Blood pressure and cardiac autonomic adaptations to isometric exercise training: a randomised sham-controlled study.

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Abstract

Isometric exercise training (IET) is increasingly cited for its role in reducing resting blood pressure (BP). Despite this, few studies have investigated a potential sham effect attributing to the success of IET, thus dictating the aim of the present study. Thirty physically inactive males (n=15) and females (n=15) were randomly assigned into 3 groups. The IET group completed a wall-squat intervention at 95% peak heart rate (HR) using a prescribed knee joint angle. The sham group performed a parallel intervention, but at an intensity (<75% peak HR) previously identified to be inefficacious over a 4-week training period. No-intervention controls maintained their normal daily activities. Pre- and post-measures were taken for resting and continuous blood pressure and cardiac autonomic modulation. Resting clinic and continuous beat to beat systolic (-15.2±9.2 and -7.3±5.6 mmHg), diastolic (-4.6±5 and -4.5±5.1) and mean (-7±4.2 and -7.5±5.3) BP, respectively, all significantly decreased in the IET group compared to sham and no-intervention control. The IET group observed a significant decrease in low frequency normalised units of heart rate variability concurrent with a significant increase in high frequency normalised units of heart rate variability compared to both the sham and no-intervention control groups. The findings of the present study reject a non-specific effect and further support the role of IET as an effective anti-hypertensive intervention.

Introduction

Hypertension is well-established as the leading modifiable risk factor for both cardiovascular disease and all-cause mortality worldwide (Lim *et al.*, 2012). The global prevalence of hypertension is estimated at 1.13 billion, which is associated with significant economic burden on healthcare services (Zhou *et al.*, 2017). Isometric exercise training (IET) has emerged as a convenient, time-efficient intervention, which has produced clinically significant blood pressure (BP) reductions in both hypertensive and normotensive populations (Inder *et al.*, 2016). The anti-hypertensive effects of IET have been supported in multiple meta-analytical studies (Carlson *et al.*, 2014; Inder *et al.*, 2016; López-Valenciano *et al.*, 2019), with reductions similar to or greater than those observed in traditional aerobic exercise training (Cornelissen and Smart, 2013).

While the efficacy of IET appears unequivocal, researchers have rarely evaluated this modality using rigorous research designs involving a placebo control, which is considered gold standard for medical interventions (Fudim *et al.*, 2019). The current evidence is therefore limited in determining whether the outcomes of IET are owing to the actual intervention or to other non-specific factors, such as the placebo effect (Beedie *et al.*, 2018; Hurst *et al.*, 2019). The magnitude of the placebo effect on exercise interventions has been suggested to have a small to medium effect (Hurst *et al.*, 2019) and can account for up to half of the observed psychological benefits of exercise (Lindheimer, O'Connor and Dishman, 2015), as well as accounting for 34% and 47% of the anti-hypertensive drug response for systolic and diastolic BP respectively (Wilhelm *et al.*, 2016). Given the absence of appropriate placebo-controlled studies, the efficacy of IET may be overestimated.

Controlling for non-specific factors in exercise interventions is complicated by the inability to blind participants (i.e. participants are likely to be aware that they are, or they are not, receiving IET). Researchers have therefore advocated the use of sham controls resembling the intervention, but in a variant proven to be ineffective (Lindheimer, O'Connor and Dishman, 2015; Beedie *et al.*, 2018). To our knowledge, there is only one IET study utilising a sham-design, in which the sham group performed a handgrip protocol, but were instructed not to generate any force during the exercise bouts (Ray and Carrasco, 2000). This design is problematic as the participants are likely to be aware that they are not performing the intervention and are therefore not sufficiently blinded. Thus, the application of a sham-design IET intervention which effectively blinds the participants is imperative. It has previously been shown that 4-weeks of IET at 95% peak heart rate (peak HR) significantly improved resting blood pressure (Wiles, Goldring, & Coleman, 2017), whereas 4-weeks of IET at 75% peak HR had no effect (Wiles, Coleman, & Swaine, 2010). Given that these interventions are identical beside from the intensity, these results suggest that 4-weeks of IET at 75% peak HR, could be used as an appropriate sham for 4-weeks of IET at 95% peak HR.

