Continuous cardiac autonomic and haemodynamic responses to isometric exercise in females

O'Driscoll, J., Boucher, C., Vilda, M., Taylor, K. and Wiles, J.

Continuous Cardiac Autonomic and Haemodynamic Responses to Isometric Exercise in Females

Jamie M. O'Driscoll, PhD; Claire Boucher, BSc; Meliz Vilda, MSc; Katrina A. Taylor, PhD; Jonathan D. Wiles, PhD.

Author Affiliations:

[1] School of Human and Life Sciences, Canterbury Christ Church University, Kent, CT1 1QU

Corresponding Author: Correspondence to Dr Jamie O'Driscoll, School of Human and Life Sciences, Canterbury Christ Church University, Kent, CT1 1QU. Email: jamie.odriscoll@canterbury.ac.uk; Telephone: 01227 782711

Running Title: Isometric exercise in Females

Key words: Baroreceptor reflex sensitivity, Blood pressure, Heart rate variability.

Abstract

Purpose: Hypertension is associated with impaired haemodynamic control mechanisms and autonomic dysfunction. Isometric exercise (IE) interventions have been shown to improve autonomic modulation and reduce blood pressure (BP) in predominantly male participants. The physiological responses to IE are under explored in female populations; therefore, this study investigated the continuous cardiac autonomic and haemodynamic response to a single bout of IE in a large female population.

Methods: Forty physically inactive females performed a single, individually prescribed isometric wall squat training session. Total power spectral density of heart rate variability (HRV) and associated low frequency (LF) and high-frequency (HF) power spectral components, were recorded in absolute (ms2) and normalised units (nu) pre, during and post an IE session. Heart rate (HR) was recorded via electrocardiography and baroreceptor reflex sensitivity (BRS) via the sequence method. Continuous blood pressure was recorded via the vascular unloading technique and stroke volume via impedance cardiography. Total peripheral resistance (TPR) was calculated according to Ohm's Law.

Results: During IE, there were significant reductions in HRV (p<0.001) and BRS (p<0.001), and significant increases in heart rate (p<0.001), systolic, mean and diastolic BP (p<0.001 for all). In recovery following the IE session, cardiac autonomic parameters returned to baseline (p=0.974); however, total peripheral vascular resistance significantly reduced below baseline (p<0.001). This peripheral vascular response was associated with significant reductions in systolic (-17.3±16.5 mmHg, p<0.001), mean (-18.8±17.4 mmHg, p<0.001) and diastolic BP (-17.3±16.2 mmHg, p<0.001), below baseline.

Conclusion: A single IE session is associated with improved haemodynamic cardiovascular responses in females. Cardiac autonomic responses return to baseline values, which suggests alternative mechanisms are responsible for the post exercise haemodynamic improvements in females. Future mechanistic research is required to investigate the acute and chronic effects of IE in female populations with different resting BP profiles.

Abbreviations

BEI – Baroreceptor effectiveness index

BP – Blood pressure

BRS – Baroreceptor reflex sensitivity

DBP – Diastolic blood pressure

HF – High frequency

HR – Heart rate

HRV – Heart rate variability

IE – Isometric exercise

IET – Isometric exercise training

LF – Low frequency

MBP – Mean blood pressure

$\dot{Q}$ - Cardiac output

SBP – Systolic blood pressure

SV – Stroke volume

TPR – Total peripheral resistance

Introduction

Hypertension is a leading modifiable risk factor for cardiovascular disease. International guidelines encourage the use of non-pharmacological interventions, including regular engagement in physical activity to maintain optimal blood pressure (BP). Research supports the use of isometric exercise training (IET) for the treatment of elevated blood pressure (Taylor et al. 2018) and one meta-analysis research has reported that IET elicits greater BP reductions in comparison to traditional aerobic exercise training (Cornelissen and Smart 2013).

Immediate post exercise hypotension has been demonstrated following isometric exercise (IE), in populations with and without elevated BP (Peters et al. 2006). Existing literature suggests that central and peripheral mechanisms are important contributing factors to a reduction in mean arterial pressure, via altered modulation of cardiac output ($\dot{Q}$) and/or total peripheral resistance (TPR) (Millar et al. 2014).

Mechanisms associated with improved BP following IE have been demonstrated through alterations in cardiac autonomic control, evidenced by a relative parasympathetic over sympathetic dominance (Taylor et al. 2017). In addition, acute improvements in cardiac function and left ventricular systolic and diastolic mechanics have been demonstrated following IE (O'Driscoll et al. 2017). Peripheral responses following IE include reductions in total peripheral vascular resistance (Taylor et al. 2017), which may be the result of purinergic signalling (Burnstock 2009), endothelium-derived hyperpolarizing factor (Sandow 2004), increased nitric oxide synthesis in response to increased shear stress (Tinken et al. 2010),

cyclic guanosine monophosphate, β-2 adrenergic receptor activation (Fassini et al. 2015) and/or histamine (H_1 and H_2) receptor activation.

