Myocardial work and left ventricular mechanical adaptations following isometric exercise training in hypertensive patients.

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Abstract

Purpose: Hypertension is a major risk factor for cardiovascular disease. Isometric exercise training (IET) reduces resting and ambulatory blood pressure; however, few studies have investigated the myocardial adaptations following IET.

Methods: We randomly assigned 24 unmedicated hypertensive patients in a cross-over study design to 4-weeks of IET and control period, separated by a 3-week washout period. Speckle tracking echocardiography was used to measure left ventricular (LV) mechanics, and global myocardial work indices were derived from non-invasive LV pressure-strain loops constructed from global longitudinal strain (GLS) indexed to brachial systolic blood pressure.

Results: IET significantly improved GLS (-2.3±2%, $p<0.001$) and global work efficiency (2.8±2%, $p<0.001$), and significantly reduced global wasted work (-42.5±30 mmHg%, $p<0.001$) with no significant change during the control period.

Conclusions: This is the first evidence to demonstrate that IET significantly improved cardiac health in a relevant patient population. Our findings have important clinical implications for patients with high blood pressure and support the role of IET as a safe and viable therapeutic and preventative intervention in the treatment of hypertension.

Key words: Cardiac mechanics, hypertension, myocardial work, isometric exercise training.

Abbreviations:
Blood pressure (BP)
Diastolic blood pressure (dBP)
Global constructive work (GCW)

Global longitudinal strain (GLS)
Global wasted work (GWW)
Global work efficiency (GWE)
Global work index (GWI)
Isometric exercise training (IET)
Left Ventricle (LV)
Left ventricular ejection fraction (LVEF)
Systolic blood pressure (sBP)

Introduction

Despite the availability of low cost anti-hypertensive medication and primary preventative interventions, arterial hypertension remains a leading modifiable risk factor for cardiovascular disease and all-cause mortality (Lim et al. 2012; Millar et al. 2014). As a result of increased after-load, long-standing hypertension elicits detrimental cardiac maladaptations, which may induce a progressive deterioration in structural, functional and cardiac mechanical parameters, leading to poor clinical prognosis (Oh and Cho 2020).

Current exercise guidance for the management of blood pressure (BP) is unlikely to benefit long-term cardiovascular risk (Williamson et al. 2016). Indeed, a recent consensus document (Hanssen et al. 2021) highlights that greater reductions in BP across the population may be achievable with personalised exercise prescription. Isometric exercise training (IET) is a recommended (Hanssen et al. 2021) and personalised intervention, which produces clinically significant reductions in resting (López-Valenciano et al. 2019) and ambulatory BP (Taylor et al. 2019) with a magnitude greater than the average BP reduction achieved with a single, standard dose anti-hypertensive drug (Law et al. 2009). However, despite the potential implications of these findings for cardiac health, very little research has directly investigated the effects of IET on myocardial parameters.

Left ventricular (LV) global longitudinal strain (GLS) is a measure of myocardial deformation and has been shown to detect sub-clinical LV dysfunction, even when LV ejection fraction (LVEF) remains within normal range (Tops et al. 2017). Indeed, GLS is commonly reduced in patients with hypertensive heart disease (Soufi Taleb Bendiab et al. 2017) and has prognostic value in predicting cardiovascular (Biering-Sørensen et al. 2017) and all-cause mortality (Stanton et al. 2009). However, it has been shown that GLS is load dependent which may lead to misinterpretation of the true contractile function of the myocardium,(Sutherland et al. 2004) especially in response to interventions which alter after-load. Myocardial work is a novel parameter for the assessment of myocardial function, which is derived from LV pressure-strain loop analysis, which incorporates GLS and arterial BP (loading conditions). When compared to controls, hypertensive patients had significantly elevated myocardial global work index (GWI) and global constructive work (GCW) compared to controls, despite GLS and LVEF being preserved (Chan et al. 2019).

Previous research from our laboratory demonstrated significant improvements in LV mechanics immediately following a single session of isometric exercise (O'Driscoll et al. 2017). However, it is unknown if these acute responses translate into sustained adaptations. As such, the aim of this study is to investigate adaptations in global myocardial work and LV mechanics following a short-term programme of IET.

Methods

Study population and ethical approval

We studied twenty-four physically inactive participants (43.8±7.3 years, 177.2±7 cm, 88.3±12 kg), classified as stage 1 hypertensive in accordance with current guidelines (Whelton et al. 2018). All participants had no history of cardiac or metabolic disease, were non-smokers and presented with normal clinical cardiovascular examination and 12-lead ECG. None of the participants were under any acute or chronic pharmacotherapy, including antibiotics. This research study conformed to the Declaration of Helsinki principles and was approved by the local ethics committee (Ref:12/SAS/122). Written informed consent was obtained from all participants before testing.

