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Taylor, K, Wiles, J, Coleman, D, Leeson, P., Sharma, R and O'Driscoll, J. (2018) Neurohumoral and ambulatory haemodynamic adaptations following isometric exercise training in unmedicated hypertensive patients. *Journal of Hypertension*. ISSN 0263-6352.

Link to official URL (if available):

<http://dx.doi.org/10.1097/HJH.0000000000001922>

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Neurohumoral and ambulatory haemodynamic adaptations following isometric exercise training in unmedicated hypertensive patients

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Running Title: Isometric exercise in hypertension

Key words: Blood pressure, Cardiac autonomic function, Hypertension, Inflammation, Isometric Exercise.

Word Count: 5172

Abbreviations

ABPM – ambulatory blood pressure monitoring
ADMA – asymmetric dimethylarginine
ARV – average real variability
BP – blood pressure
BRS – baroreceptor reflex sensitivity
CVD – cardiovascular disease
dbP – diastolic blood pressure
ECG – electrocardiogram
HF – high frequency
HR – heart rate
HRV – heart rate variability
hs-CRP – high sensitivity C reactive protein
HTN - hypertension
ICAM-1 – intercellular adhesion molecule
IET – isometric exercise training
IL-10 – interleukin 10
IL-6 – interleukin 6
LF – low frequency
ln – log transformed
mBP – mean blood pressure
NO – nitric oxide
nu – normalised units
PP – pulse pressure
PSD – power spectral density
Q̇ - cardiac output
RPP – rate pressure product
sBP – systolic blood pressure
SV – stroke volume
TFM – Task Force[®] Monitor
TNF- α - tumor necrosis factor alpha
TPR – total peripheral resistance
VCAM-1 – vascular cellular adhesion molecule

Abstract

Objective: Hypertension remains the leading modifiable risk factor for cardiovascular disease (CVD). Isometric exercise training (IET) has been shown to be a useful non-pharmacological intervention for reducing resting blood pressure (BP). This study aimed to measure alterations in office BP, ambulatory BP, cardiac autonomic modulation and inflammatory and vascular biomarkers following a programme of IET in unmedicated hypertensive patients.

Methods: Twenty-four unmedicated stage 1 hypertensive patients (age 43.8 ± 7.3 years; height, 178.1 ± 7 cm; weight 89.7 ± 12.8 kg) were randomly assigned in a cross-over study design, to 4-weeks of home based IET and control period, separated by a 3-week washout period. Office and Ambulatory BP, cardiac autonomic modulation, and inflammatory and vascular biomarkers were recorded pre and post IET and control periods.

Results: Clinic and 24-hour ambulatory BP significantly reduced following IET by $12.4/6.2$ mmHg and $11.8/5.6$ mmHg in systolic/diastolic BP, respectively ($p < 0.001$ for both), compared to the control. The BP adaptations were associated with a significant ($p = 0.018$) reduction in the average real variability of 24-hour ambulatory BP following IET, compared to control. Cardiac autonomic modulation improved by 11% ($p < 0.001$), baroreceptor reflex sensitivity improved by 47% ($p < 0.001$), and interleukin-6 and asymmetric dimethylarginine reduced by 10% ($p = 0.022$) and 19% ($p = 0.023$), respectively, which differed significantly to the control period.

Conclusion: This is the first evidence of durable BP reduction and wider CVD risk benefits of IET in a relevant patient population. Our findings support the role of IET as a safe and viable therapeutic and preventative intervention in the treatment of HTN.

Introduction

Systemic hypertension (HTN) remains the leading attributable risk factor for cardiovascular disease and all-cause mortality globally [1]. Recent evidence suggests that the prevalence of HTN is increasing [2], which places a substantial economic burden on public health services. A recent clinical trial reported lower rates of fatal and nonfatal major cardiovascular events and all-cause mortality when blood pressure (BP) is treated to within the normal range [3]. However, rates of diagnosis remain relatively low and treatment for HTN is frequently suboptimal [4], especially in younger adults [5].

Traditional aerobic exercise training is a current guideline lifestyle recommendation for the non-pharmacological treatment of HTN [6]. However, a recent meta-analysis demonstrated that current exercise guidance provided to reduce BP is unlikely to benefit long-term cardiovascular risk [7]. Thus, novel therapeutic exercise training interventions may be of particular importance.

