Comparisons between individual studies are difficult due to the alteration of multiple exercise characteristics.

2.3.2 Training Frequency

In the only published study to directly examine training frequency, Badrov and colleagues [44] compared the effects of 3×/week and 5×/week isometric handgrip training on resting BP in an RCT design. They observed that resting systolic BP was reduced equally following 8 weeks of training in both groups of normotensive participants, although training 5×/week, but not 3×/week, was associated with reductions in systolic BP after 4 weeks. This may suggest that a greater exercise dose may accelerate adaptations. From comparisons of the available literature it may also be extrapolated that increased training frequency does accelerate the time course of training adaptations [29], but again these interpretations are confounded by concomitant differences in contraction intensity and duration.

2.3.3 Training Duration

Current evidence suggests that 4–5 weeks of isometric exercise training is sufficient to detect significant reductions in resting BP, if present, with larger reductions observed after 8–10 weeks [45]. Present studies are limited to training durations of 4–10 weeks, an important consideration given that a longitudinal BP analysis failed to detect a plateau in training reductions within this timeframe [45]. This is particularly relevant considering hypertension is a chronic disease requiring continuous lifelong treatment. Further research is required to determine the chronic long-term effects of isometric exercise training on BP.

2.3.4 Muscle Mass

The use of different modes of training, such as unilateral handgrip and bilateral leg isometric exercise, introduces the potentially confounding factor of differences in contracting muscle mass. Howden and colleagues [31] completed a head-to-head cohort-controlled study of bilateral isometric arm and leg training on BP, with both protocols similarly reducing mean resting BP (arm, Δ12/6 mmHg; leg, Δ10/4 mmHg). An important limitation of this study, aside from its non-randomized design, is that the two protocols were not completed at the same relative intensity (arm, 30 % MVC; leg, 20 % MVC). In general, isometric

bilateral leg training has been conducted at lower relative intensities than handgrip (or bilateral arm) training protocols, making comparisons difficult. The consistent reductions in resting BP evident from both of these training protocols suggests that the effects are largely independent of the muscle mass involved.

2.3.5 *Maintenance of Training Adaptations*

No information is available on the long-term maintenance of isometric training adaptations over periods longer than 10 weeks of time. Investigation of minimal training requirements to maintain adaptations is important to be considered a potential hypertension therapy.

Three studies have reported on the effects of detraining following isometric exercise training. Wiley and colleagues [29] documented large reductions in resting BP (Δ 16 mmHg for systolic BP) following 5 weeks of isometric handgrip training that were reversed significantly after only 2 weeks of detraining and gradually returned to pre-training values after 5 weeks, a time course equal to the training period. More recently, reductions in systolic BP [Δ 5–12 mmHg (means)] were lost after only 7–10 days [31, 40]. The rapid nature of these detraining responses may suggest that the mechanisms responsible influence cardiovascular function rather than structure.

2.4 Safety Considerations of Isometric Exercise Training

Isometric exercise is described classically as inducing a pressure load on the heart based on its potential to increase both systolic and diastolic BP. In comparison, dynamic aerobic exercise induces a volume load due to concomitant increases in cardiac output and reductions in total peripheral resistance. The large BP responses observed with high-intensity isometric contractions to fatigue [46–48] raised concerns that isometric exercise should be avoided in many clinical populations, including hypertension [28, 49, 50].

In the context of this review, it is important to remember that current isometric exercise training studies have been performed at low-to-moderate intensity. In the only published study of acute haemodynamic responses, isometric handgrip exercise (4 × 2-min, 1-min rests, 30 % MVC) was reported to modestly increase heart rate [Δ 3 ± 4 bpm (mean ± SD)] and BP [Δ 16 ± 10/7 ± 6 mmHg (mean ± SD)] in older, primarily coronary artery disease patients [51]. Further delineation of the acute responses across a wide range of patient cohorts should be completed to ensure normative responses. A number of studies have reported that a single isometric contraction produces equivalent, or lower, systolic BP and heart rate responses than dynamic aerobic exercise [52–56], particularly when the exercise is performed at the same peak tension development [57]. As a result, the rate-pressure product (systolic BP × heart rate), an index of myocardial oxygen consumption, can be lower following submaximal isometric handgrip compared with submaximal treadmill exercise [58].