Experimental Procedures

All participants were randomized in a cross-over design to a 4-week IET intervention or a 4-week control period, separated by a 3-week washout period (Figure 1). All participants were required to fast for at least 4 hours and refrain from alcohol and caffeine consumption 24-hours before testing, whilst maintaining normal dietary and circadian routines throughout the study and each phase of testing. Participants were required to attend the Canterbury Christ Church University Laboratory on five separate occasions. The initial visit comprised of an incremental isometric wall-squat test to determine the appropriate individualised knee joint angle for effective IET intensity prescription (previously described by Taylor et al. (Taylor et al. 2019)), with the remaining sessions dedicated to the acquisition of the relevant cardiovascular parameters.

Conventional echocardiography

Transthoracic echocardiography was performed pre and post the 4-week IET intervention and control period. All cardiac measures were recorded according to current guidelines(Lang et al. 2015) and stored for offline analysis using commercial software (EchoPAC, V202, GE

Healthcare). Participants were measured in the left lateral decubitus position by one consistent sonographer using a Vivid-q ultrasound system (GE Healthcare, Milwaukee, Wisconsin) with a 1.5-3.6 MHz phased array transducer (M4S-RS Matrix cardiac ultrasound probe). Images were acquired in the parasternal short and long-axis and apical 2-,3- and 4- chamber views. LV ejection fraction was determined via the modified biplane Simpson's rule. Transmitral early (E) and late (A) diastolic-filling velocities were assessed from the apical 4-chamber view via pulsed-wave tissue doppler imaging, with the sample volume placed at the tips of the mitral valve. Further tissue doppler imaging was captured at the lateral and septal mitral annulus to assess peak longitudinal (S'), peak early diastolic (E'), and peak late diastolic (A') velocities, with values averaged. LV filling pressure was estimated from the mitral E/E' ratios (Ommen et al. 2000).

Cardiac mechanics and global myocardial work parameters

Two dimensional speckle tracking imaging was utilised to acquire strain and time-derivative strain rate measures. LV longitudinal strain and strain rate were obtained from the apical 2-, 3- and 4 chamber views. Peak global strain rate during early and late diastole and their ratio as indices of diastolic mechanics was calculated as previously described (Wang et al. 2007). The highest quality images were used for tracing the endocardium and a full-thickness myocardial region of interest was selected to ensure effective application of speckle tracking analysis. All images were reviewed and excluded if any failed to meet the required optimisation and standardisation. Images were optimized for scan depth and sector width to obtain high frame rates (>60 Hz) and kept consistent throughout each participant examination. The trace line of the endocardium and/or region-of-interest width was readjusted to ensure an adequate tracking score. The reproducibility of speckle-tracking measures from the present sonographer has been reported in previous work (O'Driscoll et al. 2017, 2018).

Global myocardial work parameters were achieved through non-invasive methodology which has been previously validated (Russell et al. 2012, 2013). With the acquired GLS parameters and resting clinic BP, a non-invasively estimated LV-pressure strain loop curve was produced. With this, myocardial work was computed segmentally by strain values over time which elicited segmental shortening rate. This was subsequently multiplied by LV pressure, which was then integrated over time to produce the global and segmental myocardial work parameters as a function of time. Global wasted work (GWW) was defined as the work performed during segmental shortening against a closed aortic valve during isovolumetric relaxation, or segmental lengthening during systole. Conversely, GCW was defined as the work performed during segmental shortening in systole or during lengthening in isovolumetric relaxation. Global work efficiency (GWE) was acquired via calculating the total sum of constructive work in all segments and divided by the sum of GCW and GWW in all segments, resulting in the percentage of constructive over total work. Global work index was acquired by measuring the total amount of work performed (total area under the pressure-strain curve).

Resting clinic blood pressure

Brachial artery BP was recorded 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 (Whelton et al. 2018).

Isometric exercise training intervention

The 4-week IET intervention period consisted of unsupervised home-based isometric wall squat training, performed 3 days per week (12 sessions total). Each session comprised of 4 x 2 min bouts of isometric wall squat, separated with 2-min rested intervals. All IET sessions were performed at an individualised knee joint angle to ensure an effective intensity. Each participant recorded their heart rate at the end of each IET bout (Polar RS400 Computer and a

Polar WearLink V2 transmitter; Polar Electro Oy, Kempele, Finland) and uploaded their data to a personal online database to allow for close monitoring and regulation of exercise intensity. All training sessions were separated by 48 hours recovery. During the control period, participants were requested to maintain their usual routine and daily activities with adherence to this confirmed prior to laboratory assessment.

