Left atrial mechanics and aortic stiffness following high intensity interval training: a randomised controlled study.

Navazh Jalaludeen[1], Samuel J. Bull[2], Katrina A. Taylor[2], Jonathan D. Wiles[2], Damian A. Coleman[2], Lucinda Howland[2], Omar Mukhtar[1], Joseph Cheriyan[1], Ian B. Wilkinson[1], Rajan Sharma[3], & Jamie M. O'Driscoll[2,3]

Author Affiliations:

[1] Cambridge Clinical Trials Unit, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK.

[1] School of Human and Life Sciences, Canterbury Christ Church University, Kent, UK.

[3]Department of Cardiology, St George's Healthcare NHS Trust, Blackshaw Road, Tooting, London, UK.

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

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Abbreviations

ANCOVA – Analysis of covariance

BP – Blood pressure

CVD – Cardiovascular disease

dBP – Diastolic blood pressure

HIIT – High intensity interval training

IVSd = Interventricular septal diameter diastole

LA – Left atrial

LV – Left ventricle

mBP – Mean blood pressure

MPI – Myocardial performance index

NO – Nitric oxide

PALS – Peak atrial longitudinal strain

PA – Physical activity

PWd – Posterior wall thickness diastole

ROI – Region of interest

sBP – Systolic blood pressure

VSM – Vascular smooth muscle

Abstract

Purpose: High intensity interval training (HIIT) has been shown to improve important health parameters, including aerobic capacity, blood pressure, cardiac autonomic modulation and left ventricular (LV) mechanics. However, adaptations in left atrial (LA) mechanics and aortic stiffness remain unclear.

Methods: Forty-one physically inactive males and females were recruited. Participants were randomised to either a 4-week HIIT intervention (n=21) or 4-week control period (n=20). The HIIT protocol consisted of 3x30-second maximal cycle ergometer sprints with a resistance of 7.5% body weight, interspersed with 2-minutes of active unloaded recovery, 3 times per week. Speckle tracking imaging of the LA and M-Mode tracing of the aorta was performed pre and post HIIT and control period.

Results: Following HIIT, there was significant improvement in LA mechanics, including LA reservoir (13.9±13.4%, p=0.033), LA conduit (8.9±11.2%, p=0.023) and LA contractile (5±4.5%, p=0.044) mechanics compared to the control condition. In addition, aortic distensibility (2.1±2.7$cm^2 \cdot dyn \cdot^{-1} \cdot 10^3$, p=0.031) and aortic stiffness index (-2.6±4.6, p=0.041) were improved compared to the control condition. In stepwise linear regression analysis, aortic distensibility change was significantly associated with LA stiffness change R^2 of 0.613 (p=0.002).

Conclusion: A short-term programme of HIIT was associated with a significant improvement in LA mechanics and aortic stiffness. These adaptations may have important

health implications and contribute to the improved LV diastolic and systolic mechanics, aerobic capacity and blood pressure previously documented following HIIT.

Introduction

Physical activity (PA) and exercise training are considered important strategies in reducing mortality as well as preventing cardiovascular disease (CVD) risk (Paffenbarger et al. 1986). Large scale observational studies demonstrate that regular exercise is cardioprotective and reduces the incidence of numerous chronic diseases, including coronary artery disease, diabetes, hypertension, cancer, and obesity (Warburton et al. 2006). As such, physical activity is a viable therapeutic and prophylactic intervention for the primary prevention of CVD. However, despite substantial health benefits observed when meeting international guideline recommendations for PA (150-minutes of moderate-intensity or 75 minutes of vigorous-intensity, or an equivalent combination, per week), adherence is poor and lack of time is often cited as a common barrier.

High intensity interval training (HIIT) has generated significant interest as an exercise modality to improve cardiovascular health, with significant improvements in functional capacity (Weston et al. 2014), metabolic health (Gibala et al. 2012), and cardiac autonomic modulation (O'Driscoll et al. 2018), while remaining time-efficient. Recent work has demonstrated improved left ventricular (LV) mechanics, including systolic and diastolic torsion and arterial blood pressure following 2-weeks of HIIT (O'Driscoll et al. 2018). The impact these adaptations have on left atrial (LA) and aortic function are not yet reported following HIIT. The proximal aorta plays a pivotal role in preserving the arterial-ventricular coupling by buffering the systolic load during each ventricular ejection (O'Rourke 1994) and notably, the left atrium plays a key role in regulating left ventricular function. Numerous studies have shown a close association between reduced arterial compliance and LV diastolic impairment (Zito et al. 2014; Xu et al. 2011). Moreover, using cardiac magnetic resonance