Isometric exercise is also associated with an increase in diastolic BP [28, 59], in contrast to no change with dynamic aerobic exercise. This may act to increase coronary perfusion pressure [60] and, in combination with a reduced rate-pressure product, decrease the potential for exercise-induced myocardial ischaemia [61]. One key facet of ensuring appropriate BP responses during isometric exercise protocols is the maintenance of spontaneous breathing without the use of the Valsalva manoeuvre (forced expiration against a closed glottis) [62]. Overall, while low-to-moderate intensity isometric exercise acutely increases BP, it may be clinically permitted in hypertensive patients recommended for equivalent intensity dynamic exercise, with appropriate consideration of standard absolute and relative contraindications to exercise (such as uncontrolled BP >180/110 mmHg) [14, 63].

Additionally, isometric contractions can be accompanied by secondary symptoms of local paraesthesia and minor discomfort. This is most often observed near the end of each set, particularly during protocols with contractions lasting >2 min, and likely relates to the reduction in intramuscular blood flow and accumulation of local metabolites. All symptoms quickly subside upon contraction release and the restoration of adequate blood flow. In the collective experience of the authors, who have independently completed >25,000 isometric exercise training sessions, there have been no reports of lasting physical impairments or significant unfavourable clinical events during or resulting from isometric exercise training.

3 Potential Mechanisms Responsible for Isometric Training-Induced Reductions in Resting BP

3.1 General Background

Practically speaking, the mechanism whereby resting BP is reduced after isometric exercise training must involve one (or both) factors that determine mean arterial pressure (MAP): cardiac output and total peripheral resistance. Two observations may provide insight into potential mechanisms: (i) the lower responder rate in medicated hypertensive patients suggests a potential overlap between pathways involved in pharmacologically treating high BP; and (ii) the temporal sequence of training and detraining adaptations in resting BP suggest at least an initial alteration in cardiovascular function, rather than structure. Of

course, this latter observation does not preclude the possibility of a biphasic pattern involving initial adaptations in function, followed by longer-term structural adaptations, as observed with aerobic exercise training [64]. The following sections will discuss the potential mechanisms responsible for isometric training-induced changes in resting BP.

3.2 Cardiac Adaptations

Studies in young normotensive participants suggest no significant changes in either stroke volume or cardiac output following isometric bilateral leg training, despite concomitant post-training reductions in mean systolic and diastolic BP (Δ 4–5/3 mmHg) [39, 40]. Curiously, these studies also failed to report a change in total peripheral resistance, suggesting that the re-breathing technique applied may be insensitive to small changes over time. Further investigation of cardiac haemodynamics in different populations (e.g. older or clinical), with alternative methodologies (e.g. Doppler ultrasound), and following larger training-induced reductions in resting BP are required.

3.3 Autonomic Nervous System Adaptations

3.3.1 Cardiac Autonomic Regulation

The majority of isometric training data have not supported an adaptation in resting heart rate [29–40, 42–44], a hallmark feature of aerobic exercise training associated with increased vagal modulation [19]. In contrast, Baross and colleagues [41] recently reported a reduction in resting mean heart rate (Δ 5 bpm) in concert with reductions in resting BP, the first such report, following isometric leg training in older, unmedicated, pre-hypertensive and hypertensive men. These results suggest that changes in resting heart rate may be population specific and influenced by baseline medication status.

An important consideration is that average resting heart rate may not accurately represent the beat-to-beat contributions of the autonomic nervous system. The non-invasive assessment of heart rate variability (HRV) provides insight in to the relative changes in cardiac sympathetic and vagal modulations [65–67]. The majority of studies have failed to detect training differences in power spectral or time-domain measures of HRV [38, 39, 42–44]. In contrast, both to the weight of the evidence and to previous research in well-controlled medicated hypertension [42], Taylor and colleagues [32] reported significant increases in power spectral high frequency area, a marker of cardiac vagal modulation [67], concomitant with a large reduction in mean systolic BP (Δ 19 mmHg) following 10 weeks of isometric handgrip training in uncontrolled hypertensive patients. Millar and colleagues [38] detected increases in non-linear heart rate complexity (sample entropy), a measure primarily associated with cardiac vagal modulation [68] and thought to be more sensitive to subtle modulations than traditional linear frequency or time-domain HRV measures, in well-controlled medicated hypertensive patients. Taken together, this work suggests that isometric exercise training may elicit cardiac neural adaptations in some individuals with hypertension, and the medication status of the patients may play a role in determining one's capacity for change. Studies with adequate statistical power are needed to fully elucidate the effects of isometric exercise training on HRV, and should employ assessments of non-linear heart rate dynamics in addition to the traditional time- and frequency-domain measures.

