Mechanisms for blood pressure reduction following isometric exercise training: A systematic review and meta-analysis.

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Abbreviations

BABF - brachial artery blood flow

BAD - brachial artery diameter

BP – blood pressure

BRS - baroreceptor reflex sensitivity

CO – cardiac output

dBP – diastolic blood pressure

FMD - flow-mediated dilatation

HF – high frequency

HR – heart rate

HRV – heart rate variability

IET – isometric exercise training

LF – low frequency

mBP – mean blood pressure

sBP – systolic blood pressure

SV – stroke volume

TPR – total peripheral resistance

Abstract

Objective: Isometric exercise training (IET) is established as an effective anti-hypertensive intervention. Despite this, the physiological mechanisms driving blood pressure (BP) reductions following IET are not well understood. Therefore, we aimed to perform the first meta-analysis of the mechanistic changes measured following IET.

Methods: PubMed, Cochrane library and SPORTDiscus were systematically searched for randomised controlled trials published between January 2000 and December 2021 reporting the effects of IET on resting BP and at least one secondary mechanistic parameter following a short-term intervention (2-12 weeks).

Results: Eighteen studies with a pooled sample size of 628 participants were included in the final analysis. IET produced significant reductions in resting systolic and diastolic BP of 9.35 mmHg (95%CI=-7.80 to -10.89, $p<0.001$) and 4.30mmHg (CI=-3.01 to -5.60, $p<0.001$), respectively. Mechanistically, IET produced a statistically significant reduction in resting heart rate (MD:-1.55bpm, CI=-0.14 to -2.96, p=0.031) and a significant increase in stroke volume (MD:6.35ml, CI=0.35 to 12.60, p=0.038), with no significant change in cardiac output. Conversely, total peripheral resistance (TPR) significantly decreased following IET (MD:-100.38 dyne·s^{-1}·cm^5, CI=14.16 to -186.61, p=0.023), with significant improvements in the low frequency to high frequency heart rate variability ratio (MD:-0.41, CI=-0.09 to -0.73, p=0.013) and baroreceptor reflex sensitivity (MD:7.43ms·$mmHg^{-1}$, $p<0.001$).

Conclusion: This work demonstrates that a reduction in TPR, potentially mediated through enhanced autonomic vasomotor control, is primarily responsible for BP reductions following IET. Furthermore, this novel analysis suggests wall squat interventions to be the most effective IET mode, with clinically relevant differences in BP reductions compared to handgrip and leg extension IET; although future direct comparative research is required.

Introduction

As a leading cause of morbidity and mortality [1], hypertension remains a global health crisis at an estimated prevalence of over 1.4 billion [2]. Despite advancements in pharmacotherapy, the worldwide burden of hypertension continues to rise, especially in low- and middle-income countries [2]. As such, the implementation of non-pharmacological, cost-effective anti-hypertensive interventions is a public health priority.

Isometric exercise training (IET) is established as an efficacious anti-hypertensive intervention, with research trials demonstrating clinically significant reductions in resting office [3] and ambulatory [4] blood pressure following a short-term IET intervention. Specifically, multiple previous meta-analyses have reported reductions similar to, or greater than that typically observed following standard dose anti-hypertensive monotherapy [5].

While the efficacy of IET appears unambiguous, the underlying mechanisms driving such blood pressure (BP) changes are not well understood. Of interest, the majority of trials have suggested adjustments to local and systematic vascular resistance to be the predominant cause of a reduction in BP [4,6], while only a few studies have implicated a reduction in cardiac output (CO) via heart rate (HR) and/or stroke volume (SV) changes [7,8]. In addition to this, the literature is largely unsettled as to the magnitude of contribution from various physiological mediators, such as autonomic, baroreflex and inflammatory pathways [6,9]. As to whether this current lack of clarity in the mechanistic literature is the result of differences in measured populations and modes of IET is also not understood. As such, there remains significant gaps in the current literature as to the overarching mediators of BP change following IET, the underlying regulation of these mediators, and the role of population and

IET mode heterogeneity in these mechanistic processes. Therefore, we aimed to perform the first meta-analysis of the underlying physiological mechanisms driving reductions in resting BP following IET, with sub-group analyses according to hypertensive and medication status, and IET mode. Furthermore, to enhance the clinical applicability of this exercise, we aimed to establish the most effective IET mode by performing a comparative analysis between wall squat, leg extension and handgrip IET.