imaging, the DALLAS heart study (Maroules et al. 2014) and MESA study (Redheuil et al. 2014) demonstrated a close association between reduced aortic distensibility and all-cause mortality (Redheuil et al. 2014). Furthermore, previous studies have demonstrated a close association between LV diastolic dysfunction and arterial stiffness (Cauwenberghs et al. 2016; Kaess et al. 2016). In addition, LA performance is impaired in patients with hypertension and diabetes despite normal LA size in comparison to controls (Mondillo et al. 2011). Aerobic exercise is associated with decreased arterial stiffness (Gates et al. 2003) and improved LA performance (Edelmann et al. 2011). However, little is known about the interaction between arterial compliance and LA function following HIIT. The purpose of this study is to investigate the effects a four-week HIIT intervention has on LA deformation, LV function and aortic compliance (aortic mechanics), evaluated non-invasively by echocardiography compared to a control group, in a physically inactive population. We hypothesized that HIIT would significantly improve LA mechanics and aortic stiffness.

Methods

This study was a single-centre, 4-week randomised controlled trial comparing a HIIT intervention with a control group. The study took place at the School of Human and Life Sciences at Canterbury Christ Church University (CCCU) in the UK. This study was performed with approval from the Ethics Committee of CCCU in accordance to the Declaration of Helsinki. All participants recruited provided signed informed consent and the CONSORT guidelines were followed during the course of the research (Schulz et al. 2010).

Participants

Forty-four physically inactive males and females (aged 23±2.7 years) volunteered for the study. Resting arterial blood pressure (BP) was recorded in a temperature controlled room pre and post the HIIT intervention and control condition using a validated automated device (Dinamap Pro 200 Critikon; GE Medical Systems, Freiburg, Germany), according to recent guidelines (Williams et al. 2018). Participant height was recorded at baseline using a stadiometer (Seca 217 Stadiometer, Hamburg, Germany), weight was measured pre and post the HIIT intervention and control condition using column scales (Seca 700 Mechanical Column Scales, Hamburg, Germany), and body surface area was calculated according to Mosteller's formula (Mosteller, 1987). All participants had no prior medical history and completed a physical activity readiness questionnaire prior to recruitment. Participants were randomised using stratified randomisation for gender to the HIIT or control group, in order to avoid gender bias in each group (Good 2006). All participants were advised to adhere to the same dietary and physical activity habits, refrain from alcohol and caffeine intake 24 hours before each visit and to avoid food intake at least 4 hrs prior to the laboratory visits to avoid

postprandial haemodynamic changes. Any participants presenting with any cardiovascular/metabolic disease or taking any medication was excluded from the study.

High intensity interval training intervention

The HIIT intervention was comprised of twelve sessions over a 4-week period (3 sessions/week), with each session consisting of three Wingate tests separated by a 2-minute active (unloaded) recovery period. Each Wingate test was characterised by 30 seconds of maximal cycling against a resistance equal to 7.5% of each participant's body mass and performed on a Wattbike trainer (Nottingham, England). Each participant performed a 5-minute warm up before and a 5-minute cool down after each HIIT session. Strong verbal encouragement was provided during exercise and participants were unaware of the time remaining in each 30-second sprint.

Transthoracic Echocardiography

A standardized transthoracic echocardiogram and Doppler examination was performed using a commercially available Vivid-q ultrasound system (GE Healthcare, Milwaukee, Wisconsin) with a 1.5 – 3.6 MHz phased array transducer. All images were acquired at baseline and post intervention in the HIIT and control group by the same sonographer. The images were stored in raw archive DICOM data for offline analysis and measurements were recorded by an experienced echocardiographer (NJ) who was blinded to participant characteristics and group allocation. Echocardiographic studies were performed and standardized in accordance to current ASE/EACVI guidelines (Evangelista et al. 2008). LV dimension, wall thickness, geometry, mass, and LV systolic and diastolic parameters were assessed. LV ejection fraction

was estimated using Simspon's rule. LV diastolic function was assessed using the EACVI diastolic guidelines (Nagueh et al. 2016) in the apical 4 chamber view using PW Doppler flow at the tips of the mitral valve to obtain mitral E ($m \cdot s^{-1}$), mitral A ($m \cdot s^{-1}$) and E wave deceleration time (ms). Using tissue Doppler imaging at the annular level of the mitral valve, the septal and lateral peak early diastolic (E'), late diastolic (A') and peak longitudinal systolic velocity (S') of the myocardium were recorded. LV filling pressure was estimated from the Mitral E/E'.