Isometric exercise training (IET) has been shown to produce clinically significant reductions in resting BP in pre-hypertensive and hypertensive populations [8-10]. In addition, meta-analytical studies report greater reductions in resting BP following IET, compared to traditional aerobic exercise [11]. Mechanisms for the reduction in resting BP include modifications in central and peripheral cardiovascular control [8,10,12-15]. However, few studies have investigated the wider cardiovascular benefits of IET. Therefore, the aims of this study were to investigate changes in office BP, ambulatory BP, cardiac autonomic modulation and inflammatory and vascular biomarkers following a 4-week home-based IET intervention in a group of unmedicated hypertensive patients. We hypothesize that IET will

reduce ambulatory BP and inflammatory and vascular biomarkers and improve cardiac autonomic modulation.

Method

Study Design

This study was a prospective single centre, randomised cross-over controlled trial. Eligible patients recruited were those that satisfied the inclusion and exclusion criteria, which included; unmedicated stage 1 hypertension, defined as a blood pressure of 130-139 systolic and/or 80-89 diastolic [6], aged between 30 and 65 years old, no history of cardiac or metabolic disease, non-smokers and presenting with a normal clinical cardiovascular examination and 12-lead electrocardiogram. All participants were physically inactive (self-reported and defined as not meeting current recommendations) [16] and were not taking any acute (<3 months) or chronic medications, including antibiotics.

All procedures for this investigation conformed to the Declaration of Helsinki principles and the local ethics committee approved the study (Ref: 12/SAS/122). All participants provided signed, written informed consent.

Study Procedures

All tests were performed at Canterbury Christ Church University. Twenty-four (43.8 ± 7.3 years) unmedicated stage 1 hypertensive participants were randomised in a cross-over design to a 4-week programme of IET or 4-week control period (Figure 1), which was separated by a 3-week washout period. Each participant was required to visit the laboratory on 5-separate occasions. The first visit comprised a continuous incremental isometric exercise test, as previously described [14,15], which was used to determine each participants' IET knee joint

angle (see online-only Data Supplement). The four remaining laboratory visits comprised the recording of physiological data as described below. All participants were required to maintain their normal circadian and dietary patterns, fast for ≥ 8 -hours and abstain from caffeine and alcohol for 24-hours before testing, as well as attend the laboratory at the same time of day.

Blood Pressure Measurements

Brachial artery office BP was measured in a temperature controlled room pre and post the IET intervention and control period using a validated automated device (Dinamap[®] Pro 200 Critikon, GE Medical Systems, Freiburg, Germany) and according to current guidelines [6]. Ambulatory 24-hour BP monitoring (ABPM) was measured pre and post the IET intervention and control period using a commercially available and validated oscillometric brachial cuff sphygmomanometer (Welch Allyn 6100 ambulatory BP monitor, Welch Allyn Inc. Skaneateles Falls, NY, USA). The participants were asked to perform their usual daily activities but were not allowed to exercise during the 24-hour recording period. Systolic BP (sBP), mean BP (mBP), diastolic BP (dBP) and heart rate (HR) were measured every 20-minutes between 6.00am and 10:00pm and every 30-minutes in the remaining time period. All BP readings were stored on the device and uploaded to a computer (Welch Allyn CardioPerfect[™] Workstation software for Windows[®], Welch Allyn Inc. Skaneateles Falls, NY, USA) for evaluation. The data were analysed for the whole 24-hour period, as well as separately for the day time (9.00am to 9:00pm) and the night time (1:00am to 6:00am) period [17]. All participants confirmed that they slept during the specified night time hours. The average real variability (ARV) of ambulatory sBP, mBP and dBP were calculated as a measure of BP variability as previously described [18].

