Continuous Cardiac Autonomic and Haemodynamic Responses to Isometric Exercise in Pre-Hypertensive Males

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Abstract

Purpose: Elevated arterial blood pressure (BP) is associated with autonomic dysfunction and impaired haemodynamic control mechanisms. Isometric exercise (IE) training has been demonstrated effective at reducing BP; however, the continuous cardiovascular responses during IE are underinvestigated. We hypothesized that reflex autonomic cardiovascular control is an important mediator in reducing BP. To test our hypothesis, we investigated continuous cardiac autonomic modulation and baroreceptor reflex sensitivity (BRS) in response to IE.

Methods: Twenty-five pre-hypertensive participants performed a single IE 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 (ms^2) and normalised units (nu) pre, during and post an IE session. Heart rate (HR) was recorded via electrocardiography and 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 ($p<0.05$) and BRS ($p<0.05$) and significant increases in HR ($p<0.001$), systolic, diastolic, and mean BP (all $p<0.001$). In recovery from IE, HRV ($p<0.001$) HFnu ($p<0.001$) and BRS ($p<0.001$) significantly increased with a significant decrease in LFnu ($p<0.001$) and LF:HF ratio ($p<0.001$), indicative of predominant parasympathetic over sympathetic activity. This autonomic response was associated with a significant reduction in systolic (23.2±18.1 mmHg, $p<0.001$),

diastolic (18.7 ± 16.9 mmHg, $p<0.001$) and mean (15.8±15.5 mmHg, $p<0.001$) BP, below baseline and a significant reduction in TPR ($p<0.001$).

Conclusions: A single IE session is associated with improved cardiac autonomic modulation and haemodynamic cardiovascular control in pre-hypertensive males. These acute responses may be mechanistically linked to the chronic reductions in resting BP reported following IE training interventions.

Introduction

Pre-hypertensive populations have up to 12 times the risk of developing hypertension (43) which remains the leading attributable risk factor for global mortality (45). Additionally, compared to optimal blood pressure (BP), pre-hypertensive individuals have greater risk of accelerating the development of cardiovascular disease (43). The principal aim of anti-hypertensive interventions is to reduce cardiovascular and all-cause mortality by lowering BP, which can be achieved through lifestyle modification alone or in combination with pharmacotherapy.

The role of aerobic exercise training as a lifestyle modification for BP reduction is well established, with positive cardiac, vascular, and neurohumoral adaptations all potential mechanisms improving arterial haemodynamics (33). However, evidence has shown that isometric exercise (IE) training is also capable of reducing resting arterial BP in normotensive (46), pre-hypertensive (3) and hypertensive populations (40). Importantly, mean BP reductions of 10.9 mmHg systolic (sBP) and 6.2 mmHg diastolic (dBP) have been reported with IE training, which are greater than traditional aerobic exercise and dynamic resistance training programmes (8).

Isometric handgrip training (IHG) has been the most commonly prescribed IE training intervention, possibly due to mobility issues with some older and physically inactive adults. However, research has suggested that a larger muscle mass may influence the magnitude of BP reductions (14). As such, other groups have utilised isometric leg training (46), which has produced notable reductions in BP, of a similar level to IHG training, even when performed at a lower relative percentage of maximal voluntary contraction (26).

Mechanisms responsible for the BP reductions seen with IE training remain unclear. However, central and peripheral factors are likely involved via altered modulation of cardiac output and peripheral vascular resistance, which influence mean arterial BP (mBP) (28). Central adaptations have been demonstrated through improved cardiac autonomic control, evidenced with a reduction in sympathetic nervous system activity and increased parasympathetic modulation (40). Peripheral changes following IE training have been explored in relative detail, with training adaptations including an increase in resting endothelium-dependent vasodilation in trained limbs (25), improved resistance vessel function (2) and an increase in femoral artery diameter (3).

It has been suggested that the arterial baroreflex, under the control of central command, is intricately involved in the regulation of post exercise HR recovery (17). A single session of IHG training of 4 x 2-min bilateral contractions, which is the most commonly prescribed protocol (28), has been shown to elicit acute improvements in cardiac autonomic regulation during recovery (increased parasympathetic modulation), accompanied by post exercise systolic hypotension (27). The increased parasympathetic activity and systolic hypotension seen following IE may be associated with an improved baroreceptor reflex sensitivity (BRS). However, few studies have recorded the spontaneous BRS response to IE. We hypothesized that IE would induce an increase in sympathetic modulation followed by a directionally opposite response in recovery with greater parasympathetic over sympathetic activity, mediated by an increase in baroreceptor reflex control of heart rate. Therefore, the aim of this study was to investigate the transient cardiac autonomic, central and peripheral haemodynamic responses; measured continuously pre, during and immediately post a single IE session.