Methods

Search strategy

This systematic review and meta-analysis was performed in accordance with the PRISMA guidelines [10]. Electronic database searches were performed in PubMed (MEDLINE), the Cochrane library and SPORTDiscus for research trials reporting on the effects of IET on BP. Developed by a research librarian, the search strategy included MeSH terms, key words, and word variants for isometric exercise training, static contraction, exercise training, blood pressure and hypertension. English language articles published between the 1st January 2000 and 12th December 2021 were considered. The strategic exclusion of papers published prior to year 2000 was based on methodological, statistical and protocol limitations of previous work relative to today's evidence base. Reference lists of relevant articles and reviews were hand searched for additional papers and where appropriate, corresponding authors were contacted to ascertain whether non-published data was available or in the pre-print stage.

Study eligibility, outcome measures and data collection

Two authors (JE and JOD) independently screened all papers for eligibility. Studies were initially screened by title and abstract and any disagreements or inconsistencies were discussed by the researchers and a consensus was reached. For those articles in which information was not reported, but the methodology indicates that this information would have been recorded, the authors were contacted. The corresponding authors for 3 separate studies were contacted for additional data, of which 1 effectively responded with the relevant data and was subsequently included [11]. Studies retained for the next step of assessment were evaluated by full-text and considered if they reported pre-post IET intervention BP changes, as well as at least one of the following secondary (mechanistic) outcomes: HR, SV, CO, total peripheral resistance (TPR), low frequency (LF) heart rate variability (HRV), high frequency (HF) HRV, LF/HF ratio, baroreceptor reflex sensitivity (BRS), brachial artery blood flow (BABF), brachial artery diameter (BAD), flow-mediated dilatation (FMD) and peripheral pulse wave velocity (PWV). There was no exclusion criteria on the methodological acquisition of any of the included variables. While several studies primarily acquired data through collective non-invasive beat-to-beat haemodynamic and autonomic monitoring using validated devices such as the Task Force Monitor [4,12] or Finometer [7,13], other trials employed single-lead ECG recording [14] or a heart rate monitoring [15]. There were differences in BP measurement protocols and guidelines applied between studies. All vascular measures were acquired via homogenous doppler ultrasound and applanation tonometry means [8,15,16].

Only randomised controlled trials, including cross-over design studies with an intervention duration of 2 to 12 weeks were eligible. As such, acute response data was not included. Participants were required to be ≥18 years of age with no limitations on baseline BP or pre-existing co-morbidities. As the primarily employed IET protocols, this work analysed studies of handgrip, wall squat, or leg extension IET. The hypertension status of the relevant study populations were based on mean baseline BP (>140mmHg), while trials were considered medicated if any number of participants were disclosed as taking anti-hypertensive agents.

Study quality

Study quality and risk of bias was evaluated using the TESTEX scale [17], which is a 12 item (15 point) tool designed to assess exercise intervention research trials. Two reviewers (JE and JOD) independently scored all eligible articles. Any disputes detected in study scoring were discussed by the researchers and agreements were reached. Detailed TESTEX scoring for each study can be found in the supplementary file (Table S1).

Statistical analysis

The extracted raw data was manually entered into the statistical software Comprehensive Meta-Analysis (Comprehensive Meta-Analysis Version 3, Biostat, Englewood, NJ, USA). As all outcomes were measured across the same scales, all results are presented as weighted mean differences (WMD) with 95% confidence intervals. Pooled analyses of effect sizes were conducted for resting systolic, diastolic and mean BP (sBP, dBP and mBP) and all secondary mechanistic outcomes. Sensitivity analysis was performed for the primary outcomes using the in-built CMA 'one-study removed' analysis method, which did not significantly influence any of the overall effect sizes. Sub-group analyses of IET mode (isometric handgrip, wall squat and leg extension), hypertension status, and medication status were performed on all primary and secondary outcomes. Additionally, meta-regression analyses were performed to test for any moderator effects on sBP and dBP. The analysed moderators were mean baseline BP and study duration. Statistical heterogeneity was assessed via the I^2 statistic alongside all pooled analyses, with a significance threshold of >40% [18]. Once this threshold had been breached, random effects analyses was applied to account for inter-study variability [18], and post-hoc Egger's test were systematically planned to account for potential publication bias by assessing the presence of funnel plot asymmetry [19]. The results of the pooled analysis were considered significant with a P value of <0.05 and a Z-value of >2.