3.3.2 Neural Regulation of Vascular Tone

Limited data exists on the impact of isometric exercise training on peripheral sympathetic nerve activity or the modulation of vascular tone. Ray and Carrasco [30] reported that 5 weeks of isometric handgrip training reduced diastolic BP and MAP in young healthy participants without altering resting muscle sympathetic nerve activity (MSNA), assessed by microneurography. In addition, isometric training did not alter MSNA responses to a 2-min isometric handgrip contraction (30 % MVC) or subsequent post-exercise muscle ischaemia. These results suggest that BP reductions in healthy normotensive patients are not dependent on reductions in central efferent sympathetic outflow, although it is important to remember that direct measurements of nerve traffic are not always correlated with end-organ effects [69], and that in this small sample, resting MSNA was not elevated (compared with values typically observed in hypertensive patients).

In contrast, in an RCT of older patients with difficult-to-control medicated hypertension, Taylor and colleagues [32] reported that 10 weeks of isometric handgrip training reduced systolic BP and MAP in concert with significant reductions in the low-frequency spectra of systolic BP variability, a marker of baroreflex-mediated peripheral sympathetic modulation [70, 71]. Thus, in patients with primary hypertension, a condition characterized by increased sympathetic outflow [72, 73], isometric training may reduce BP through attenuations in peripheral sympathetic vasoconstrictor activity. Baross et al. [41], recently observed increases in femoral artery diameter and vascular conductance following 8 weeks of bilateral isometric leg training in healthy normotensive patients, but did not investigate the mechanism for this alteration. Further work is required to elucidate the role of isometric exercise training in altering sympathetic vasomotor tone.

3.4 Vascular Adaptations

A number of investigations have examined the effects of isometric exercise training on conduit artery endothelial function. McGowan and colleagues [33, 34] reported that 8 weeks of unilateral isometric handgrip training in medicated hypertensive patients increased nitric oxide (NO)-dependent, but not NO-independent, vasodilation in the brachial artery of the trained arm only (i.e. no adaptations in the contralateral untrained arm). These increases in NO-dependent brachial dilation were not replicated in normotensive participants, despite modest yet significant reductions in resting BP [35]. This may be interpreted to suggest that improved systemic NO-dependent vasodilation is not a required mechanism for the reductions in resting BP following isometric exercise training. However, it is important to consider the methodology used to assess NO-dependent vasodilation in these studies, namely brachial artery flow-mediated dilatation, which measures the response of the NO vasodilator system to a maximal hyperaemic stimulus. It is therefore plausible that an increase in the basal capacity of the NO vasodilator system to produce, release and/or utilize NO may contribute to the observed training-induced reductions in resting BP in either population. In support of a vascular mechanism, 4 weeks of isometric handgrip in normotensive participants increased peak reactive hyperaemic blood flow, a marker of functional changes in the resistance vessel (small arteries and arterioles) vasculature [35], which are the beds primarily responsible for determining BP [74]. More recently, 8 weeks of isometric handgrip improved reactive hyperaemic blood flow, suggestive of improved resistance vessel function in a young normotensive cohort training 3×/week or 5×/week using a prospective RCT design [44]. Importantly, while BP was reduced with 5×/week training after 4-weeks of training, this was not accompanied by improvements in the resistance vessel vasculature, suggesting other mechanisms are also involved. Thus, whether improved resistance vessel endothelial function, similar to that observed following aerobic endurance training [75], principally contributes to the training-induced reduction in resting BP requires further elucidation.

The evidence that isometric exercise training is a sufficient stimulus to cause adaptations in the local exercising vasculature is also supported by increases in femoral, but not brachial artery, diameter, blood flow, and blood velocity following 8 weeks of isometric bilateral leg extension training [41]. In this RCT, the changes in resting femoral diameter strongly correlated with the changes in resting BP. Unfortunately, it is not possible to distinguish between structural vessel remodelling or functional changes in basal vasodilator capacity (likely as a result of the noted increase in blood velocity) or tonic vasoconstrictor activity (reduced sympathetic outflow).

Overall, isometric exercise training is associated with increases in local conduit artery NO-dependent dilatation in patients with hypertension, but these adaptations are not observed in normotensive participants. As BP is primarily regulated at the level of the resistance vessels, evidence supporting improved resistance vessel function provides one plausible mechanism responsible for reductions in resting BP.

3.5 Oxidative Stress

Increased oxidative stress is thought to play a key role in the pathophysiology of hypertension [76]. Preliminary evidence suggests that isometric exercise training may improve oxidative stress, in so far as, in one uncontrolled trial, 6 weeks of isometric handgrip training improved the ratio of resting whole blood glutathione to oxidized glutathione and reduced aerobic exercise-induced ROS production, in concert with reductions in resting BP in unmedicated hypertensive patients [36]. Additionally, since isometric training can increase local conduit artery NO-dependent vasodilation in individuals with hypertension [33, 34] and basal NO-dependent resistance vessel function [35], changes in oxidative stress may be mediated by increased availability of NO, a potent antioxidant and anti-inflammatory molecule [76].