In this study, we compared BP and cardiac autonomic modulation adaptations following 4-weeks of IET with 4-weeks of sham IET and a no-intervention control. We hypothesised that the IET will reduce resting clinic and continuous beat to beat BP, along with improvements in cardiac autonomic modulation compared to sham and no-intervention controls.

Method

Participants

Thirty physically inactive (self-reported in accordance with the current guidelines) (World Health Organisation., 2010) males (n=15) and females (n=15) volunteered to participant in this study. Participants (age 30.2±8.4 years; height 170.6±9.2cm; mass 82.3±18.3kg; BMI 28.2±5.6 kg·m^2) were healthy with normal or high-normal blood pressure under no pharmacotherapy, in accordance with the ESC/ESH guidelines for blood pressure classifications (<140/<90mmHg) (Williams *et al.*, 2018). All testing and data collection occurred at Canterbury Christ Church University. Informed consent was signed by all participants before testing. Canterbury Christ Church University Ethics Committee approved this research, ensuring conformity to the declaration of Helsinki principles (18/SAS/47C).

Resting clinic blood pressure

Participants were randomised into either the IET group, sham group or no-intervention control group through a single-blinded protocol prior to any baseline measures. There were no significant differences in the participant physical characteristics between the groups (Table 1). Participants were required to refrain from strenuous exercise, caffeine and alcohol consumption for 24 hours and fast for 8 hours prior to testing (Whelton *et al.*, 2018). Participants attended the laboratory on two occasions for pre and post-intervention measures.

Baseline resting systolic (sBP), mean (mBP) and diastolic (dBP) BP measures were recorded from the brachial artery as an average of 3 measures, separated by 5-min following 15-min of rest using an automated oscillometric BP monitor (Dinamap Pro 200 Critikon; GE Medical Systems, Freiburg, Germany) in accordance with the current guidelines (Whelton *et al.*, 2018).

Continuous blood pressure and cardiac autonomics

Cardiac autonomic variables were measured using the Task Force® Monitor (TFM), which is a validated non-invasive beat-to-beat monitoring system providing automatic calculations of all outputs. Using the TFM, continuous sBP, mBP and dBP measures were acquired via the vascular unloading technique at the proximal limb of the index or middle finger, which was automatically corrected to oscilliometric BP values obtained at the brachial artery of the opposite arm.

Heart rate (HR) was recorded through a six-channel electrocardiogram and cardiac autonomic modulation was assessed by the oscillating fluctuations in the frequency and amplitude of each R-R interval using power spectral analysis and applying an autoregressive model (Akselrod *et al.*, 1981). Through the TFM's automatic QRS algorithm, high and low frequency parameters of heart rate variability were calculated and automatically expressed in both absolute (ms^2) and normalised units (nu) (Pan and Tompkins, 1985; Li, Zheng and Tai, 1995). All outcomes were acquired from a 5-minute recording period in the supine position as per recommended guidelines (Malik et al., 1996).

Baroreceptor reflex sensitivity was recorded via the sequence method which relies on the linear regression of continuous changes in sBP and the lengthening or shortening of the R-R interval (Taylor *et al.*, 2017). From all regressions, a mean slope of BRS was calculated and only sections with correlation coefficients of r >0.95 were analysed.

Isometric exercise training protocol

For the IET group, participants were required to complete a wall squat, consisting of resting their back against a fixed wall with their feet parallel, shoulder width apart, and their arms relaxed down by their side. As previously described (Goldring, Wiles, & Coleman, 2014; O'Driscoll, Taylor, Wiles, Coleman, & Sharma, 2017; Wiles, Allum, Coleman, & Swaine, 2008), peak HR was determined via an incremental isometric wall-squat test with beat-to-beat HR responses in accordance to the prescribed knee angle (Wiles et al., 2017). In line with previous evidence (Wiles et al., 2017), the intervention group were prescribed a 4-week IET programme at a knee joint angle predicted to elicit 95% peak HR. This intervention comprised of 4 x 2-minute bouts separated by 2-minute rest intervals, performed 3 times per week (12 IET sessions in total); ensuring a minimum of 48 hours recovery between each session. To ensure that participants were working at the desired intensity, each participant was instructed to monitor HR throughout each session using a Polar RS400 (Polar Electro Oy, Professorintie 5, FIN-90440 Kempele, Finland) HR monitor and report the HR data back to the researchers, in which the knee joint angle could be adjusted accordingly if required. Each participant used a 'bend and squat' device (made in-house), which was individually adjusted to govern the prescribed knee joint angle (Wiles et al., 2017).