Results

Figure 1 details the PRISMA systematic review flowchart [10]. The initial search found 3053 studies. Following all screening, 18 IET studies constituting 628 participants were included in the final analysis. All relevant study characteristics are presented in Table 1 and the full reference list of all analysed studies are provided in the supplementary file.

As observed in Table S1, the TESTEX risk of bias assessment demonstrated several inherent limitations within the current IET literature. Specifically, the participants and investigators were generally aware of group allocation and thus future IET research should employ sham-design methodology to blind the participants to their group allocation. In addition, most research fails to perform intention-to-treat analysis where appropriate or monitor control group activity. Separately, there was evidence of publication bias for dBP, which should be considered in the interpretation of such findings.

Of the included trials, 11 employed handgrip IET, 4 wall squat IET and 3 leg extension IET. There were 8 trials of hypertensive cohorts and 6 medicated study populations. While all protocols were performed at a frequency of 3 times per week, the intervention duration ranged from 4-12 weeks. The majority of handgrip IET was performed at 30% maximal voluntary contraction, while wall squat and leg extension IET was performed at 95% heart rate peak. The number of effect sizes analysed for each variable can be found in the supplementary file (Table S2).

Blood pressure

sBP, dBP and mBP significantly reduced following IET compared to the control group by a weighted mean difference of 9.35mmHg (95%CI= -7.80 to -10.89, Z= 11.86, $p<0.001$), 4.30mmHg (95%CI= -3.01 to -5.60, Z= 6.509, p<0.001) and 5.21mmHg (95%CI= -4.34 to -6.07, Z= 11.800, p<0.001), respectively. There was significant statistical heterogeneity between studies for sBP (I2=56.75%), dBP (I2= 64.86%) and mBP (I2= 34.84%) (Figures S1-S3). Post-hoc Egger's regression test was only significant for dBP (p=0.003, Figures S4 and S5). The results of additional parameter-specific analyses can be found in the supplementary file.

IET mode sub-group analyses on sBP and dBP demonstrated no significant differences between wall squat (MD: -11.41/-5.09mmHg, 4 studies, Z=7.01 and 3.47, p<0.001 and p=0.004), leg extension (MD: -9.96/-3.69mmHg, 3 studies, Z=4.95 and 1.83, p<0.001 and p=0.068) or handgrip (MD: -8.34/-4.10mmHg, 11 studies, Z=8.01 and 4.83 p<0.001 for both) exercise, respectively (Between p=0.267 and p=0.805). There were also no significant differences in the reduction in sBP and dBP following IET in normotensive, pre-hypertensive or hypertensive cohorts, and no significant sub-group differences between medicated and unmedicated. When only handgrip IET was analysed, there was again no significant difference in sBP and dBP reduction in hypertensive or normotensive cohorts. Meta-regression analyses demonstrated no statistical significance for study duration and baseline resting BP.

Heart rate, stroke volume and cardiac output

Resting HR significantly reduced following IET compared to the control group by 1.55bpm (95%CI= -0.14 to -2.96, Z= 2.155, p=0.031). While there was no significant effect of IET mode or hypertension status, IET produced greater HR reductions in medicated compared to unmedicated study populations (Q= 5.438, p=0.020). SV significantly increased following

IET compared to the control group (MD: 6.35ml, 95%CI= 0.35 to 12.60, Z= 2.075, p=0.038). Consequently, there was no significant change in CO following IET compared to the control group (MD: 0.28l/min, 95%CI= -0.11 to 0.67, Z= 1.430, p=0.153). There was insufficient data to perform any sub-group analyses on SV or CO.