Another important mechanism reported following IE is improved baroreceptor reflex control. The baroreflex is a negative feedback control system involved in regulating BP. Baroreceptors continuously relay information to the brainstem regarding beat-to-beat changes in BP and provide information to modulate heart rate and/or peripheral vascular resistance in order to maintain BP homeostasis. Early research demonstrates that during the post-exercise recovery phase of IE, the arterial baroreflex initiates the process of HR recovery (Iellamo et al. 1999). A recent study reported a 16-fold increase in baroreceptor reflex sensitivity (BRS) following an acute bout of lower limb IE in men (Taylor et al. 2017). More recently, Teixeira et al. (2018) also demonstrated that following acute isometric handgrip exercise, BRS and cardiac vagal activity increase in healthy individuals; however, the magnitude and time course of changes were different between men and women. Based upon this finding, it is feasible to suggest that there may be differences between sexes in relation to autonomic and haemodynamic responses to IE and possibly the mechanisms underpinning any chronic adaptations in resting blood pressure following IET.

Prior IET studies have demonstrated that the BP reductions are similar between hand grip and lower limb IE; however, lower limb IE is typically performed at a lower relative exercise intensity potentially increasing its effectiveness as an IE intervention. Therefore, the aim of this study was to investigate the transient cardiac autonomic and haemodynamic responses, measured continuously before, during and immediately after a single lower limb IE session in females.

Methods

Study population

Forty physically inactive (less than 150 minutes of moderate-intensity or 75 min of vigorous-intensity physical activity, or an equivalent combination, per week) (World Health Organization, 2010) females were recruited to participate in the study (age 30 ± 8.9 years, height 165 ± 4.7 cm, weight 75 ± 19.3 kg). Resting BP was normal in 27 participants, elevated in 6 participants and 7 participants were stage 1 hypertensive (Whelton et al. 2017). Based on body mass index (27 ± 7 $kg \cdot m^2$ for the population), 14 participants had a normal BMI, 19 were classified as overweight and 7 were classified as obese (World Health Organization, 1995). All participants reported no prior cardiovascular disease, were non-medicated, non-smokers and free from injury and no participant was pregnant. All participants reported an alcohol intake less than 14 units per week, which is within recommendations to keep health risks from alcohol low (Department of Health, 2016).

Participants were required to attend the laboratory on three separate occasions, abstain from food for at least 4 h before each laboratory visit, caffeine or alcohol for 24 h before each visit, and lastly, avoid strenuous exercise 24 h before each session. During the first visit, a seated resting BP was recorded and each participant completed an isometric wall squat test to establish their personalised exercise intensity (Taylor et al. 2017; Wiles et al. 2017). The second visit took place a minimum of 48 hours after the first visit and participants were familiarised with the isometric wall squat exercise session. Data collection for the present study was conducted on the third laboratory visit, which was performed 48-hours after the second visit. The study was approved by the Canterbury Christ Church University Ethics

Committee and all procedures were performed in line with the 1964 Declaration of Helsinki. All participants provided signed informed consent before testing.

Isometric Exercise Session

Participants exercised at a prescribed isometric wall squat knee joint angle (117° ± 17), based on HR and BP responses to an incremental isometric wall squat test performed during their first laboratory visit (see, Taylor *et al*., 2017, Wiles *et al*., 2017, and Supplementary file for details).

During the laboratory based IE session, a clinical goniometer (MIE Medical Research, Leeds, UK) was used to ensure the desired knee joint angle was achieved and maintained (Goldring et al. 2014). Participants performed a total of four, 2-minute wall squats, each interval separated by 2-minutes rest (See figure 1). HR and BP were monitored during the IE session to ensure they remained within safe exercising limits defined by the American College of Sports Medicine (Riebe 2018). Verbal encouragement was given and participants were informed of the elapsed time. Participants were reminded to breathe normally throughout the exercise to avoid performing a Valsalva manoeuvre.

Autonomic and Haemodynamic Assessment

All testing was conducted in a controlled laboratory environment. Upon arrival at the laboratory, BP was measured (Carescape V100, GE Healthcare, United Kingdom) according to current guidelines (Whelton et al. 2017). A SECA 213 stadiometer was used to measure

height and weight was measured using SECA 700 mechanical collumn scales (SECA gmbh & co, Germany).