For the sham group, participants performed the same incremental isometric wall squat test and parallel IET intervention. However, their training was prescribed at a knee joint angle, which would elicit an intensity of <75% peak HR so they did not achieve a sufficient physiological stimulus for BP adaptation to occur (Wiles et al., 2010). No-intervention control participants were required to perform pre- and post-measures, maintaining their normal routine and daily activities, which was confirmed prior to laboratory assessment.

Sample Size

Based on previous studies utilizing wall squat isometric exercise training for BP reduction, we expected the IET intervention to result in a decrease in resting sBP of at least 6 mmHg (Taylor et al., 2019; Wiles, Goldring, & Coleman, 2017) in the training group with no statistically significant change in the control group. This difference was considered to be clinically relevant. Using the likely changes and the coefficient of variation of sBP (4.6%) from Wiles, Coleman & Swaine (2010), we estimated a sample size of 10 participants, with 80% power, and P less than 0.05.

Statistical analysis

Before analysis, all data were checked for conformity with parametric assumptions. All data were analysed using SPSS (V22.0, release version for windows; Armonk, NY: IBM Corp) and presented as mean ± standard deviation. Comparison of data collected pre and post intervention between the IET, sham and no-intervention control groups were analysed using analysis of covariance (ANCOVA) with baseline parameters used as covariates to assess whether changes in BP and cardiac autonomic parameters following the intervention, sham and no-intervention control groups are influenced by initial baseline values. Statistical significance was deemed a priori as $p < 0.05$.

Results

All thirty participants completed the study with no adverse events reported. Resting clinic HR, BP, continuous beat to beat BP and cardiac autonomic variables were successfully acquired from all participants.

Resting clinic and continuous blood pressure

Participants in the IET group showed significant reductions in resting clinic sBP (-15±9 mmHg, p=0.003), mBP (-7±4, p=0.004) and dBP (-5±5, p=0.02), with no significant change in the sham (sBP -1±5 mmHg, p=0.98; mBP 0±4, p=0.72; and dBP 0±2, p=0.77) and no-intervention control (sBP 1±6 mmHg, p=0.98; mBP 1±4, p=0.72; and dBP 1±4, p=0.77) groups (Table 2). Similarly, participants in the IET intervention showed significant reductions in continuous sBP (-7±6 mmHg, p=0.001), mBP (-8±5 mmHg, p=0.03) and dBP (-5±5 mmHg, p=0.004), with no significant changes in the sham (sBP 0±4 mmHg, p=0.94; mBP -1±5, p=0.91; and dBP 0±4, p=0.49) and no-intervention control (sBP 0±3 mmHg, p=0.94; mBP -1±3, p=0.91; and dBP -1±3, p=0.49) groups (Table 2 and Figure 1). Figure 2 demonstrates the density distribution, mean and individual changes in continuous sBP, mBP and dBP following IET, control and sham conditions.

Cardiac autonomic modulation

There was a significant decrease in low frequency normalised units (-12±14%, p=0.01) parallel to a significant increase in high frequency normalised units (12±14%, p=0.01) in the IET group compared to both the sham (5±12%, p=0.98 and -5±12%, p=0.98) and no-intervention control (8±7%, p=0.98 and -8±7%, p=0.98) groups, for low frequency and high frequency respectively. There were no differences in total power spectral density, absolute high frequency, absolute low frequency HRV, LF/HF ratio, HR or BRS between IET, sham and no-intervention controls (Table 3).

Discussion

This study examined the efficacy of 4-weeks of IET on BP and cardiac autonomics in comparison to a sham and no-intervention control. In line with our research hypothesis, we found that a 4-week IET intervention significantly reduced resting clinic and continuous blood pressure measures compared to a 4-week sham intervention and no-intervention control group. These findings suggest that BP responses to IET are fundamentally intensity dependant, and that 75% HRpeak is an intensity insufficient to elicit such responses over this training period duration.