Left atrial parameters

LA deformation was evaluated from the septal and lateral wall of the left atrium in the apical four chamber view (Figure 1). LA strain imaging was analysed offline using a GE EchoPac workstation. During image acquisition, frame rates between 60-90 frames$\cdot s^{-1}$ were recorded. The software automatically generates a region of interest (ROI) with a default width of 15mm and tracing of the left atrium was performed. If tracking of the LA myocardium was inadequate, the ROI was manual adjusted to enhance tracking. The automated software generated traces depicting the regional longitudinal strain for each segment and calculated global longitudinal strain. Using P wave onset enabled us to define the first negative peak, which occurred at maximal LA contraction and represented its contractile function (contractile strain), the first positive peak, which occurred at mitral valve opening and represented LA conduit function (conduit strain), and the difference of these peaks, which represented reservoir function (reservoir strain). Global LA strain parameters were assessed as the average of six segmental values. Peak atrial longitudinal strain (PALS) was measured from the onset of the QRS to the positive peak of strain at the onset of the P wave (Mondillo et al. 2011). LA stiffness was estimated using the formula, LA stiffness = (E/E')/PALS.

Aorta parameters

Two-dimensional guided M-mode assessment of the ascending aorta in the parasternal long axis view during systole and diastole was used to measure the elastic properties of the aorta (Figure 2). The formulas used to calculate the aortic parameters were as follows:

- Aortic strain (%) = (aortic systolic diameter – diastolic diameter) x 100 / diastolic diameter.

- Aortic Distensibility ($cm^2 \cdot dyn^{-1}$) = (2 x aortic strain) / (systolic pressure - diastolic pressure).

Sample size calculation

Based on operator coefficient of variation for diastolic function and estimated filling pressure (E/E') using transthoracic echocardiography, a sample size of 14 to 17 participants in each group has 80% power to detect a significant difference in diastolic function and estimated filling pressure, respectively, with a 2-sided $p<0.05$. It was estimated a drop-out rate of between 10-30% leading to an overall sample size of 44 participants (22 in each group).

Statistical analysis

Unless otherwise stated, continuous variables are expressed as mean ± standard deviation. All data analysis was performed using the Statistical Package for Social Sciences (SPSS V22.0, release version for windows; SPSS Ins., Chicago, IL, USA). Normal distribution of all

continuous variables was confirmed using the Shapiro-Wilk test (Field 2018). Comparison of data collected pre and post intervention between the control and HIIT groups (change scores) was analysed using a one-way analysis of covariance (ANCOVA) with baseline parameters used as covariates to assess whether changes in echocardiographic and BP parameters following both intervention and control periods are influenced by initial baseline values. Stepwise linear regression analysis using LA stiffness as the dependent variable was conducted. Statistical significance was deemed *a priori* as $p<0.05$.

Results

A total of 41 participants completed the HIIT intervention (n=21, age 21±1.7 years, height 173.7±9.5 cm) and control period (n=20, age 22±3.5 years, height 172.4±8.8 cm). Two participants dropped out the study at randomisation and 1-participant from the control group discontinued, without giving a reason. Descriptive characteristics are presented in Table 1. No differences were apparent between conditions for participant's age, height, or BP at baseline. Following 4-weeks of HIIT there was a statistically significant reduction in resting systolic BP (-6.86±8.76 mmHg) compared to the control condition (-1.15±9.4 mmHg, p=0.041).

Conventional cardiac structural and functional parameters

The conventional cardiac structural and functional parameters at baseline and following HIIT and control periods are displayed in Table 2. HIIT significantly increased LV ejection time (p=0.001), lateral S' (p=0.018), lateral E' (p<0.001), and septal S'(p=0.01), and significantly reduced LV internal diameter in systole (p=0.027) and myocardial performance index (p=0.039) compared to the control condition.