The Task Force® Monitor is a validated non-invasive monitoring system (Fortin et al. 2001), which was used for the continuous beat-to-beat monitoring and automatic online calculation of all cardiac autonomic and haemodynamic parameters. Indices of 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. As detailed previously, the Task Force® Monitor uses an online QRS detector algorithm to determine HRV indices of cardiac autonomic function. The algorithm enables the QRS complex to be distinguished from high P or T waves, noise, baseline drift and artefacts. ECG traces were also manually screened to confirm traces were clear of any erroneous data. High (predominantly parasympathetic modulation) and low (predominantly sympathetic modulation) (Akselrod et al. 1981) frequency parameters of heart rate variability (HRV) were automatically calculated by the Task Force® Monitor and expressed in absolute (ms^2) and normalised units (nu). The ratio of low to high frequency HRV is an accepted measure of cardiac sympathovagal balance (Ditor et al. 2005). Spontaneous BRS was automatically evaluated via the sequence method, based on computer identification of a series of successive increases or decreases in systolic BP (sBP) and lengthening or shortening of the R-R interval (Valipour et al. 2005). Linear regression of increments or decrements in sBP and R-R interval were computed, with only episodes with correlation coefficient of $r>0.95$ selected. From all regressions, a mean slope of BRS is calculated for each period. The baroreceptor effectiveness index (BEI), which is defined as the ratio between the number of sBP ramps followed by the reflex pulse interval ramps and the total number of sBP ramps observed in a

given time, was used to quantify the BRS effectivness in mediating changes in HR in response to spontaneous BP changes (Di Rienzo et al. 2001).

Continuous measurement of BP (sBP, mean [mBP] and diastolic [dBP]) was recorded by use of the vascular unloading technique at the proximal limb of the index or middle finger, which was automatically corrected to oscillometric BP values obtained at the brachial artery of the contralateral arm. HR was recorded through a 6-channel electrocardiogram and beat-to-beat stroke volume (SV) was measured with impedance cardiography via one electrode band applied to the nape of the neck and two placed either side of the thorax in line with the xiphoid process. Cardiac output ($\dot{Q}$) was calculated as the product of HR and SV, rate pressure product as the product of HR and sBP, and total peripheral resistance (TPR) was calculated according to Ohm's law. Following 15 minutes of supine rest, baseline autonomic and haemodynamic function were recorded continuously for 5 minutes. All measures were then recorded continuously throughout each 2-minute interval of IE. Autonomic and haemodynamic paramaters were then recorded during a 5-minute recovery period in the supine position immediately following the IE session.

Intervention marks enable the separation of the cumulative data into independent stages of the IE session. Intervention marks were set at baseline, at each 2-minute exercise period and in recovery. All biological signals were recorded with a sample frequency of 1000Hz and 16-bit resolution.

Statistics

Unless otherwise stated, continuous variables are expressed as mean ± standard deviation. All data were analysed using the statistical package for social sciences (SPSS 22 release version for Windows; SPSS Inc., Chicago IL, USA). A one-way repeated measures analysis of variance was performed, followed by Bonferroni post hoc tests for multiple comparisons. An alpha level of $p<0.05$ was regarded as statistically significant.

Results

All participants completed the full IE session at their prescribed knee joint angle (training intensity), determined in the first visit to the laboratory. Baseline demographic information is shown in Table 1.

Cardiac Autonomic Response

Heart Rate Variability

Indices of cardiac autonomic function at baseline, during each period of IE and in the recovery phase, are shown in Figure 2. IE produced a significant stepwise reduction in R-R power spectral density from baseline (3773.8 ± 540.4) to IE1 (2114.8 ± 304.8, $P<0.05$), IE2 (1193.4 ± 178.2, $P<0.001$), IE3 (901.4 ± 209.1, $P<0.001$) and IE4 (709.9 ± 126.4, $P<0.001$), followed by a significant increase in R-R power spectral density from IE4 to recovery (2794.8 ± 600.0, $P<0.05$) (Figure 2A).

Frequency Domain Analysis

Absolute HF (ms^2) and LF (ms^2) HRV data are shown in Table 2. All frequencies decreased significantly between baseline and IE2, IE3 and IE4 ($P<0.05$) and then increased significantly after IE4 into recovery ($P=0.001$). When analysing HRV in normalized units, LFnu increased significantly ($P=0.001$) during the first interval of IE and remained above baseline during all four bouts of IE (46.8% ± 2.1% to 67.2% ± 2.2%). There was a significant decrease in LFnu during the recovery period (68.0% ± 2.3% to 48.3% ± 2.3%, $P<0.001$). Since LFnu and

HFnu are interdependent and inherently reciprocal, an inverse response was recorded in HFnu (see Figure 2B). The low to high frequency ratio increased during the first interval of IE and remained above baseline throughout the IE session. Following this, there was a significant reduction (3.600 ± 0.410 to 1.100 ± 0.100, $P<0.001$) from IE4 into the recovery phase (see Figure 2C).

Baroreceptor Reflex

BRS decreased significantly ($P<0.001$) between baseline and all four IE intervals. During the recovery phase, BRS increased significantly from IE4 to recovery ($P<0.001$; Table 2). Similarly, the BEI decreased significantly ($P<0.001$) between baseline and all four IE intervals, and increased significantly from IE4 to recovery ($P<0.001$; Figure 2D). There were no significant differences between baseline and recovery for BRS or BEI ($P=1$ for both).

Haemodynamic response

Haemodynamic parameters at baseline, during each period of IE and in the recovery phase are reported in Table 2 and Figure 3.