Methods

Study Population

Twenty-five physically inactive pre-hypertensive males, aged 30-65 years volunteered to take part in the study. Participants reported no prior cardiovascular disease; however, 11-participants (44%) reported a positive family history of hypertension. All participants were non-medicated, non-smokers with no prior history of smoking and had a mean waking ambulatory sBP of ≥120 mmHg and ≤140 mmHg and/or dBP of ≥80mmHg and ≤90mmHg. Inclusion in the study was subject to a normal cardiovascular examination and electrocardiogram. Participants were required to attend the laboratory on 3 occasions. Participants maintained an abstinence from food for at least 4 hours prior to each laboratory visit, and did not consume caffeine or alcohol for 24 hours before each visit. During the first visit, a seated resting blood pressure was performed in the laboratory to confirm pre-hypertension and eligible participants completed an isometric wall squat test to establish an appropriate exercise intensity. Table 1 displays the haemodynamic responses to the incremental isometric wall squat test. 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. This investigation conformed to the Declaration of Helsinki principles and was approved by the institutional research ethics committee (Ref: 12/SAS/122). All participants provided signed informed consent before testing.

Isometric Exercise Session

Participants exercised at a prescribed isometric wall squat knee joint angle, based on HR and BP responses to an incremental isometric wall squat test performed during their first laboratory visit (See supplemental digital content (SDC) 1 for description of the incremental isometric wall squat exercise test used to ascertain knee joint training angle and SDC 2 for accompanying images).

During the laboratory based session, a clinical goniometer (MIE Medical Research, Leeds, UK) was used to ensure the desired knee joint angle was achieved and maintained. The goniometer was placed on the side of the participants left knee joint to measure the internal angle between the femur and fibula. The fulcrum was aligned with the lateral epicondyle of the femur, the moving arm was placed on the lateral midline of the femur using the greater trochanter for reference and the stationary arm was on the lateral midline of the fibula using the lateral malleolus and fibular head for reference. A spirit level was attached to the stationary arm to ensure that the lower leg remained vertical during exercise. The goniometer was secured to the participants lower and upper leg using elasticated Velcro strapping.

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. 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 3 times at 5-minute intervals following a 15-minute period of quiet seated rest to confirm pre-hypertension (Carescape V100, GE Healthcare, United Kingdom). 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 (TFM) is a validated non-invasive monitoring system (11), which was used for the continuous beat-to-beat monitoring and automatic online calculation of all cardiac autonomic and haemodynamic parameters. 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. The TFM uses an online QRS detector algorithm combined from Pan and Tompkins (30) and Li, Zheng and Tai (21) 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 outflow) and low (predominantly sympathetic outflow) (1) frequency parameters of heart rate variability (HRV) were automatically calculated by the TFM and expressed in absolute (ms^2) and normalised units (nu). Normalisation of the frequency components of HRV has proven crucial to the interpretation of these data (23). The ratio of LF-to-HF (LF:HF ratio) is an accepted measure of cardiac sympathovagal balance (10). Spontaneous BRS was automatically evaluated via the sequence method, based on computer identification of a series of successive increases or decreases in sBP and lengthening or shortening of the R-R interval (42). Linear regression of increments or

decrements in sBP and R-R interval were computed, with only episodes with correlation coeffiencts of r>0.95 selected. From all regressions, a mean slope of BRS is calculated for each period. All parameters were indexed to body surface area.

Continuous measurement of BP (sBP, dBP and mBP) 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 (ICG) 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 (RPP) 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 repeated measures analysis of variance (ANOVA) was performed, followed by Bonferroni post hoc tests for multiple comparisons. A p value of <0.05 was regarded as statistically significant.

Results

All participants completed the entire IE session at their pre-prescribed knee joint angle. Baseline demographic information is shown in Table 2.