Cardiac Autonomic Assessment

Cardiac autonomic modulation was assessed using a validated non-invasive and continuous beat-to-beat monitoring system (Task Force[®] Monitor; TFM) [19]. Heart rate variability (HRV) as an index of cardiac autonomic function was determined from the oscillating fluctuations in the frequency and amplitude of each R-R interval using power spectral analysis and applying an autoregressive model. Electrocardiogram (ECG) traces were also manually screened to confirm traces were clear of any erroneous data. High (predominantly parasympathetic outflow) and low (predominantly sympathetic outflow) [20] frequency parameters of 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 [21]. The ratio of LF-to-HF (LF:HF ratio) is an accepted measure of cardiac sympathovagal balance [22]. Spontaneous baroreceptor sensitivity (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 [23]. Linear regression of increments or decrements in sBP and R-R interval were computed, with only episodes with correlation coefficients 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.

HR was recorded through a 6-channel ECG 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 (RPP) as the product of HR and sBP, pulse pressure (PP) as the difference between sBP and dBP, 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 biological signals were recorded with a sample frequency of 1000Hz and 16-bit resolution.

Inflammatory Biomarkers

Serum high sensitivity C-reactive protein (hs-CRP) was determined by enzyme-linked immunosorbent assay (ELISA; Siemens ADVIA Systems, New York, USA), and serum interleukin 6 (IL-6), IL-10 and tumour necrosis factor alpha (TNF- α) were also measured by ELISA (R&D Systems, Inc. Minneapolis, USA) using standard techniques.

Vascular Biomarkers

Serum asymmetric dimethylarginine (ADMA), vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) were measured by ELISA (R&D Systems, Inc. Minneapolis, USA), using standard techniques.

Isometric Exercise Training Intervention

During the IET intervention period, all participants completed a 4-week unsupervised home-based isometric wall squat training programme. Training was completed 3-days per week for 4 successive weeks (12 sessions in total) with 48-hours between training sessions. Each training session was composed of 4 x 2 minute bouts of isometric wall squat exercise interspersed with 2-minutes of seated rest between bouts. All training sessions were

completed at a participant specific knee joint angle (see online-only Data Supplement) as previously described [15,24] and the mean knee joint training angle was $114^{\circ}\pm 19$. In order to monitor training intensity and confirm that the prescribed training angle elicited the required HR response, each participant recorded their HR at the end of each stage (Polar RS400 Computer and a Polar WearLink V2 transmitter, Polar Electro Oy, Kempele, Finland) and uploaded their data to a personal online database, which was monitored by the experimenter. During the control period, participants were required to maintain their normal daily routine for a 4-week period and abstain from any form of exercise they did not habitually perform.

Sample Size Estimation

Based on previous studies utilising home-based isometric exercise training for BP reduction, we expected the IET intervention to result in a decrease in resting systolic BP of ≥ 5 mmHg in the training group with no statistically significant change in the control group [25]. This difference was considered to be clinically relevant. Using the likely changes ($\sim 4.3\%$) and the coefficient of variation of systolic BP (4.6%) from Wiles et al., [25] we estimated a sample size of 18 participants, with 80% power, and $p < 0.05$. We estimated the dropout rate to be 20-30%, leading to an overall sample size of 24 participants.

Statistical Analysis

Continuous variables are expressed as mean \pm standard deviation. Analysis of Covariance was performed on change scores (post-pre) for the two conditions, with order of the intervention included as a covariate in the analysis. Where outcome measures were positively skewed these were log transformed (ln) prior to analysis. All data were analysed using the

statistical package for social sciences (SPSS 22 release version for Windows; SPSS Inc., Chicago IL, USA).

Results

All 24 participants completed the IET intervention and control period. Resting office blood pressure, daytime ABPM, cardiac autonomic function and haemodynamics were successfully acquired on all participants. However, 1-participant refused to wear the ABPM during the night, therefore night time BP results are reported from 23 participants. In addition, inflammatory and vascular biomarker analysis was performed on 21 participants.

Importantly, there were no significant differences between measurements at time points 1 and 3 between or within groups, which confirms that the 3-week washout period was long enough for those participants who initially performed IET to return to baseline.

Resting Blood Pressure, Haemodynamics and Cardiac Autonomic Function

As shown in Table 1, resting office sBP, mBP and dBp significantly decreased post IET compared to control (-12.4 ± 3.9 mmHg, -8 ± 4.3 mmHg and -6.2 ± 3.8 mmHg respectively, all $p<0.001$). Following IET, there was a significant increase in SV ($p<0.001$), \dot{Q} ($p=0.003$), and significant reduction in TPR ($p<0.001$) compared with the control condition. These results were similar when indexed to body surface area. However, there was no significant difference ($p=0.571$) in HR between IET and control conditions (Table 1).