3.6 Summary of Mechanisms

The mechanisms responsible for the reductions in resting BP following isometric exercise training have not been fully clarified. It is most likely that multiple adaptations in the above pathways are collectively responsible for the post-training reductions in BP and determined by the individual pathological profiles of each participant. In general, the current literature investigating the potential mechanisms responsible for training adaptations is limited by small sample sizes. Isometric exercise training trials to date have primarily been powered to detect changes in resting BP, and inadequately powered to probe the role of specific regulatory pathways. While the reductions in resting BP are likely mediated via a reduction in total peripheral resistance, similar to aerobic exercise training [19], the specific roles of the sympathetic nervous system, conduit and resistance vessel structure and function, and oxidative stress require greater investigation.

4 Clinical Implications

In addition to the discussed interventional studies, Buck and Donner [77] conducted an epidemiological study of 4,273 men and classified hypertension incidence based on

occupational isometric activity. They reported that following adjustment for known confounders (age, social class, obesity, and alcohol consumption), moderate to heavy occupational isometric exercise was associated with a lower incidence of hypertension [77]. While this association does not prove causality, it is in agreement with the prospective data and may suggest a role for isometric exercise training in both prevention and management of hypertension.

It is important to remember that for those with or without hypertension, even small reductions in systolic and diastolic BP ($\geq$2 mmHg) can translate into significant reductions in the incidence of coronary artery disease, myocardial infarction, stroke, and mortality [78–80], and less need for medications and thus less probability of undesirable side effects. However, while BP remains a significant contributor to overall cardiovascular health, the ability of isometric exercise training to modulate other CVD risk factors, such as insulin sensitivity, cholesterol, or inflammation remain largely unexplored. We identified only one study to investigate the effects of isometric exercise training on additional CVD correlates other than BP. In this uncontrolled cohort study, isometric handgrip training did not alter total, high- or low-density cholesterol [34]. Thus, in comparison to dynamic exercise training (aerobic and resistance), which consistently demonstrates a number of important improvements (e.g. body composition, metabolic, maximal aerobic capacity), the benefits of isometric training may be confined to BP. Studies designed to test the clinical efficacy of isometric exercise training are needed.

5 Future Directions

Isometric exercise training, and in particular isometric handgrip training, which is easily applicable (i.e. easy to use and can be performed anytime and anywhere), inexpensive and hence accessible to the global population, could offer a valuable new therapeutic adjunct in the overall approach for treating hypertension [81]. However, despite these encouraging findings, a number of important research questions remain with respect to the (i) value of the training modality compared with or in addition to currently recommended aerobic exercise training protocols; (ii) identification of the most effective isometric exercise program to maximize and maintain BP reductions; (iii) efficacy of isometric exercise training in lowering ambulatory 24-h BP, a more clinically relevant measure [82]; and (iv) mechanisms responsible for the observed BP reductions. Importantly, each of these issues needs to be systematically investigated before isometric exercise can be universally recommended.

6 Conclusion

Hypertension is a global disease with a high residual lifetime risk (upwards of 90 % in some populations) [10], and represents a major contributor to the growing pandemic of CVD and stroke [1]. Approximately 54 % of strokes and 47 % of heart disease cases are directly attributable to elevated BP [83]. In the context of this large and growing disease burden, strategies to improve population health are of utmost importance. This review has summarized the available literature on the effects of isometric exercise training on BP [24–45]. From the current prospective studies and meta-analyses, isometric exercise training appears to be as or more effective in lowering BP when compared with dynamic aerobic [16–20], or resistance exercise training [20, 22–25], even though it requires substantially less time. The observation that resting BP can be reduced in participants already undergoing chronic aerobic and dynamic resistance training [32, 34, 35, 37, 39, 40] suggests a specific adjunct role for isometric exercise training. However, while these largely preliminary results appear promising, concerns regarding small samples sizes and uncontrolled study designs exist. We believe that the current level of evidence substantiates a large-scale RCT designed to address these previous limitations and determine potential clinical significance. Further investigation is also required to elucidate the mechanisms responsible for these observations, although much like hypertension pathophysiology, multiple regulatory pathways are likely involved, and dependent on individual pathological states. The potential impact of isometric exercise training in combating hypertension warrants future research to delineate important questions necessary for its adoption as an adjunct exercise therapy.

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