Cardiac Autonomic Response

Cardiac autonomic function at baseline, during each period of IE and in recovery is shown in Figure 2 and Table 3. IE produced a statistically significant change in mean R-R power spectral density (PSD) of HRV between baseline, IE and recovery time points ($F(2.504, 57.601) = 23.926$, $p<0.001$). Figure 2A, demonstrates that there was a significant stepwise reduction in R-R PSD from baseline to IE2 ($p<0.02$), IE3 ($p<0.001$), and IE4 ($p<0.001$), followed by a significant increase in R-R PSD above baseline from IE4 to recovery ($p<0.001$). Absolute HF (ms^2), LF (ms^2) and very low frequency (VLF ms^2) HRV data is shown in Table 3. All frequencies decreased significantly between baseline and IE3 and IE4 ($p<0.05$), then increased significantly following IE4 into recovery ($p<0.001$). When analysing HRV in normalised units, LFnu increased during the first interval of IE, and remained above baseline during all 4 bouts (59.9 ± 16.6% to 70.5 ± 14.7%). There was a significant decrease in LFnu during the recovery period (70.1 ± 15.9% to 46.3 ± 14.3%, $p<0.001$). An inverse response was recorded in HFnu (see Figure 2B). The LF:HF ratio increased during the first interval of IE and remained above baseline throughout the IE session, followed by a significant reduction (4.4 ± 4.1 to 1.1 ± 0.7, $p<0.05$) from the final IE bout into recovery (see Figure 2C).

BRS decreased significantly ($F(1.125, 14.625) = 51.382$, $p<0.001$) between baseline and all four intervals of IE. During recovery BRS increased significantly above baseline ($p<0.001$), as shown in Figure 2D.

Haemodynamic Response

Haemodynamic parameters at baseline, during each period of IE and in recovery are shown in Figure 3 and Table 3. A significant stepwise increase in sBP ($F(3.387, 81.284) = 54.165$, $p<0.001$) occurred during the IE session from baseline (132.6 ± 5.6 mmHg) to IE1 (141.5 ± 15.7 mmHg), IE2 (145.9 ± 17.5 mmHg), IE3 (152.4 ± 15.8 mmHg), and IE4 (165.9 ± 21 mmHg) (all $p<0.05$). Following cessation of the IE session, there was a significant reduction ($p=<0.001$) in sBP from 165.9 ± 21 mmHg in IE4 to 109.4 ± 19.5 mmHg during recovery, which was also significantly lower than baseline sBP ($p<0.001$). The same trend was observed in dBP ($F(3.073, 73.757) = 72.521$, $p<0.001$), with significant increases from baseline and all periods of the IE session ($p<0.001$) followed by a significant reduction from IE4 into recovery ($p<0.001$), which was also significantly lower than baseline dBP ($p<0.001$). The mBP response during the IE session demonstrated a similar pattern to sBP and dBP with the same differences ($p<0.05$) (see Figure 3A). In the recovery intervals between IE bouts, mean sBP was 132.8 ± 24.5 mmHg between bout 1 and 2; 121.1 ± 17.9 mmHg between bout 2 and 3 and 125 ± 15.7 mmHg between bout 3 and 4. Mean dBP was 79.7 ± 27.5 mmHg between bout 1 and 2; 75.2 ± 18 mmHg between bout 2 and 3 and 77.6 ± 16.4 mmHg between bout 3 and 4.

There was a significant stepwise increase in HR ($F(2.887, 69.277) = 85.511$, $p<0.001$) from baseline through each IE interval (all $p<0.001$), followed by a significant reduction in HR

from IE4 into recovery from 108.5 ± 17 to 70.3 ± 14.8 b·min^{-1} ($p<0.001$). In the recovery intervals between IE bouts, mean HR was 68.3 ± 11.8 b·min^{-1} between bout 1 and 2; 73.4 ± 12 b·min^{-1} between bout 2 and 3; and 77.9 ± 13.1 b·min^{-1} between bout 3 and 4. As a consequence of the HR and BP responses, there was a significant linear increase in RPP from baseline through all IE intervals ($F(2.309, 55.422) = 102.716$, $p<0.001$), followed by a significant decrease in RPP from IE4 into recovery ($p<0.001$) to below baseline (See Figure 3B).

TPR (Figure 3C) demonstrated an initial increase during IE1, followed by a stepwise decrease during the remaining IE intervals ($F(2.665, 63.952) = 13.356$, $p<0.001$), and was significantly lower during the recovery period compared with baseline ($p<0.05$). TPR indexed data is presented in Table 3.