There was an increase in HRV expressed as R-R PSD (ms^2) (1031 ± 975), which was significantly different to the control period ($p<0.001$). There was also a significant increase in HF (nu) ($11.9\pm 17.5\%$; $p=0.017$) accompanied by a reciprocal decrease in LF (nu) ($-11.9\pm 17.5\%$; $p=0.017$) following IET.

There was no significant difference in LF (ms^2) between IET and control conditions ($p=0.2$). However, following IET, an increase in HF (ms^2) (540 ± 357 ; $p<0.001$) was evident, which was significantly different to the control condition ($p<0.001$). These cardiac autonomic responses resulted in a significant decrease in the LF/HF ratio between the IET and control conditions (1.86 ± 2.85 ; $p=0.029$). In addition, change in BRS was significantly greater following IET than control (8.2 ± 5.2 vs 0.03 ± 1.8 ; $p<0.001$) (Table 1).

Ambulatory Blood Pressure

As shown in Table 2, 24-hour ambulatory sBP, mBP and dBP decreased post IET (-11.8 ± 3.5 mmHg, -5.7 ± 4.38 mmHg and -5.6 ± 3.3 mmHg respectively, all of which were significantly different to the control period; $p<0.001$). There were also significant reductions compared to the control condition for daytime ambulatory sBP, mBP and dBP (-13.9 ± 4.1 mmHg, -7.4 ± 5 mmHg and -5.6 ± 4.1 mmHg respectively, all $p<0.001$) and night time ambulatory sBP, mBP and dBP (-9.4 ± 8.5 mmHg, $p<0.001$; -3.9 ± 2.2 mmHg, $p=0.013$; -4.9 ± 4.7 mmHg, $p=0.002$ respectively). Figure 2 demonstrates the density distribution, mean and individual changes in ambulatory sBP, mBP and dBP following IET and control conditions. In addition, Figure 3 demonstrates the difference in mean hour-by-hour ambulatory BP, pre and post IET for sBP, mBP and dBP.

There was no significant differences in 24-hour ($p=0.691$), daytime ($p=0.911$) or night time ($p=0.073$) ambulatory HR between IET or control conditions (Table 2). As a result of the BP changes following IET, 24-hour ambulatory, day time and night time pulse pressure (-5.8 ± 7.08 mmHg; $p<0.001$; -7.39 ± 10 mmHg; $p<0.001$, and -4.25 ± 6.22 mmHg; $p=0.003$,

respectively) and RPP (-1118 ± 706 ; $p<0.001$; -1254 ± 767 ; $p<0.001$, and -1073 ± 1041 ; $p<0.001$, respectively) significantly reduced compared to the control condition.

As shown in table 2, 24-hour ambulatory ARV for sBP significantly decreased post IET compared to control (-2.33 ± 1.4 mmHg; $p=0.018$); however, there was no significant change in ARV for mBP or dBP (1.7 ± 2.8 mmHg, $p=0.076$; -1.42 ± 1.2 mmHg; $p=0.1$, respectively). There was a significant reduction in daytime systolic ARV (-2.45 ± 1.5 mmHg; $p=0.022$). In addition, there were significant reductions in night time ARV for mBP and dBP post IET (-3.1 ± 1.9 mmHg; $p=0.001$, and -2.21 ± 1.8 mmHg; $p=0.008$, respectively) with no significant change in night time ARV for sBP (-2.62 ± 1.6 mmHg; $p=0.127$).

Biochemical Variables

Following IET, IL-6 (ln) and ADMA (ln) significantly decreased (-0.04 ± 0.07 , $p=0.022$ and -0.05 ± 0.11 , $p=0.023$, respectively) compared with the control period. There was no significant change in hs-CRP, TNF- α , VCAM-1 or ICAM-1 following IET or control condition.

There was no significant change in IL-10 (ln) following IET (1.24 ± 0.2 to 1.25 ± 0.2 , $p=0.19$). However, there was a significant reduction in the IL-6/IL-10 ratio (0.91 ± 0.26 to 0.86 ± 0.24 , $p=0.02$) following IET.