Blood Pressure

At the onset of IE, there was a significant increase in sBP from baseline to IE1 (114 ± 23.4 to 151 ± 26 mmHg), followed by a plateau from IE1 (151 ± 26 mmHg) to IE2 (150 ± 28.2 mmHg) IE3 (151 ± 26.1 mmHg) and IE4 (147 ± 25.2 mmHg) ($P<0.001$ for all compared to baseline). In recovery, there was a significant reduction in sBP (96.8 ± 15 mmHg, $P<0.001$),

which was significantly lower than baseline sBP (P=0.001). A similar increase was noted in dBP from baseline to each phase of the IE session (69 ± 20 to 102 ± 21 mmHg, P<0.001), followed by a significant reduction in dBP from IE4 into the recovery phase (93.4 ± 17 to 51.7 ± 9 mmHg, P<0.001) which was significantly below baseline (P<0.001). The mBP response during the IE session demonstrated a similar pattern to sBP and dBP, in which there was a reduction in mBP during the recovery phase, which was significantly lower than baseline (87 ± 15.9 to 68.2 ± 13.5 mmHg, P<0.001) (see Figure 3A).

Heart Rate

HR (Figure 3B) demonstrated a significant stepwise increase at the onset of IE, from baseline to IE1 (69 ± 16 to 104 ± 15 b·min^{-1}), to IE2 (110 ± 17.5 b·min^{-1}) to IE3 (115 ± 19.1 b·min^{-1}) and IE4 (119 ± 20.1 b·min^{-1}) (P<0.001 for all compared to baseline), followed by a significant reduction in HR from IE4 into recovery (119 ± 20.1 to 71 ± 11.3 b·min^{-1}, P<0.001). There was no significant difference between baseline and recovery HR (P=0.711).

Rate Pressure Product

As a consequence of the HR and sBP responses, there was a significant increase in rate pressure product from baseline through all IE intervals (P<0.001), followed by a significant decrease in rate pressure product from IE4 into recovery (P<0.001) (Figure 3B). There was no significant difference between baseline and recovery rate pressure product (P=0.184).

Total Peripheral Vascular Resistance

TPR (Figure 3C) demonstrated a significant increase during the onset of IE, from IE1 to IE2 (1062 ± 309 to 1471 ± 449 dyne·s·cm^5, P<0.001) followed by a stepwise decrease during the remaining IE intervals, from IE3 (1066 ± 295.1 dyne·s·cm^5) to IE4 (956 ± 287.4 dyne·s·cm^5). In recovery, TPR was significantly lower compared to baseline measures (P<0.001).

Stroke Volume

SV (Figure 3D) demonstrated a significant (P<0.001) decrease at the onset of IE, from baseline to IE1 (99.7 ± 23 to 80.7 ± 16 ml·min^{-1}, P<0.001) and plateaued through to IE4. In recovery, SV significantly increased from IE4 into recovery (79.4 ± 15 to 112.7 ± 23 ml·min^{-1}, P<0.001) and this increase was significantly greater compared baseline (P=0.005).

Cardiac Output

$\dot{Q}$ demonstrated a stepwise increase from baseline and at each exercise interval (P<0.05 for all), mediated by an increase in HR. During the recovery phase, there was a significant reduction in $\dot{Q}$ from IE4 (P<0.029). There was no significant difference between baseline and recovery $\dot{Q}$ (P=0.114).

Discussion

This study explored the acute continuous cardiac autonomic and haemodynamic regulatory responses following a single bout of IE in a female population. At the onset of IE, there was a stepwise reduction in the total power spectrum of HRV with a greater proportion of the frequency domain within the LF (ms^2) band, which suggests a relative increase in sympathetic activity. This sympathetic response is supported by the stepwise increase in LFnu, reciprocal decrease in HFnu and alteration in the low to high frequency ratio, which has been shown to represent alterations in sympathovagal balance, during IE. Previous research in men and/or using isometric hand grip has reported similar responses (Millar et al. 2009; Taylor et al. 2017; Teixeira et al. 2018).

During the recovery phase, the results demonstrated a significant increase in HRV, restoring baseline readings, with a predominant increase in the HF (ms^2) domain, supporting a relative parasympathetic dominance. The authors acknowledge that although HF (ms^2) is considered a reliable index of relative parasympathetic influence, it is prone to sympathetic antagonism of the parasympathetic branch (Cohen & Taylor 2002; Taylor 2001). Teixeira et al. (2018) demonstrated that the HRV response in recovery following isometric hand grip training is greater in males compared to females. Indeed, compared to the current study, males experienced an increase in HRV above baseline readings following wall squat IE (Taylor et al. 2017). The mechanism(s) responsible for this warrant's further investigation; however, it is thought that men experience a larger BRS pressor response during an isometric contraction in comparison to women (Jarvis 2011). Indeed, our results support this concept, since males experienced a 16-fold increase in BRS immediately following IE (Taylor et al. 2017) compared to the 3.6-fold increase in this study. Nonetheless, this increase in BRS was