Stroke Volume (SV) ($F(2.380, 57.113) = 10.271$, $p<0.001$) decreased significantly from baseline to IE1 ($p<0.05$) and remained below baseline throughout the IE session. In recovery, SV significantly increased ($p<0.05$) and was higher than baseline (Figure 3D). Stroke index data is presented in Table 3. Cardiac output ($\dot{Q}$) ($F(2.698, 64.749) = 25.977$, $p<0.001$) increased from baseline at each IE interval. During recovery there was a significant reduction in $\dot{Q}$ and cardiac index (CI) ($p<0.05$). There was a significant difference between baseline and recovery CI ($p<0.05$), as shown in Table 3.

Discussion

This study provides the first insight into the continuous cardiac autonomic and haemodynamic regulatory responses to a single isometric wall squat exercise session in a pre-hypertensive male population. IE elicits a stepwise reduction in the total power spectrum of HRV. A greater proportion of the frequency domain parameters remained in the LF (ms^2) band, which indicates greater sympathetic activity and parasympathetic withdrawal. This response is supported by a reciprocal increase and decrease in LFnu and HFnu, respectively and changes in the LF:HF ratio. Cessation of IE resulted in an overall increase in HRV above baseline, with a greater proportion in the HF (ms^2) domain. This indicates predominant parasympathetic modulation and sympathetic withdrawal. This response is similar to previous IE protocols (17, 27, 38).

Importantly, the cardiac autonomic response seen in recovery is different from aerobic exercise. Martinmaki and Rusko (24) demonstrated that overall LF (ms^2) and HF (ms^2) increased upon cessation of aerobic exercise; however, baseline was not restored following 10 minutes of recovery. Furthermore, during the first 5 minutes of recovery from aerobic exercise, increases in HRV can be attributed to an increase in the LF component of HRV (18). This suggests that there is sustained sympathetic activity in the recovery period following aerobic exercise, which may be related to differences in the levels of circulating catecholamines. The parasympathetic response following IE may be associated with up regulation of the nitric oxide pathway, a response that would facilitate vagal cholinergic activity and heightened antagonism of cardiac sympathetic activity (32). Indeed, baroreceptor synapses in the cardiac vagal neurone pathway in the medulla are positively regulated by an

intrinsic nitric oxide mechanism. In our study, there was a three-fold increase in BRS (19.9 ± 10.3 ms·mmHg^{-1} to 60.04 ± 53.1 ms·mmHg^{-1}) in recovery, which supports this concept.

During IE, there was a step-wise decrease in vagally controlled BRS, which marks the active resetting of baroreceptors and accounts for the directionally opposite, sympathetically controlled increases in HR and BP (15) resulting in the pressor response associated with this type of exercise. Iellamo, Massaro, Raimondi, Peruzzi and Legramante (16) reported that a drop in BRS during an isometric contraction is dependent on muscle mass and intensity. It was suggested that a greater muscle mass activation, such as the large muscle group and relatively high contraction intensity used in this study, may enable a greater engagement of the muscle metaboreflex, eliciting a reflex inhibition of cardiac vagal tone and increase in sympathetic nerve activity (15). The three-fold increase in BRS during the recovery period contrasts findings from dynamic resistance and aerobic training (13, 29), which have reported a reduction in BRS, sustained for 20-60 minutes following acute exercise. Prior research indicates that the differences in BRS may be related to both mechanical and neural responses. Willie, Ainslie, Taylor, Jones, Sin and Tzeng (47) demonstrated that carotid artery diameter is significantly reduced following aerobic exercise and detailed that this mechanical response mediates a reduction in BRS. However, Black, Stohr, Stone, Pugh, Stembridge, Shave and Esformes (4) demonstrated that when performing single isometric double-leg press, carotid artery diameter is preserved in the recovery period. Importantly, the single isometric contraction was only 5-seconds in duration. The impact a 4 x 2-minute IE session would have on carotid artery mechanics is of interest for future research.

The differences in the acute cardiac autonomic response between exercise modes, may in part, explain the greater exercise induced BP reductions following IE compared to aerobic exercise.

Furthermore, these acute responses may also be important mechanisms producing greater BP reductions following a programme of IE training compared to traditional aerobic exercise.

Activation of mechanoreceptors when a contraction commences, followed by excitation of the cardiovascular centres, initiates an immediate haemodynamic response. When contraction intensity is high, motor units are recruited constantly to maintain muscle tension, sustaining the excitatory state of the central nervous system. Sympathetic activation by central command and metaboreceptors during IE, induced linear increases in HR, sBP and $\dot{Q}$. These responses have been previously reported by Stewart, Montgomery, Glover and Medow (38) during a single 2-minute isometric contraction.