Discussion

To the best of our knowledge, the present study is the first to prospectively investigate the wider cardiovascular benefits of IET, including ABPM, cardiac autonomic modulation, central haemodynamics and inflammatory and vascular biomarkers in a randomised cross over controlled study design. Importantly, this is the first study that investigated a non-medicated hypertensive population utilising home based wall squat isometric exercise.

Confirming our initial hypothesis, IET reduced office BP, ambulatory BP, IL-6, ADMA, and improved cardiac autonomic modulation.

Blood Pressure

In the general population, ABPM is more predictive of mortality compared to office BP [26] and is recognised to be more predictive of target organ damage [27], which supports its use within the current study. However, the magnitude of BP reduction following IET was similar between office BP (12.4 mmHg sBP and 6.2 mmHg dBP) and ambulatory BP (11.8 mmHg sBP and 6 mmHg dBP) in our study. Nonetheless, the magnitude of BP reduction following IET in our population is of clinical significance, since it is greater than the average BP reduction (9.1 mmHg sBP and 5.5 mmHg dBP) achieved with a single, standard dose anti-hypertensive drug [28] and is associated with reduced cardiovascular mortality [29]. Similar to most pharmacological treatments for BP [28], greater reductions in BP have been shown in groups with higher baseline BP values following exercise training [11]. The magnitude in BP reduction reported in our study is greater than traditional exercise training in normotensive and hypertensive individuals [11], as well as following a recent home-based wall squat IET intervention in participants with BP in the normal range [15]. As such, it may be postulated

that wall squat IET may exert a greater anti-hypertensive effect in patients with more severe hypertension and/or act as an adjunctive therapy in those with multiple anti-hypertensive agents or resistance hypertension. However, this has not been tested in our study and requires further research. Our results also show a significant reduction in day time and night time BP, as well as PP and RPP. These parameters are associated with reduced mortality and myocardial work. Importantly, in our study, 2-participants were initially classified as non-dippers (4% nocturnal BP drop), which may be an important indicator of advanced vascular disease [30]. However, following IET these participants had a mean nocturnal BP dip of 16%. As such, IET may be an important non-pharmacological intervention in non-dippers.

Research has demonstrated that a greater tendency for BP to vary within a 24-hour period, favours the development of cardiac [31] and vascular damage [32], as well as cardiovascular mortality [33]. IET significantly reduced 24-hour ambulatory and night time systolic, mean and diastolic ARV as well as day time systolic ARV, which may have prognostic significance. Increased sympathetic activity, altered baroreceptor reflex sensitivity and vascular dysfunction are factors known to increase BP variability and cardiovascular events, which are hallmarks of HTN [34]. In addition, the increased BP variability may induce direct endothelial damage and alter autoregulation capacities of target organs, which may be directly responsible for cardiovascular events [34].

Cardiac Autonomic Modulation

Evidence suggests that autonomic dysfunction, which is characterised by greater sympathetic drive, may have a causative or co-causative role in the aetiology and progression of human HTN [35,36]. The beneficial effect of exercise training on cardiac autonomic modulation,

with a tonic decrease in sympathetic activity and augmented vagal modulation, has been well documented in clinical and experimental studies. Our study demonstrated a significant increase in the total power spectrum of HRV and HF component, with no significant change in the LF component, which resulted in a significant reduction in the LF/HF ratio following IET. This finding suggests an increase in cardiac vagal control following IET. Previous work from our laboratory demonstrated similar acute responses following a single isometric exercise session [14] and a potential mechanism for the improved cardiac autonomic modulation was improved BRS, which is under the control of central command. Indeed, BRS significantly increased following IET, which supports this mechanistic pathway. The arterial baroreflex is an important short and long-term regulator of arterial BP and research has demonstrated that BRS is inversely related to mBP and positively correlated with HRV [37]. Our findings are consistent with this response and suggest that a more sensitive baroreflex may function to reduce BP throughout 24-hours, which is supported by our ambulatory BP results. It may be postulated that IET promotes alterations in cardiovascular control sites, via neural remodelling or endogenous factors, such as the nitric oxide pathway, which would facilitate vagal cholinergic activity, improved baroreflex response and heightened antagonism of cardiac sympathetic activity [38], all of which act to reduce arterial BP.