298 associated with reductions in BP following IE, and a similar association has been reported
299 following a 4-week IET intervention (Taylor et al. 2018). The decrease in BEI complemented
300 the BRS response during IE, yet in recovery the BEI significantly increased from IE4 to
301 above baseline values. Research has reported that the BEI maybe a more sensitive measure of
302 altered autonomic modulation (Watso 2017). As such, the implications of this finding warrant
303 further investigation. However, Teixeira et al. (2018), demonstrated significant increases in
304 BRS independent of acute reductions in arterial BP following isometric hand grip training.
305 Despite this finding, there are differences in the populations studied, where in Teixeira et al
306 (2018) study, all participants had optimal BP (113 ± 2 mmHg and 100 ± 1 mmHg, for male
307 and female participants, respectively) and they performed IE using handgrip. In addition,
308 Iellamo (2001) stated that the BRS and the muscle metaboreflex may be differently
309 modulated in relation to the muscle activity being performed, including type, intensity, and
310 size of active muscle mass.
311
312 Previous research findings have argued that changes in LF (ms^2) reflect baroreflex
313 modulation as opposed to an index of cardiac sympathetic tone (Billman 2013; Goldstein et
314 al. 2011; Notarius & Floras 2001; Rahman et al. 2011). Our results may support these
315 findings, since during IE, LF (ms^2), BRS and BEI demonstrated a stepwise decrease,
316 followed by an increase in recovery. Indeed, 4-weeks of IET (Taylor et al. 2018) produced an
317 increase in LF (ms^2) and significant increase in BRS (as well as total HRV and HF (ms^2)),
318 which may further support this association. However, Teixeira et al (2018) results do not
319 support an association of LF (ms^2) and BRS following handgrip IE. Future work investigating
320 the acute and chronic autonomic nervous system responses to IE, may benefit from invasive
321 measures, such as microneurography combined with HRV analysis.

This study demonstrated that IE elicits an initial increase in BP from baseline to the first IE bout, followed by a plateau in the remaining three IE bouts. It can be seen that this is associated with a significant rise in TPR during the first IE bout. Following this, TPR gradually decreased in the remaining exercise bouts, through to recovery, which was significantly lower than baseline. Similar findings have been reported in males (Taylor et al. 2017) and the authors suggest that an initial rise in BP at the onset of IE may be due to a conjoint increase in both $\dot{Q}$ and TPR. However, whilst Taylor et al., (Taylor et al. 2017) identified a continued rise in BP for the remaining IE intervals; the current study demonstrated a plateau in BP despite a reduction in TPR. Previous literature suggests that this may be explained by the differences in female body size and structure in comparison to males (Wheatley 2014).

In recovery, there was a significant reduction in BP (15.1% [-17.3 ± 16.5 mm Hg], 21.6% [-18.8 ± 17.4 mm Hg] and 25.1% [-17.3 ± 16.2 mm Hg] for sBP, mBP and dBP, respectively) in comparison to baseline readings. If these acute reductions in BP represent the chronic adaptations following a programme of lower limb IET in females, this response may be clinically important. As mean arterial pressure is determined by HR, SV ($\dot{Q}$) and TPR, any reduction in resting BP is likely to be moderated by either of these variables (Pescatello 2004). Baroreceptors are vital in the short-term regulation of BP via alterations to $\dot{Q}$ and TPR, regulated by the SNS and the renin-angiotensin-aldosterone system (Guyton 1972). Any short-term changes in mean arterial pressure initiate the baroreceptor reflex mechanism, which directly effects the heart and blood vessels and thus influence $\dot{Q}$ and TPR (Chopra 2011). Therefore, during IE, it has been reported that the baroreflex control of HR and BP are said to be reset simultaneously (Gallagher 2006) by central command (Ogoh 2002) and the exercise pressor reflex (Smith 2003). However, it has been suggested that the magnitude of

BRS gain is dependent upon the intensity and duration of the IE (Franke 2000). The carotid sinus and aortic arch baroreceptors are particularly sensitive to beat-to-beat changes in systemic BP (Bristow 1969), and tonically regulate chronotropy through modulation (withdrawal or enhancement) of parasympathetic tone (Guyton 1972), that allow increases or provoke declines in HR, and are essential in sending information to the brain and the rest of the body (Chopra 2011). In order to maintain homeostasis, HR (cardiac baroreflex) or peripheral vascular outflow (sympathetic baroreflex) (Fadel 2008) is modulated. Any reductions in TPR during the IE bouts indicate arterial dilation, which may be the predominant mechanism for the acute BP reductions following IE in females.

Limitations

This study revealed changes in physiological variables applicable to physically inactive females, and as such, these findings cannot be generalised to other populations. Although a control group was not used in this study, which may be seen as a limitation, the resting BP measurements are shown to be accurate and reliable in our laboratory. Therefore, it is with great certainty, that any changes in BP during the exercise protocol are attributed to IE. However, any possible changes that may occur after the 5-minute rest period were not measured; therefore, the duration of the post exercise hypotension remains unclear. Further research is required to explore additional time points to determine if there is a prolonged effect of IE on BP control in female participants.