Vascular parameters

IET produced significant reductions in TPR compared to the control group (MD: -100.38 dyne·s^{-1}·cm^{5}, 95%CI= -14.16 to -186.61, Z= 2.282, p=0.023). There was no significant change in BABF (MD: -7.98 ml/min, 95%CI= 0.93 to -16.89, Z= 1.755, p=0.079), BAD (MD: -0.10cm, 95%CI= -0.24 to 0.04, Z= -1.362, p=0.173), FMD (MD: 0.09mm, 95%CI= -0.01 to 0.19, Z= 1.834, p=0.186) or PWV (MD: 0.23m/s, 95%CI= -0.41 to 0.87, Z= 0.700, p=0.484) following IET compared to the control group. There was insufficient data to perform any sub-group analyses on TPR, BABF or FMD.

Cardiac autonomics and baroreceptor reflex sensitivity

IET produced a significant reduction in LF normalised units (MD: -0.73%, 95%CI= -0.37 to -1.09, Z= 4.001, p<0.001) and a significant increase in HF normalised units (MD: 5.52%, 95%CI= 0.88 to 10.16, Z= 2.331, p<0.001) compared to the control group. As a result, the LF/HF ratio significantly decreased following IET (MD: -0.41, 95%CI= -0.09 to -0.73, Z= 2.486, p=0.013) compared to the control group. Additionally, BRS significantly increased following IET (MD: 7.43ms·mmHg^{-1}, 95%CI= 4.29 to 10.57, Z= 4.633, p<0.001) compared to the control group.

Discussion

This is the first study to meta-analyse the mechanistic physiological parameters behind BP reductions following IET. As expected, IET produced statistically significant reductions in sBP, dBP and mBP, with wall squat IET producing the greatest magnitude of reduction. Mechanistically, HR significantly decreased and SV significantly increased. Consequently, CO did not significantly change following IET. TPR significantly decreased, alongside significant improvements in the LF/HF ratio and BRS. There were no significant changes in BABF or FMD post-IET. As such, the findings of this study suggest that reductions in BP following IET are predominantly driven by changes in vascular resistance, potentially mediated by improvements in central command regulation. There is currently insufficient data to assess whether these mechanistic changes are independent of hypertension and/or medication status.

Similar to previous meta-analyses [3,9,20,21], the findings of this work demonstrates IET as a clinically effective anti-hypertensive interventional strategy, regardless of hypertensive or medication status. Novel to this study, IET appears effective across the three primarily employed IET modes, with sBP and dBP reductions following isometric wall squat, leg extension, and handgrip exercise by -11.41/-5.09, -9.96/-3.69 and -8.34/-4.09mmHg, respectively. Although not statistically significant, the difference in magnitude of reduction between these modes is considered clinically relevant, with differences of >3mmHg in sBP between wall squat IET and the traditionally employed handgrip mode. Therefore, this work suggests wall squat IET may be the most effective form of IET, which is probably attributable to differences in the extent of recruited muscle mass and thus surface area of occluded vasculature when compared to handgrip protocols [6]. However, these results should be interpreted with consideration of the current disparity in the quantity of trials between modes, with this analysis including 11 handgrip, but only 4 wall squat and 3 leg extension studies; therefore highlighting the need for direct comparative randomised trials.

Fundamentally, a decrease in resting BP must be mediated via changes to cardiac output and/or total peripheral resistance as the two determining factors of arterial pressure. As previously reported [21], pooled analyses of the IET literature produces small statistically significant reductions in resting HR, which are likely facilitated by the observed cardiac autonomic and baroreflex adaptations [22]. Interestingly, IET produced greater HR reductions in medicated study cohorts compared to non-medicated. The reason for this finding is not clear, but may be related to various methodological factors such as during-study medication changes, as well as the varying intricate physiological effects of IET in combination with differing anti-hypertensive medication classes. Separately, SV appears to significantly increase, which is unsurprising given our recent work showing significant improvements in cardiac function, mechanics and global myocardial work efficiency as by-products of a reduction in cardiac after-load following IET [23]. Accordingly, CO does not appear to significantly change after an IET intervention with the data conversely trending towards an increase, and therefore is generally not responsible for the observed BP changes.