Left atrial mechanics and aortic function

Following 4-weeks of HIIT, there was significant improvement in LA mechanics compared to the control condition. LA reservoir (p=0.033), LA conduit (p=0.023), and LA contractile (p=0.044) mechanics significantly improved following HIIT compared to the control condition. HIIT was also associated with a statistically significant reduction in LA stiffness

compared to the control condition (p=0.032). There was a significant reduction (p=0.012) in the ascending aortic diastolic diameter and significant improvement in aortic distensibility (p=0.031) following HIIT compared to the control condition. These adaptations were associated with a significant reduction in aortic stiffness (p=0.041) following HIIT compared to control. The LA mechanical and aortic functional parameters at baseline and following HIIT and control periods are displayed in Table 3. Following stepwise linear regression analysis with LA stiffness as the dependent variable, aortic distensibility (ß = -0.557, p=0.002) and LA conduit function (ß = -0.772, p<0.001) were significantly associated with LA stiffness. The overall model fit was R^2 = 0.613 (Figure 3).

Discussion

The present study is the first randomised controlled study to investigate the effect HIIT has on LA deformation and aortic mechanics in a cohort of physically inactive individuals. The results of the study demonstrate that HIIT significantly improved LA mechanics and aortic distensibility compared to a control condition. Reductions in aortic bioelasticity and LA performance negatively effects LV systolic and diastolic function (Pandey et al. 2017). As such, these findings may have wider health and clinical implications in not only individuals who are unable to meet current PA guidelines, but clinical groups, such as hypertensive, diabetic and heart failure patients with preserved ejection fraction.

Left atrial performance

During each cardiac cycle, the left atrium deforms such that during systole the left atrium stretches and recoils to its original shape during diastole. It is evident from previous studies that there is a closer interlink between LA stretch and LV global longitudinal strain, LA volume and LA ejection fraction (Russo et al. 2012). All parameters of LA mechanics were significantly improved following HIIT in our study compared to control conditions. In addition, HIIT was associated with a significant improvement in LA compliance, which was estimated using a non-invasive calculation of LA stiffness. When the left atrium is highly compliant, mean LA pressure is lower due to a steady transformation of venous flow into the LV (Suga 1974). Ultimately, our findings suggest these adaptations in LA deformation may improve cardiac performance. Indeed, our study demonstrated significant improvements in markers of cardiac performance, including ejection time, lateral and septal S', lateral E', and myocardial performance index. These results are also supported by recent research from our groups laboratory, which demonstrated significant improvements in systolic and diastolic LV mechanics (O'Driscoll et al. 2018). In addition, animal studies have shown increased calcium

reuptake by the sarcoplasmic reticulum up to 30% higher in the myocardium following aerobic interval training (Matsunaga et al. 2007), which determines LV relaxation. A greater calcium reuptake from myofilaments augments active relaxation and improving LV filling (Carrick-Ranson et al. 2012).

Aortic mechanics

Aortic distensibility is a parameter, which is closely related to the bioelastic function of the aorta and which serves as a marker for CVD (Laurent et al. 2006). The results of this study show that aortic distensibility and aortic stiffness index was significantly improved following 4-weeks of HIIT. Erol et al. (2002) demonstrated an increase in aortic distensibility and decreased aortic stiffness in elite athletes compared to a control group. Since our study was observational, the underlying mechanisms by which improved ascending aorta compliance are induced is unclear. However, improved arterial compliance following HIIT demonstrated in the present study may be due to local and systemic influences.

Any proposed mechanism must be consistent with structural and functional changes in the vascular system. Structurally, arterial compliance/distensibility is primarily determined by the composition of the arterial media such as vascular smooth muscle (VSM) and connective tissue (elastin and collagen fibres) (MacDonald and Nichols 2011). The elastin/collagen ratio in the proximal thoracic aorta determines the physical properties and the degree of VSM tone determines the functional properties. Relaxation of the VSM transfers less stress from collagen to elastin, which increases aortic compliance as a result of the active adaptation (Belz 1995). It is reasonable to assume that short term HIIT influences active adaptation of the aorta locally and systemically in improving arterial compliance. The significant reduction

in resting systolic blood pressure supports this concept. There is also suggestion that exercise can suppress sympathetic-adrenergic tone which increases arterial compliance (Tanaka et al. 2000). However, several studies have shown conflicting results regarding the role of arterial compliance modulated by sympathetic-adrenergic tone of smooth muscle in the arterial wall (Raper and Peterson 1969; Boutouyrie et al. 1994). It has been known for a long time that aortic diameter and compliance are influenced by vasoactive receptors such as Angiotensin II and noradrenaline, which exist within the large arteries (Bolton 1979; Vanhoutte et al. 1981). It seems reasonable to speculate that release of vasoactive substances may exert autocrine and paracrine influences on vascular tone and be a potential modulator for aortic compliance secondary to HIIT. It is also conceivable that, episodic shear stress on the endothelium of the arteries during exercise due to enhanced blood flow, releases nitric oxide (NO) thereby supporting flow dependant dilatation (Endo et al. 1994). Nonetheless, the present findings indicate that compared to control conditions, short term HIIT in a sedentary population significantly improves aortic elastic properties.