It is also necessary to note that HRV and BRS analysis used in the current study are non-invasive measures, which have been widely used in the clinical setting in both healthy and diseased individuals (Kamath 1993; Vanderlei 2009). In addition, guidelines recommend

HRV measurements are taken over a minimum duration of 5-minutes (Marek et al. 1996). However, conventional IE training methodology dictates 2-minute contractions. As such, all IE parameters are reported as mean responses from a 2-minute period, which has been performed previously (Taylor et al. 2017).

Clinical applications

Hypertension accelerates the development of atherosclerosis, reduces myocardial efficiency and increases peripheral vascular dysfunction, which all contribute to reduced haemodynamic cardiovascular control. Autonomic dysfunction is an independent predictor of all-cause mortality (Schroeder 2003), whilst increased BRS has been associated with cardioprotective mechanisms (La Rovere 2008). In addition, endothelial dysfunction is widely reported in individuals with HTN (Phillips 2015) and is associated with decreased vasodilatory capacity (Pescatello 2010). Our findings indicate that a single session of IE (composed of 4 x 2-minute bouts) elicits significant post exercise hypotension, which may be due to improved vascular function, which is evidenced by a significant reduction in TPR both during and post IE.

Conclusion

A single session of IE was associated with improved haemodynamic cardiovascular responses in a physically inactive female population. However, the cardiac autonomic responses return to baseline values, which suggests alternative mechanisms are responsible for the post exercise haemodynamic improvements in females. Peripheral vascular responses may be an important mechanism for attenuating BP post exercise and further research is

required to ascertain if these acute responses translate into chronic adaptations in female populations with different baseline BP profiles.

Acknowledgements: None

Grants: None

Conflicts of Interest: No conflicts of interest, financial or otherwise, are declared by the author(s).

Author Contributions

J.O'D, C.B, M.V., K.A.T, and J.D.W conception and design of research; J.O'D, C.B, M.V., and K.A.T performed experiments; J.O'D, C.B, M.V., and K.A.T. analysed data; J.O'D, C.B, M.V., K.A.T, and J.D.W. interpreted results of experiments; J.O'D prepared figures; J.O'D, C.B, M.V., K.A.T, and J.D.W. drafted manuscript; J.O'D, C.B, M.V., K.A.T, and J.D.W. edited and revised manuscript; J.O'D, C.B, M.V., K.A.T, and J.D.W. approved final version of manuscript.

References

Akselrod S, Gordon D, Ubel F, Shannon D, Berger A, Cohen R (1981) Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 213 (4504):220-222.

Billman GE (2013). The LF/HF ratio does not accurately measure cardiac sympatho-vagal balance. Front Physiol, 4, 26.

Bristow JD, Brown JE, Cunningham DJ, Goode RC, Howson MG, Pickering TG, Sleight P (1969) Changes in Baroreflex Sensitivity at the Transitions Between Rest and Exercise. J Physiol 202:84-85.

Burnstock G (2009) Purinergic regulation of vascular tone and remodelling. Auton Autacoid Pharmacol 29 (3):63-72.

Chopra S, Baby C, Jacob JJ (2011) Neuro-endocrine regulation of blood pressure. Indian J Endocrinol Metab 15:S281-S288.

Cohen MA, Taylor JA (2002). Short-term cardiovascular oscillations in man: Measuring and modelling the physiologies. J Physiol, 542:669-683.

Cornelissen VA, Smart NA (2013) Exercise training for blood pressure: a systematic review and meta-analysis. J Am Heart Assoc 2 (1):e004473.

Di Rienzo M, Parati G, Castiglioni P, Tordi R, Mancia G, Pedotti A (2001) Baroreflex effectiveness index: an additional measure of baroreflex control of heart rate in daily life. Am J Physiol Regul Integr Comp Physiol 280 (3):R744-751.

443 Ditor DS, Kamath MV, MacDonald MJ, Bugaresti J, McCartney N, Hicks AL (2005) Effects
444 of body weight-supported treadmill training on heart rate variability and blood
445 pressure variability in individuals with spinal cord injury. J Appl Physiol 98 (4):1519-
446 1525.

447 Fadel PJ (2008) Arterial baroreflex control of the peripheral vasculature in humans: rest and
448 exercise. Med Sci Sports Exer 40:2055-2062.

449 Fassini A, Antero LS, Correa FM, Joca SR, Resstel LB (2015). The prelimbic cortex
450 muscarinic M(3) receptor-nitric oxide-guanylyl cyclase pathway modulates
451 cardiovascular responses in rats. J Neurosci Res, 93:830-838.

452 Fortin J, Haitchi G, Bojic A, Habenbacher W, Grullenberger R, Heller A, Pacher R, Wach P,
453 Skrabal F (2001) Validation and Verification of the Task Force Monitor® Results of
454 Clinical Studies for F DA 510(k) n°: K014063:1-7

455 Franke WD, Boettger, C.F., McLean, S.P. (2000) Effects of varying central command and
456 muscle mass on the cardiovascular responses to isometric exercise. Clin Physiol
457 20:380-387.