TPR significantly decreased following IET compared to the control group. Interpreting this finding in the context of no significant change in CO, indicates vascular changes to be primarily responsible for the observed BP reductions. Unfortunately, the current literature has not comprehensively addressed the degree to which these vascular changes following IET are locally regulated via endothelial-dependant mechanisms [14], or systemically modulated via structural remodelling [8] and/or functional adaptations in autonomic vasomotor control [4,6]. The present analysis did not find any significant changes in FMD, PWV, BABF or BAD as localised measures of vascular function and structure. However, these findings may be subject to statistically underpowered analyses with insufficient data to draw definitive conclusions. For example, only 2 studies to date have measured FMD [16,24], of which both consisted of primarily hypertensive medicated cohorts, and therefore the relative application of these findings to normotensive, or uncontrolled hypertensives is not known. To the contrary, the present HRV analysis did indeed demonstrate significant decreases in the LF/HF ratio and significant increases in BRS, which provides a strong argument for a large autonomic vasomotor contribution to the BP reductions following IET. Taken together, these mechanistic changes are highly complex and are likely to be heavily influenced by the characteristics of the measured study populations, as well as complex individual physiological profile variances. Unfortunately, there is currently insufficient data to perform mechanistic analyses based on hypertension or medication status, and thus the possibility of heterogeneous mechanistic underpinnings of BP changes in differing populations cannot be ruled out.

Limitations

Importantly, these papers were primarily statistically powered to detect changes in BP rather than the underlying mechanistic parameters analysed in this work. As such, mechanistic IET studies with larger sample sizes are required. Additionally, we found significant heterogeneity for the majority of the analysed variables in this study. This inter-study variance is likely, at least in part, owing to methodological and population differences, such as data acquisition and baseline BP differences. With this, random-effects models and meta-regression analyses were applied in an attempt to account for such heterogeneity. While the authors of the present work have vast experience in meta-analyses, inter-coder validity and reliability cannot be statistically verified. Furthermore, this meta-analysis was not database registered a priori. Finally, the post-hoc Eggers tests were statistically significant for dBP, suggesting publication bias.

Conclusion

IET produces significant reductions in resting HR and significant increases in SV, with no significant change in CO. Conversely, TPR significantly reduces following IET, together with significant improvements in the LF/HF ratio and BRS. While future research is needed to discern the contribution of localised functional and/or structural vascular changes, this work demonstrates that a reduction in TPR, potentially mediated through enhanced autonomic vasomotor control, is primarily responsible for BP reductions following IET. Furthermore, this novel analysis suggests the wall squat to be the most effective IET mode, with reductions of a clinically relevant difference compared to handgrip and leg extension IET; although future direct comparative research is required.

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Table 1. Study Characteristics.

Study	Country	Duration (weeks)	Participants	Hypertension (According to baseline BP)	Included Medication	Withdrawal (N. of participants)	Training Frequency	Exercise Mode	Exercise Training Characteristics	TESTEX score
Baddeley-White et al (2019) [25]	UK	4	n=23 (43% Female)	NTN	No	None	3 x per week	Isoball rugby handgrip/ zona plus handgrip	4 x 2 min, 1 min rest interval, 30%MVC, (n=7 isoball, n=8 zona, n=8 control).	7
Badrov et al (2013a) [14]	Canada	8	n=36 (100% Female)	NTN	No	IET= 1 Control= 3	3/5 x per week	Handgrip	4 x 2 min, 4 min rest intervals, 30% MVC, (n=12 3x per week, n=11 5 x per week, n=9 control).	10
Badrov et al (2013b) [26]	Canada	10	n=24 (46% Female)	HTN	Yes	None	3 x per week	Handgrip	4 x 2 min bilateral, 1 min rest interval, 30% MVC, (n=12 IET, n=12 control).	8
Baross et al (2012) [8]	UK	8	n=30 (100% Male)	Pre-HTN	No	None	3 x per week	Leg extension (Bilateral)	4 x 2 min, 2 min rest intervals, 14%MVC, (n=10 at 85%HRpeak, n= 10	7