Sample size estimation

Based on previous evidence (Wiles et al. 2010) available at the time of data collection, we expected this IET intervention to elicit a minimum reduction of 5mmHg in resting systolic BP, with no significant change in the control group. A reduction of this magnitude is considered clinically significant (Beevers et al. 2007). With this likely change and the coefficient of variation (4.6%) for systolic BP from Wiles et al (Wiles et al. 2010), we estimated a sample size of 18 participants, with 80% power and P less than 0.05. Considering an estimated dropout rate of 20-30%, we determined an appropriate sample size of 24 participants. Our aim was to investigate adaptations in global myocardial work and left ventricular mechanics in a cohort powered for a reduction in arterial BP.

Statistical analysis

Continuous variables are expressed as mean 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. All data were analysed using the statistical package for social sciences (SPSS 26 release version for Windows; SPSS Inc., Chicago IL, USA).

Results

All participants completed the study, with resting BP and cardiac measures successfully acquired on all participants. There were no significant between or within group differences from the initial pre-intervention measures and the post-washout measures, confirming that the 3-week washout period was sufficient for these parameters to return to baseline.

Resting blood pressure

Resting clinic systolic and diastolic BP significantly decreased following IET compared with control (-12.4±3.9 and -6.2±3.8 mmHg, respectively) (both $p<0.001$).

Cardiac function: conventional and tissue doppler measures

All baseline and post-intervention cardiac functional and tissue doppler measures are presented in Table 1. There were significant changes in measures of LV diastolic function following IET compared with control, including significant decreases in mitral valve deceleration time (-19±58, $p=0.001$) and mitral valve A velocity (-0.05±0.1, $p=0.028$). LV ejection fraction (1.5±3.4, $p=0.004$) and end-diastolic volume (5.2±8mL, $p=0.004$) significantly increased following IET compared with the control condition.

Measurement of LV tissue doppler parameters demonstrated significant increases in septal E' (0.01±0.02, $p=0.032$) and lateral A' (-0.01±0.02, $p=0.045$). In addition, estimated LV filling pressures all significantly decreased following the IET intervention compared with control, with significant decreases in lateral E/E' (-1.12±1.1, $p=0.001$), septal E/E' (-1.09±1.7, $p<0.001$) and average E/E' (-1.1±1.3, $p=0.001$).

Cardiac mechanics and global myocardial work parameters

As presented in Table 2, there were significant changes in global myocardial work parameters in the IET condition compared with control, with a significant decrease in global wasted work (-42.5±30mmHg%, $p<0.001$) and a significant increase in global work efficiency (2.8±2%, $p<0.001$). However, there were no significant differences in global work index ($p=0.379$) or global constructive work ($p=0.165$) between the IET or control conditions. Furthermore, there were significant improvements in both peak LV global longitudinal strain (-2.3±2, $p<0.001$) strain rate (-0.23±0.1, $p<0.001$) and strain rate early diastole (0.1±0.2, $p=0.018$) following IET compared to the control condition.

Discussion

To our knowledge, this is the first study to investigate cardiac functional, mechanical and myocardial work adaptations following a short-term IET intervention. The significant reductions in BP following IET, as previously reported (Taylor et al. 2019), are associated with significant improvements in cardiac mechanics and global myocardial work parameters. The significant improvement in GLS following 4-weeks of IET is greater than the improvement following aerobic team sport exercise (4.7% and 7.8% improvement in GLS at 4 and 12 months, respectively) and resistance training exercise (6.7% and 6.2% improvement in GLS at 4 and 12 months, respectively) in untrained older adults (Schmidt et al. 2014). In addition, the improvement in GLS is greater than the 6.1% improvement following pharmacological BP management in newly diagnosed hypertensive patients (Tzortzis et al. 2020). A depressed GLS is well-established as an early marker of LV dysfunction, with previous research demonstrating its value in predicting outcomes. Specifically, Kalam et al (2014) reported GLS to be a superior prognostic tool for predicting adverse cardiac events to LV ejection fraction, which has been long respected as a staple measure of LV function (Kalam et al. 2014). Using outcome data from the general population, the 13.3% increase in GLS seen in the current study is associated with a >24% reduced risk of all-cause mortality and >32% lower risk of heart failure (Biering-Sørensen et al. 2017). As such these results may have significant clinical implications, especially in light of the substantial prevalence of impaired GLS reported in hypertensive populations (Biering-Sørensen et al. 2017; Soufi Taleb Bendiab et al. 2017).