Aerobic exercise is associated with an increase in sBP and a plateau or small decrease in dBP. However, during IE, there is an initial significant rise in dBP in the first IE bout followed by a non-significant rise in dBP in the remaining IE bouts. This was associated with a significant rise in TPR in the first IE bout, followed by a gradual non-significant decrease in the remaining bouts. The rise in dBP in the first IE bout is likely due to the increase in $\dot{Q}$ and TPR. However, in the remaining IE bouts, the small continued rise in dBP despite small progressive reductions in TPR may be explained by the continued rise in $\dot{Q}$ in association with impaired left ventricular diastolic function (44) and/or increased end-diastolic pressure, which is supported by the reduced stroke volume seen during IE.

A step-wise increase in $\dot{Q}$ was primarily mediated by a linear increase in HR, since SV significantly decreased at the onset of IE and remained plateaued until recovery. This is in contrast to aerobic exercise, which demonstrates an increase in SV due to increased preload. A reduced SV has been noted during the Valsalva manoeuvre and isometric handgrip testing

when there is an increase in intrathoracic pressure, cardiac afterload and LV end-systolic volume (44).

The recovery period was associated with a significant decrease in arterial BP compared with baseline. Post IE arterial BP reductions of 17.4% (23.2 ± 18.1 mmHg), 23.7% (18.7 ± 16.9 mmHg) and 16.5% (15.8 ± 15.5 mmHg) below baseline were demonstrated for sBP, dBP, and mBP, respectively. This represents a greater degree of post exercise hypotension compared to unilateral IHG exercise, which has revealed reductions of 3 mmHg sBP (27), and following acute aerobic exercise which has elicited reductions of ≈14 mmHg sBP and ≈9 mmHg dBP (22). The recovery BP response to isometric wall squat exercise could be mediated by the significant post exercise changes in TPR and autonomic regulatory responses (HRV and BRS) as these parameters have not previously been reported following an acute bout of IE. The magnitude of BRS gain and BP reduction in recovery demonstrates parasympathetic reactivation, and the extent of the responses observed in this research could be explained by the type of isometric contraction. Indeed, Iellamo (15) stated that BRS and the muscle metaboreflex may be differently modulated in the relation to the muscle activity being performed, including type, intensity and size of active muscle mass.

Modulation of TPR is implicated in the early haemodynamic response to an IE contraction. However, the reduction in TPR during successive intervals of IE suggests that arterial dilatation occurs, and that the release of sympathetic neurotransmitters may be superseded by a more dominant vascular reaction. During aerobic exercise, functional hyperaemia occurs to meet added oxygen (O_2) demand causing muscle cell metabolism and O_2 uptake to increase. During IE, only the working muscles receive hyperaemic blood flow, therefore the extent of the hyperaemic response is muscle mass dependent. During a contraction, there is a drop in

PO_2 in the capillaries and arterioles. The detection of hypoxic conditions induces the release of adenosine triphosphate (ATP) from red blood cells into the lumen via purinergenic signalling, which may indirectly assist with relaxation of smooth muscle (5). It has been previously suggested that accumulation of exercise-mediated vasodilator NO within the static leg musculature, through increased cell metabolism may cause an attenuated vascular response to vasoconstriction during IE (20). In addition to the recognised function of NO, it has been suggested that other endothelial cells may be able to induce the hyperpolarisation of vascular smooth muscle (7). An endothelium-derived hyperpolarising factor (EDHF) transmitted via electrical coupling through myoendothelial gap junctions between endothelial and vascular smooth muscle, to contractile cells in the vascular wall, may assist in inducing vasodilation (35). The high metabolic demands induced by an isolated muscle group during an isometric leg contraction, and hyperaemia demonstrated by increased $\dot{Q}$, may explain the reduction in TPR during and following the IE session. Increased concentrations of NO and ATP and an EDHF may act to down regulate the release of noradrenaline produced by sympathetic activation.