									at 75%Hrpeak, n=10 control).	
Baross et al (2013) [27]	UK	8	n=20 (100% Male)	Pre-HTN	No	None	3 x per week	Leg extension (Bilateral)	4 x 2 min, 2 min rest intervals, (85%Hrpeak n=10 exercise group, n=10 control).	7
Cahu Rodrigues et al (2019) [16]	Brazil	12	n=72 (67% Female)	HTN	Yes	IET=31 Control=8	3 x per week	Handgrip	4 x 2 min, 1 min rest interval, (n=17 30%MVC, n=16 control).	10
Carlson et al (2016) [13]	Australia	8	n=40 (62.5% Female)	HTN	Yes	IET= 2	3 x per week	Handgrip	4 x 2 min, 1 min rest intervals, (n= 18 at 30%MVC, n=20 5%MVC exercise control).	13
Correia et al (2020) [24]	Brazil	8	n=102 (sex unknown)	HTN	No	IET=21 Control= 2	3 x per week	Handgrip	4 x 2 min, 4 min rest intervals, (n=29 30%MVC, n=50 control).	9

Decaux et al (2021) [12]	UK	4	n=20 (50% Female)	Pre-HTN	No	None	3 x per week	Wall squat	4 x 2 min, 2 min rest intervals, (n=10 95% Hrpeak, n=10 non exercise control).	7
Lea et al (2021) [28]	UK	4	n=20 (20% Female)	Pre-HTN	No	IET= 3	3 x per week	Wall squat	4 x 2 min, 2 min rest intervals, (n=10 95% Hrpeak, n=10 non exercise control).	
Millar et al (2013) [29]	Canada	8	n=23 (22% Female)	HTN	Yes	None	3 x per week	Handgrip	4 x 2 min, 1 min rest intervals, (n=13 30%MVC, n=10 control).	7
Okamoto et al (2020) [30]	Japan	8	n=22 (59% Female)	HTN	No	None	3 x per week	Handgrip	4 x 2 min, 1 min rest interval. (n=11 30% MVC, n=11 control).	10
Punia et al (2019) [31]	India	8	n=40 (50% Female)	HTN	Yes	None	3 x per week	Handgrip	4 x 2 min, 4 min rest intervals, (n=20 30%MVC, n=20 non-exercise control group).	10

Taylor et al (2003) [32]	Canada	10	n=17 (42% Female)	HTN	Yes	None	3 x per week	Handgrip	4 x 2 min, 1 min rest intervals, (n=9 30%MVC, n=8 non-exercise control group).	7
Taylor et al (2018) [4]	UK	4	n=48 (100% Male)	Pre-HTN	No	None	3 x per week	Wall squat	4 x 2 min, 2 min rest intervals, (n=24 95% Hrpeak, n=24 non exercise control).	7
Wiles et al (2009) [33]	UK	8	n=33 (100% Males)	NTN	No	None	3 x per week	Leg extension (Bilateral)	4 x 2 min, 2 min rest intervals, (n=11 HI-95%Hrpeak, n=11 LO-75%Hrpeak, n=11 control group).	8
Wiles et al (2016) [7]	UK	4	n=28 (100% Male)	NTN	No	None	3 x per week	Wall squat	4 x 2 min, 1 min rest interval, (n=14 95%Hrpeak, n=14 non-exercise control).	7
Yamagata et al	Japan	8	n=20 (sex unknown)	NTN	No	None	3 x per week	Handgrip	4 x 2 min, 3 min rest intervals. (n=10 25%	9

(2020) [11]	MVC Handgrip, n=10 control group).

Figure Legend:

Figure 1: PRISMA systematic review and meta-analysis flowchart.

Figure 2: Forest plots of the overall effects of IET on sBP and dBP and dichotomized mode-dependant effects.

Figure 3: Forest plots depicting the effects of IET on TPR and LF/HF ratio.

Figure 4: Central Illustration.