Separately, our results demonstrate significant improvements in markers of diastolic function, including tissue doppler parameters and estimated filling pressure. These results also provide independent prognostic utility when considering the implications of diastolic dysfunction on mortality outcomes, even in the context of normal ejection fraction (AlJaroudi et al. 2012). Mechanistically, the functional and mechanical cardiac adaptations observed in the present study are almost all understood to be load-dependant parameters (Oh and Cho 2020) and support many of the acute cardiac responses seen following IET (O'Driscoll et al. 2017). Thus, the mechanistic underpinning of such responses may be explained via the same pathway in which resting arterial BP is reduced following IET, which although is not entirely understood, has been previously linked to enhancements in autonomic nervous system and peripheral vascular / endothelial derived parameters (Taylor et al. 2019). However, our results demonstrate that the reduced after-load significantly improves myocardial health, which together has significant clinical implications. Specifically, these findings provide support for IET as a cardioprotective intervention due to the known pathological cascade to myocardial dysfunction and mortality seen in hypertensive heart disease. In addition, IET produced a statistically significant increase in LV end diastolic volume, which remained within the normal range and may be a beneficial adaptive response in a similar instance to those observed following aerobic training (Andersen et al. 2014). As such, further research is required to investigate IET as a modality in clinical populations who demonstrate adverse cardiac remodelling.

Global myocardial work provides a novel approach to assessing cardiac function and overcomes the load dependency limitations of GLS and LV ejection fraction by incorporating arterial blood pressure (afterload) into its algorithm (Chan et al. 2019). Despite no statistically significant changes in myocardial global work index or global constructive work, we found significant improvements in global wasted work and global work efficiency. A significant improvement in global wasted work may be related to a reduction in myocardial wall stress, again linked to reductions in LV afterload; while a significant improvement in work efficiency is derived from an improved ratio of constructive work to wasted work (Chan et al. 2019). To our knowledge, this is the first study to directly investigate the effects of IET, or any short-term exercise training intervention on parameters of myocardial work, providing further insight into the cardiac adaptations following such intervention. However, future research is required to understand the prognostic value of these parameters in hypertensive populations.

Limitations

This research consisted entirely of Caucasian male participants and therefore future investigation using female and different ethnic populations is required. In addition, the impact of IET on medicated hypertensive populations requires research to investigate if BP regulation and myocardial health is improved. Our cross-over methodology demonstrated that the observed adaptations reported are reversed following a brief (3-weeks) washout period; thus, future research is required to understand the longer-term adaptations and minimum-effective training frequency required to sustain these responses. Finally, being single-centre, further prospective multi-centre studies are required to confirm these findings.

Clinical perspective

As the leading risk factor for cardiovascular disease and all-cause mortality, hypertension can elicit a progressive deterioration in cardiac performance via compensatory cardiac maladaptations, ultimately leading to poor clinical prognosis (Lim et al. 2012; Millar et al. 2014; Oh and Cho 2020). IET is a short duration, home-based exercise mode, which has been demonstrated to produce clinically significant reductions in resting BP at a magnitude superior to that of traditional exercise training modalities (Cornelissen and Smart 2013; Taylor et al. 2019; López-Valenciano et al. 2019). This is the first study to demonstrate the effects of such anti-hypertensive responses on measures of cardiac performance, with significant improvements in LV systolic and diastolic function, mechanics and global myocardial work efficiency. While these adaptations are likely primarily attributed to LV afterload changes, such findings provide evidence for the support of IET in both BP management and subsequently cardiac health, with significant prognostic implications regarding future cardiovascular risk. Given the recent consensus document provided by the European Association of Preventative Cardiology and European Society of Cardiology Council on hypertension (Hanssen et al. 2021), this work supports IET as a powerful intervention for the personalised management of BP and cardiac health in individuals with stage 1 hypertension.

Conclusion

A short duration IET intervention induced clinically significant reductions in resting BP, which produced significant improvements in measures of cardiac systolic and diastolic function, mechanics and global myocardial work efficiency. This is the first study to investigate the cardiac adaptations following a short-term IET intervention, both providing support for its efficacy as an anti-hypertensive intervention and for improved cardiac health. In addition to investigating the impact of IET in female and different ethnic populations, future long-term IET interventions are imperative to drive this field of research.

Declarations

Acknowledgments: We thank the participants who volunteered to participate in the study.

Disclosures: None.

Conflict of Interest: There are no conflicts of interest.

Ethics Approval: This research study conformed to the Declaration of Helsinki principles and was approved by the local ethics committee (Ref:12/SAS/122). Written informed consent was obtained from all participants before testing.

Data Availability: The sharing of data in an open-access repository was not included in our participants consent. Thus, in accordance with standard ethical practice, data may only be available on request from the corresponding author.

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Figure legends

Figure 1: Study flow diagram illustrating the randomized cross over design and time points of echocardiographic assessment. Note: TTE = transthoracic echocardiography.