In line with previous research (Paz *et al.*, 2016), the observed reductions in both resting and continuous sBP, mBP and dBP following the 4-week IET intervention are clinically significant at a magnitude similar to that reported with anti-hypertensive pharmacotherapy (Law, Morris and Wald, 2009). Importantly, such results are associated with statistically significant reductions in risk of cardiovascular disease and mortality; providing further support for the clinical utility of IET in BP management (Ettehad *et al.*, 2016; Brunström and Carlberg, 2018).

An important aspect of the current study was the inclusion of the sham control, which allowed us to delineate the specific and non-specific effects of the intervention. Recent evidence has shown that many exercise and blood pressure interventions can be influenced through non-specific effects, such as the placebo effect (Lindheimer, O'Connor and Dishman, 2015; Hurst *et al.*, 2019) and regression to the mean (Moore *et al.*, 2019), which may overestimate the true effect of an intervention (Beedie *et al.*, 2018). Participants in the sham control group performed the IET intervention at 75% HRpeak for 4-weeks and reported no differences in any outcome variables when compared to participants in the no-treatment control; whilst differences were observed for participants who completed 4-weeks of IET. These results support previous findings of the inefficacy of a 4-week IET at 75% HRpeak (Wiles et al., 2017; Wiles et al., 2010) and indicate its function as an appropriate sham control when used with this amount and duration of IET.

The significant BP reductions reported in the IET group compared to both sham and no-intervention control groups suggest that the BP lowering effects of IET is directly attributable to physiological adaptations due to the specific physical training stimulus resulting from exceeding a threshold intensity of IE. Specifically, as supported in previous research (Goldring et al., 2014; O'Driscoll et al., 2017; Wiles et al., 2008), our data support adaptations in cardiac autonomic modulation as an important mechanistic pathway. Although debated (Goldstein *et al.*, 2011), it is generally accepted that the low frequency component of HRV primarily represents sympathetic activity and high frequency predominantly represents parasympathetic outflow (Shaffer and Ginsberg, 2017). As such, the findings of this paper suggest an increase in cardiac vagal control with a decrease in sympathetic tone as a mechanistic pathway for the observed reduction in BP following IET (Prakash *et al.*, 2005; Taylor *et al.*, 2019). However, the changes in LF/HF ratio were not statistically significant and thus do not directly support this concept.

No significant differences in resting HR or BRS between IET, sham and no-intervention control suggest that other mechanisms are responsible for the observed reductions in BP. However, previous research has demonstrated that BRS may be a significant mechanistic pathway for the observed BP reductions (Taylor *et al.*, 2017, 2019; O'Driscoll *et al.*, 2021). It is therefore likely that the present work was underpowered to detect significant changes in BRS.

Before exercise interventions can be adopted by society, it important that researchers use appropriate controls when evaluating their efficacy. However, a fundamental challenge in establishing efficacy is the development of appropriate sham controls that are indistinguishable from the true intervention and have no clinical benefit (Beedie *et al.*, 2018; Hurst *et al.*, 2019). In this study we provide evidence that 4-weeks of IET at 75% HRpeak can be used as a valid sham control for research investigating the efficacy of 4-weeks of IET at 95%HRpeak. Research examining the efficacy of IET should adopt similar sham controls to improve accuracy of results. If these are not included, effects may be overestimated and owing to non-specific factors, such as the placebo effect, which has been shown to significantly affect the outcome of exercise interventions (Lindheimer, O'Connor and Dishman, 2015; Hurst *et al.*, 2019). We therefore suggest that researchers investigating IET include sham controls in study design to make more accurate inferences about its efficacy.

Limitations and future research

It is important to consider the limitations of this study. First, the sample size is small and underpowered. However, it should be noted that this study is one of the first to show support for the efficacy of an IET sham intervention. A larger randomised sham-controlled study should be performed in future, with measures of central (e.g., cardiac functional and mechanical responses) and peripheral (e.g., vascular function) parameters, to further ascertain a mechanistic adaptation for BP reduction. Second, baseline BP in the IET group were higher than both sham and no-intervention control groups. Previous research has identified greater reductions in BP for those with higher baseline BP, thus potentially exaggerating our observed reductions in the IET group (Cornelissen and Smart, 2013; Hu *et al.*, 2017). However, it was a randomised control study, and there were no significant baseline differences in continuous blood pressure measures between the groups. Thus, future research should aim to recruit a sample with more homogenous baseline characteristics. Furthermore, we sampled a healthy cohort with normal to high-normal baseline BP and the relative application of our findings to diseased and hypertensive populations is unknown. While the safety of this IET protocol has previously been investigated in stage 1 hypertensives (Wiles *et al.*, 2018), these findings do not extend to those with stage 2 hypertension and beyond. Researchers should consider replicating the results of our study on hypertensive participants. Finally, for a more rigorous sham design, future research should include a manipulation check and assess whether the participants in the sham group expected the intervention to be effective.