In this study, stepwise linear regression analysis revealed that aortic distensibility, which is an aortic bioelastic parameter, was significantly (p=0.002) associated with LA stiffness. In addition, LA reservoir strain was significantly associated with LA stiffness (p<0.001), which reflects the LA active relaxation. These findings are important since a reduction in aortic distensibility can impair LV active relaxation, through increased LA afterload that ultimately leads to LA myocardial fibrosis, which is key in LA systolic and diastolic dysfunction (Mondillo et al. 2011; Morris et al. 2011). Previous studies have shown increased LA stiffness is secondary to LA fibrosis in parallel with LV and large artery stiffening, secondary to subendocardial fibrosis (Morris et al. 2011) and medial degeneration (Jacob 2003) respectively. Miyoshi et al (2011) study demonstrated that LA function is related to arterial

compliance, suggesting increased arterial stiffness impairs early active relaxation (LA reservoir function), which is an early form of LA-LV-arterial decoupling.

Previous studies have attempted to study the association between LV diastolic dysfunction and arterial stiffness (Cauwenberghs et al. 2016; Kaess et al. 2016; Kim et al. 2017). Our study findings support the hypothesis that a four-week HIIT intervention improves aortic and LA mechanics and may provide some mechanistic basis for reduced cardiovascular risk in at-risk groups who undertake increased levels of exercise and consequent improved fitness. We postulate that this improved atrio-ventricular and ventriculo-arterial function after HIIT exercise may, if continued, have important health implications in cardio-metabolic diseases such as hypertension, diabetes and heart failure with preserved ejection fraction in the medium to longer term. Further studies are required to prove this in outcome driven trials of HIIT.

Strengths and limitations

This was a small, single-centre study design which recruited a Caucasian-only population. Our study does not allow the determination of a causal effect. A causal link in improving aortic and LA function following HIIT can be hypothesized; however, further longitudinal studies are needed to confirm this hypothesis. LA deformation analysis was performed using strain imaging in the apical 4 chamber view only and we used non-invasive imaging methods to analyse aortic mechanics similar to Stefanadis et al. (1990) technique, which has shown good correlation with invasive techniques. For the calculation of aortic distensibility, brachial arterial BP was used instead of aortic root pressure as there may not be any significant variation between both in healthy volunteers. Measurement of pulse wave velocity is

considered as the gold standard method for assessing arterial stiffness; however, our study focussed on utilizing transthoracic echocardiography in analysing aortic and LA function. Notwithstanding these limitations, our study was randomised and image analysis was performed by a single skilled operator blinded to participant characteristics and group allocation.

Conclusion

Our study demonstrated that a four-week HIIT intervention was associated with significant improvement in LA mechanics and aortic stiffness compared to non-exercise control conditions. The present study also suggests close interaction between aortic distensibility and LA stiffness. These adaptations may have important health implications and contribute to the improved LV diastolic and systolic mechanics, aerobic capacity and reduced arterial BP previously documented following HIIT. In light of the positive impact on the left atrium and aorta, HIIT is a promising exercise strategy for improving cardiometabolic health with minimal time commitment. Further investigation is warranted to identify the potential risks and benefit of long term HIIT and the optimal level of HIIT for cardiovascular protection.

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Figure legends

Figure 1: Left atrial strain imaging in the apical 4 chamber view. Note: AVC = Aortic valve closure; LAS_r = LA reservoir phase, LAS_{cd} = LA conduit phase, LASct = LA contraction phase, x-axis = Time (msec); y-axis = LA strain (%); top right graph illustrates segmental LA strain and bottom right graph illustrates mean LA strain.

Figure 2: Aortic distensibility measurement using M-mode in the parasternal long axis view using transthoracic echocardiography. Measurement of aortic distensibility and stiffness using the internal aortic diameter during the systolic and diastolic phase of the cardiac cycle from an M-mode tracing.

Figure 3: Correlation between delta left atrial stiffness and delta aortic distensibility following HIIT ($F(2,19)=15.062$, $p<0.001$) with an R^2 of 0.613).