Inflammatory and Vascular Biomarkers

The cascade from the development of HTN to adverse cardiovascular events remains unclear. However, altered vascular function and early structural remodelling are considered markers of subclinical organ damage in HTN and are independent predictors of CVD [39]. The endothelium plays a vital role in maintaining vascular homeostasis, and vascular endothelial dysfunction is characterised by a pro-inflammatory, pro-thrombotic and pro-constrictive

phenotype [40]. Endothelium derived nitric oxide (NO) plays a major role in flow mediated vasodilatation. In addition, NO inhibits platelet aggregation, adhesion of monocytes and leukocytes to the endothelium and inhibits vascular inflammation, which renders NO a significant anti-atherosclerotic molecule [41]. Systemic low-grade inflammation leads to increased ADMA, that may induce endothelial dysfunction and accelerate atherosclerosis. Indeed, previous research in healthy humans demonstrated that IL-6 is associated with increased ADMA levels and endothelial dysfunction [42]. Our results have demonstrated that IET significantly reduces IL-6 and ADMA. Although implied, an increase in NO bio-availability and associated vasodilatory capacitance, through a reduction in endogenous inhibitors of NO synthases may be an important mechanistic pathway for the BP reductions observed in hypertensive participants following IET. The significant reduction in TPR in our study and prior IET and aerobic exercise training studies [43,44] support this concept. Larger prospective IET interventions are required to explore inflammatory and vascular biomarker responses further, since CRP, TNF α , VCAM-1 and ICAM-1 did not significantly change following training.

Our study has several limitations. First, despite being a home-based (self-directed) exercise intervention, participants were in regular contact with the experimenter, which is likely an important stimulus for sustained behaviour. Research has demonstrated that as contact is withdrawn, intervention effect declines [7]. As such, the effects of contact withdrawal on outcome measures is unknown. Second, the IET intervention is short (4-weeks) and further research is required to ascertain the long-term benefits. Third, our study only included male Caucasian individuals and the relative transference to female and different ethnic populations, which are known to be at greater risk of HTN is unknown. Finally, the authors also acknowledge the inherent limitations of a cross over design due to the potential carry

over effect and bias. However, a 3-week washout period was selected to ensure adequate time for participants to return to baseline. Importantly, no significant difference within and between groups were seen between visit 1 and 3 of the study, indicating sufficient washout. In addition, each participant verbally confirmed that they maintained their usual habits during the study, with the exception of IET.

Perspectives

We have demonstrated that unsupervised home-based wall squat IET performed at a relatively high intensity is well tolerated, safe and is associated with clinically significant reductions in BP as well as other important markers of cardiovascular risk. The potential importance of our findings is substantial, considering a 10 mmHg lower usual sBP and 5 mmHg lower usual dBP is associated with a 40% lower risk of stroke and 30% lower risk of mortality from ischemic heart disease and other vascular causes throughout middle age [29]. Although the 4-week training intervention maybe of inadequate duration to support any claims for the long-term benefits of IET and/or ascertain changes in target organ damage and mortality benefit, our data is the first to demonstrate sustained BP lowering, improved cardiac autonomic modulation, in particular BRS, and reductions in IL-6 and ADMA, all of which are associated with improved cardiovascular health. Moreover, IET may provide a viable, cost effective and favourable alternative to traditional non-pharmacological interventions for the management of HTN, due to a lower exercise time commitment and home-based model. Although longer-term studies are required, our findings support the role of IET as a therapeutic and preventative intervention in the treatment of HTN.

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Figure Legend

Figure 1: Study flow diagram illustrating the randomised cross over design and time points of physiological measures acquired. Note: * = indicates the measurement time point for acquiring resting and ambulatory blood pressure, cardiac autonomic modulation, hemodynamics and blood sampling.

Figure 2: Illustrates the density distribution, average and individual delta change in; A, Ambulatory sBP; B, Ambulatory mBP; C, Ambulatory dBP following IET and control conditions.

Figure 3: Illustrates the difference in mean hour-by-hour ambulatory BP, pre and post IET for; A, Ambulatory sBP; B, Ambulatory mBP; C, Ambulatory dBP.