When the IE contraction is released, there is sudden perfusion of previously occluded muscle mass and a transient pressure undershoot. A short period of reactive hyperaemia, following ischaemic conditions in the contracted muscle, has been shown to cause acute increases in blood flow and shear rate and a drop in resistance in recovery from an IHG session (25). An increase in NO synthesis, in response to the shear stress induced by hyperaemic blood flow, triggering vasodilation (41), is a potential mechanism for reduced TPR. However, Halliwill, Buck, Lacewell and Romero (12) detail that histamine H_1 and H_2 receptor activation may be a primary mechanism for sustained post-exercise vasodilatation. A reduction in TPR, via vasodilation demonstrates sympathetic inhibition, while a reduction in HR demonstrates

parasympathetic reactivation during recovery, a finding supported by the measured changes in HRV observed in the present study. Redistributed blood flow accounts for restored SV in recovery through increased venous return, and a reduced $\dot{Q}$ is a consequence of restored parasympathetic HR control. These combined responses result in a reduction in arterial BP, and have been a suggested mechanism for post exercise hypotension during recovery from exercise (34).

Limitations

The study detected changes in physiological variables with findings generalised to physically inactive, pre-hypertensive males, aged 30-65, as the sample population. Given that the principle study aim was to assess changes in cardiac autonomic and haemodynamic responses during IE, a passive parallel control group was not used for comparison. Although this may present a limitation of the research, the methodology used to record resting measures has been shown to be reliable at rest, giving confidence that any changes measured from baseline can be attributed to IE.

This study recorded the recovery responses in the 5 minutes immediately following IE only; therefore the responses beyond this period remain un-explored with regards to this isometric wall squat training protocol.

Short-term HRV recordings were performed in the supine position in order to adhere with recommended guidelines (39). Furthermore, it is easier to standardise a supine position compared to a seated or upright position, due to possible confounding influence of continued isometric activity to maintain posture. In order to maintain consistency, all other measures

were also recorded in this position at baseline and during recovery. However, it is acknowledged that a change in posture and subsequent gravitational stress will influence cardiovascular haemodynamics and as such, whilst our results are likely to accurately document the gross physiological responses to IE, the exact pattern of response may differ whilst in a seated or upright position.

Inherent methodological limitations apply to non-invasive measures of cardiac autonomic modulation. In particular, the sequence technique for assessing BRS requires some degree of variability in sBP and RRI. As such, the short recordings utilised reduces the range of potential BP changes, which is a limitation of this method. Use of intravenous bolus injection of vasoactive drugs (sodium nitroprusside and phenylepherine) may have provided alternative, yet complementary support for the change in BRS following IE. However, prior research supports the sequence technique as a valuable method for measuring BRS in healthy and clinical populations (31). Furthermore, prior research has used 2-minute recordings to assess BRS using the sequence technique (6).

Guidelines recommend HRV measurements are taken over a minimum duration of 5-minutes. However, conventional IE training methodology dictates 2-minute contractions. As such, all IE parameters are reported as mean responses from a 2-minute period and baseline and recovery from a 5-minute recording. Other IE research has recorded HRV over the same truncated period (27), as has research in clinical populations (37).

Clinical Implications

Impaired autonomic function is an independent predictor of all-cause mortality and is implicated in the development of hypertension (36). In addition BRS is considered to have strong prognostic value for cardioprotection (19). A single session of IE is associated with a reduced HRV and residual predominance of sympathetic over parasympathetic activity with an attenuated BRS. In recovery there is a directionally opposite autonomic response with a residual increase in parasympathetic over sympathetic activity and increased HRV and BRS. These transient autonomic responses indicate an improvement in cardiac autonomic modulation, which differ from aerobic exercise and may be important mechanisms producing greater reductions in BP following IE training programmes. Prior research has demonstrated that a >8-week period of IHG training can elicit improvements in cardiac vagal activity (26, 40). However, few studies have reported the transient BRS response. IE training and regular exercise induced hypotension may stimulate the baroreceptors to reset to a lower operating range, which may be an important mechanistic pathway in reducing BP.

Vascular dysfunction is implicated in a range of cardiovascular diseases and may precede their development (9). Pre-hypertension is associated with impaired vascular reactivity (12). Our findings show a reduction in TPR during IE and in recovery, which may indicate an improvement in vascular function.

Conclusion

A single IE session was associated with improved cardiac autonomic modulation and haemodynamic cardiovascular control. The acute improvements seen may be mechanistically

linked to the IE training induced reductions in arterial BP. Future research is needed in order to ascertain the importance of these acute responses for long-term BP reductions and implications on cardiovascular health.

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Figure Legends

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

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

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

Supplemental Digital Content (SDC):

SDC 1: Description of incremental isometric wall squat exercise test used to ascertain knee joint training angle.

SDC2: Accompanying images of the incremental isometric wall squat exercise test stages.