458 Gallagher KM, Fadel, P.J., Smith, S.A., Strømstad, M., Ide, K., Secher, N.H., Raven, P.B.
459 (2006) The Interaction of Central Command and the Exercise Pressor Reflex in
460 Mediating Baroreflex Resetting during Exercise in Humans. Exp Physiol 91:79-87.

461 Goldring N, Wiles JD, Coleman D (2014) The effects of isometric wall squat exercise on
462 heart rate and blood pressure in a normotensive population. J Sports Sci 32 (2):129-
463 136.

Goldstein DS, Bentho O, Park MY, Sharabi Y (2011) Low-frequency power of heart rate variability is not a measure of cardiac sympathetic tone but may be a measure of modulation of cardiac autonomic outflows by baroreflexes. Exp Physiol, 96:1255-1261.

Guyton AC, Coleman, T.G, Cowley, A.W, Scheel, K.W, Manning, R.D., Norman, R.A. (1972) Arterial pressure regulation: overriding dominance of the kidneys in long-term regulation and in hypertension. Am J Med 52 (5):584-594

Iellamo F (2001) Neural mechanisms of cardiovascular regulation during exercise. Auton Neurosci 90:66-75

Iellamo F, Pizzinelli P, Massaro M, Raimondi G, Peruzzi G, Legramante JM (1999) Muscle metaboreflex contribution to sinus node regulation during static exercise: insights from spectral analysis of heart rate variability. Circulation 100 (1):27-32.

Jarvis SS, Galbreath MM, Shibata S, Okazaki K, Reelick MF, Levine BD, Fu Q (2011) Sex differences in the modulation of vasomotor sympathetic outflow during static handgrip exercise in healthy young humans. Am J Physiol Regul Integr Comp Physiol 301:R193-R200.

Kamath MV, Fallen, E.L. (1993) Power spectral analysis of heart rate variability: A noninvasive signature of cardiac autonomic function. Crit Rev Biomed Eng 21:245-311.

La Rovere MT, Pinna, G.D., Raczak, G. (2008) Baroreflex sensitivity: Measurement and clinical implications. Ann Noninvas Electro 13:191-207.

485 Millar PJ, MacDonald MJ, Bray SR, McCartney N (2009) Isometric handgrip exercise
486 improves acute neurocardiac regulation. Eur J Appl Physiol 107 (5):509-515.

487 Millar PJ, McGowan CL, Cornelissen VA, Araujo CG, Swaine IL (2014) Evidence for the
488 role of isometric exercise training in reducing blood pressure: potential mechanisms
489 and future directions. Sports Med 44 (3):345-356.

490 Notarius CF, Floras JS (2001) Limitations of the use of spectral analysis of heart rate
491 variability for the estimation of cardiac sympathetic activity in heart failure.
492 Europace, 3:29-38.

493 O'Driscoll JM, Taylor KA, Wiles JD, Coleman DA, Sharma R (2017) Acute cardiac
494 functional and mechanical responses to isometric exercise in prehypertensive males.
495 Physiol Rep 5 (7).

496 Ogoh S, Wasmund WL, Keller DM, O-Yurvati A, Gallagher KM, Mitchell JH, Raven PB
497 (2002) Role of Central Command in Carotid Baroreflex Resetting in Humans during
498 Static Exercise. J Physiology 543 (1):349-364.

499 Pescatello LS, Franklin, B.A, Fagard, R, Farquhar, W.B, Kelley, G.A and Ray, C.A. (2004)
500 Exercise and Hypertension. Med Sci Sports Exer 36 (3):533-553

501 Peters PG, Alessio HM, Hagerman AE, Ashton T, Nagy S, Wiley RL (2006) Short-term
502 isometric exercise reduces systolic blood pressure in hypertensive adults: possible role
503 of reactive oxygen species. Int J Cardiol 110 (2):199-205.

504 Phillips SA, Mahmoud, A.M., Brown, M.D., Haus, J.M. (2015) Exercise interventions and
505 peripheral arterial function: Implications for cardio-metabolic disease. Prog
506 Cardiovasc Dis 57:521-534.

507 Rahman F, Pechnik S, Gross D, Sewell L, Goldstein DS (2011) Low frequency power of
508 heart rate variability reflects baroreflex function, not cardiac sympathetic innervation.
509 Clin Auton Res, 21: 133-141.

510 Riebe D, Ehrman JK, Liguori G, Magal M (2018) ACSM's Guidelines for Exercise Testing
511 and Prescription. 10 edn. Philadelphia: Wolters Kluwer.

512 Sandow SL (2004) Factors, fiction and endothelium-derived hyperpolarizing factor. Clin Exp
513 Pharmacol Physiol 31 (9):563-570.