Conclusion

This randomised, between participant, sham-controlled study supports the role of IET as an effective anti-hypertensive intervention. We found that BP and cardiac autonomic modulation improved following 4-weeks of IET at 95%HRpeak than sham and no-intervention control groups. These findings suggest that the effects of IET are the result of the intervention and are not to other non-specific factors, such as the placebo effect. These results further support that IET produces clinically relevant reductions in both resting and continuous BP. Future research sampling a larger, hypertensive population is needed.

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Table 1: Participant physical characteristics of the IET, control and sham groups

Parameter	IET	Control	Sham
Age (years)	31.4 ± 6	28.3 ± 5.6	29.4 ± 7.8
Height (cm)	172 ± 11	170 ± 8.2	170 ± 8
Weight (kg)	83.7 ± 24	84.9 ± 21.7	79 ± 18
BMI (kg·m^2)	28.2 ± 7.8	29 ± 6.2	27.7 ± 5.8

Note: IET = isometric exercise training; BMI = body mass index.

Table 2: Resting blood pressure pre and post isometric exercise training, control and sham conditions.

Parameter	IET (n=10)		Control (n=10)		Sham (n=10)	
	Pre	Post	Pre	Post	Pre	Post
Clinic sBP (mmHg)	131±6	116±6*	119±9	120±7	120±8	119±8
Clinic mBP (mmHg)	97±5	90±5*	89±5	90±6	87±2	89±4
Clinic dBP (mmHg)	80±6	75±7*	73±6	74±8	71±6	71±6
Continuous sBP (mmHg)	117±9	110±13*	110±9	110±9	114±4	114±4
Continuous mBP (mmHg)	93±8	85±10*	84±8	83±8	87±5	86±4
Continuous dBP (mmHg)	65±11	61±11*	66±9	66±9	69±6	69±4

Note: IET = isometric exercise training; sBP = systolic blood pressure; mBP = mean blood pressure; dBP = diastolic blood pressure * = $p<0.05$.

Table 3: Cardiac autonomic parameters pre and post isometric exercise training, control and sham conditions.

Parameter	IET (n=10)		Control (n=10)		Sham (n=10)	
	Pre	Post	Pre	Post	Pre	Post
Heart rate (b·min^{-1})	68±12	67±10	70±8	67±10	78±13	80±13
PSD (ms^2)	2332±1804	2974±2916	2604±2824	2696±2199	2591±2319	2686±2901
LF (ms^2)	1109±960	918±637	883±731	1029±563	1000±665	1195±1053
HF (ms^2)	933±1057	1702±2177	1227±1528	1114±1421	1029±1120	1196±1763
LF/HF ratio	1.52±0.58	1.11±0.62	1.22±0.6	1.58±0.75	1.41±0.68	1.72±1.02
LFnu (%)	60.1±16	48.4±18*	51.3±13	59±16	55.1±13	60.5±16
HFnu (%)	39.9±16	51.6±18*	48.7±13	41±16	44.9±13	39.5±16
BRS (ms·mmHg^{-1})	22.9±12	26.3±16	19.1±7	19.2±6	23.4±11	21.4±13

Note: PSD = power spectral density; LF = low frequency; HF = high frequency; LF/HF ratio = low frequency to high frequency ratio; LFnu = normalised units low frequency; HFnu = normalised units high frequency; BRS = power spectral density; * = $p<0.05$.

Figure legends

Figure 1: Mean continuous systolic (A), mean (B) and diastolic (C) blood pressure change values for the isometric exercise training group (open circles), no intervention control group (closed circles) and sham group (arrows). Note: Error bars indicate standard error of the mean; * = $p<0.05$ between the isometric exercise training group and both control and sham condition.

Figure 2: Illustrates the density distribution, average and individual delta change in continuous systolic (A), mean (B) and diastolic (C) blood pressure following isometric exercise training, control and sham groups.