514 Schroeder EB, Liao D, Chambless LE, Prineas RJ, Evans GW, Heiss G (2003) Hypertension,
515 blood pressure, and heart rate variability: The atherosclerosis risk in communities.
516 Hypertension 42:1106-1111.

517 Smith SA, Querry RG, Fadel PJ, Gallagher KM, Strømstad M, Ide K, Raven PB, Secher NH
518 (2003) Partial blockade of skeletal muscle somatosensory afferents attenuates
519 baroreflex resetting during exercise in humans. J Physiol 551:1013-1021.

520 Taylor JA, Myers CW, Halliwill JR, Seidel H, Eckberg DL (2001). Sympathetic restraint of
521 respiratory sinus arrhythmia: Implications for vagal-cardiac tone assessment in
522 humans. Am J Physiol Heart Circ Physiol, 280: H2804-H2814.

523 Taylor KA, Wiles JD, Coleman DA, Leeson P, Sharma R, O'Driscoll JM (2018)
524 Neurohumoral and ambulatory haemodynamic adaptations following isometric
525 exercise training in unmedicated hypertensive patients. J Hypertens 37:827-836.

526 Taylor KA, Wiles JD, Coleman DD, Sharma R, O'Driscoll J M (2017) Continuous Cardiac
527 Autonomic and Hemodynamic Responses to Isometric Exercise. Med Sci Sports
528 Exerc 49 (8):1511-1519.

529 Teixeira AL, Ritti-Dias R, Antonino D, Bottaro M, Millar PJ, Vianna LC (2018) Sex
530 Differences in Cardiac Baroreflex Sensitivity after Isometric Handgrip Exercise. Med
531 Sci Sports Exerc 50 (4):770-777.

532 Tinken TM, Thijssen DH, Hopkins N, Dawson EA, Cable NT, Green DJ (2010) Shear stress
533 mediates endothelial adaptations to exercise training in humans. Hypertension 55
534 (2):312-318.

535 Valipour A, Schneider F, Kossler W, Saliba S, Burghuber O (2005) Heart rate variability and
536 spontaneous baroreflex sequences in supine healthy volunteers subjected to nasal
537 positive airway pressure. J Appl Physiol 99:2137–2143

538 Vanderlei LM, Pastre, C.M., Hoshi, R.A., Carvalho, T.D., Godoy, M.D. (2009) Basic Notions
539 of Heart Rate Variability and its Clinical Applicability. Braz J Cardiov Surg 49:503-
540 508.

541 Watso JC, Babcock, M.C., Migdal, K.U., Robinson, A.T. (2017) The baroreflex effectiveness
542 index as an early marker of autonomic dysfunction in heart failure. J Physiol 595
543 (15):5013-5014

544 Wheatley CM, Snyder EM, Johnson BD, Olson TP (2014) Sex differences in cardiovascular
545 function during submaximal exercise in humans. Springerplus 3 (445):1-13.

546 Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C,
547 DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P,
548 Ovbiagele B, Smith SC, Jr., Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams
549 KA, Sr., Williamson JD, Wright JT, Jr. (2017) 2017
550 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for
551 the Prevention, Detection, Evaluation, and Management of High Blood Pressure in

Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 71:e13-e115.

Wiles JD, Goldring N, Coleman D (2017) Home-based isometric exercise training induced reductions resting blood pressure. Eur J Appl Physiol 117 (1):83-93.

576 **Figure Legends**

577

578 Figure 1: Graphical depiction of the single isometric exercise training session. Cardiac
579 autonomic and haemodynamic function were measured at baseline, during isometric exercise
580 and in recovery.

581

582 Figure 2: Cardiac autonomic responses to isometric exercise in healthy females. Values are
583 mean ± SEM. A, R-R power spectral density (HRV) response; B, R-R normalized units low
584 frequency and high frequency responses; C, R-R LF/HF (low/high frequency ratio); D,
585 Baroreceptor effectiveness index response. IE = isometric exercise. * $P<0.05$, ** $P<0.001$
586 between baseline and all stages. § $P<0.05$, §§ $P<0.001$ between IE4 and recovery.

587

588 Figure 3: Haemodynamic responses to isometric exercise in healthy females. Values are
589 mean ± SEM. A, Systolic blood pressure (sBP), diastolic blood pressure (dBP) and mean
590 blood pressure (mBP) responses; B, Heart rate (HR) and rate pressure product responses; C,
591 Total peripheral resistance response; D, Stroke volume and cardiac output responses. IE =
592 isometric exercise. * $P<0.05$, ** $P<0.001$ between baseline and all stages. § $P<0.05$, §§
593 $P<0.001$ between IE4 and recovery.

594

595 Figure 4: Cardiovascular responses during isometric exercise (A) and following an acute
596 isometric exercise session (B). Note: TP = total power; EDHP = endothelium-derived
597 hyperpolarizing factor; ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide;

598 RAAS = renin angiotensin aldosterone system. Colour boxes represent data recorded within
599 this manuscript.