

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

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## 26 Abbreviations

27 ANCOVA – Analysis of covariance

28 BP – Blood pressure

29 CVD – Cardiovascular disease

30 dBP – Diastolic blood pressure

31 HIIT – High intensity interval training

32 IVSd = Interventricular septal diameter diastole

33 LA – Left atrial

34 LV – Left ventricle

35 mBP – Mean blood pressure

36 MPI – Myocardial performance index

37 NO – Nitric oxide

38 PALS – Peak atrial longitudinal strain

39 PA – Physical activity

40 PwD – Posterior wall thickness diastole

41 ROI – Region of interest

42 sBP – Systolic blood pressure

43 VSM – Vascular smooth muscle

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## 51 Abstract

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

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

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65 **Results:** Following HIIT, there was significant improvement in LA mechanics, including LA  
66 reservoir ( $13.9 \pm 13.4\%$ ,  $p=0.033$ ), LA conduit ( $8.9 \pm 11.2\%$ ,  $p=0.023$ ) and LA contractile  
67 ( $5 \pm 4.5\%$ ,  $p=0.044$ ) mechanics compared to the control condition. In addition, aortic  
68 distensibility ( $2.1 \pm 2.7 \text{ cm}^2 \cdot \text{dyn}^{-1} \cdot 10^3$ ,  $p=0.031$ ) and aortic stiffness index ( $-2.6 \pm 4.6$ ,  $p=0.041$ )  
69 were improved compared to the control condition. In stepwise linear regression analysis,  
70 aortic distensibility change was significantly associated with LA stiffness change  $R^2$  of 0.613  
71 ( $p=0.002$ ).

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

75health implications and contribute to the improved LV diastolic and systolic mechanics,  
76aerobic capacity and blood pressure previously documented following HIIT.

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## 100Introduction

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102Physical activity (PA) and exercise training are considered important strategies in reducing  
103mortality as well as preventing cardiovascular disease (CVD) risk (Paffenbarger et al. 1986).  
104Large scale observational studies demonstrate that regular exercise is cardioprotective and  
105reduces the incidence of numerous chronic diseases, including coronary artery disease,  
106diabetes, hypertension, cancer, and obesity (Warburton et al. 2006). As such, physical activity  
107is a viable therapeutic and prophylactic intervention for the primary prevention of CVD.  
108However, despite substantial health benefits observed when meeting international guideline  
109recommendations for PA (150-minutes of moderate-intensity or 75 minutes of vigorous-  
110intensity, or an equivalent combination, per week), adherence is poor and lack of time is often  
111cited as a common barrier.

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113High intensity interval training (HIIT) has generated significant interest as an exercise  
114modality to improve cardiovascular health, with significant improvements in functional  
115capacity (Weston et al. 2014), metabolic health (Gibala et al. 2012), and cardiac autonomic  
116modulation (O'Driscoll et al. 2018), while remaining time-efficient. Recent work has  
117demonstrated improved left ventricular (LV) mechanics, including systolic and diastolic  
118torsion and arterial blood pressure following 2-weeks of HIIT (O'Driscoll et al. 2018). The  
119impact these adaptations have on left atrial (LA) and aortic function are not yet reported  
120following HIIT. The proximal aorta plays a pivotal role in preserving the arterial-ventricular  
121coupling by buffering the systolic load during each ventricular ejection (O'Rourke 1994) and  
122notably, the left atrium plays a key role in regulating left ventricular function. Numerous  
123studies have shown a close association between reduced arterial compliance and LV diastolic  
124impairment (Zito et al. 2014; Xu et al. 2011). Moreover, using cardiac magnetic resonance

125imaging, the DALLAS heart study (Maroules et al. 2014) and MESA study (Redheuil et al.  
1262014) demonstrated a close association between reduced aortic distensibility and all-cause  
127mortality (Redheuil et al. 2014). Furthermore, previous studies have demonstrated a close  
128association between LV diastolic dysfunction and arterial stiffness (Cauwenberghs et al.  
1292016; Kaess et al. 2016). In addition, LA performance is impaired in patients with  
130hypertension and diabetes despite normal LA size in comparison to controls (Mondillo et al.  
1312011). Aerobic exercise is associated with decreased arterial stiffness (Gates et al. 2003) and  
132improved LA performance (Edelmann et al. 2011). However, little is known about the  
133interaction between arterial compliance and LA function following HIIT. The purpose of this  
134study is to investigate the effects a four-week HIIT intervention has on LA deformation, LV  
135function and aortic compliance (aortic mechanics), evaluated non-invasively by  
136echocardiography compared to a control group, in a physically inactive population. We  
137hypothesized that HIIT would significantly improve LA mechanics and aortic stiffness.

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## 150**Methods**

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152This study was a single-centre, 4-week randomised controlled trial comparing a HIIT  
153intervention with a control group. The study took place at the School of Human and Life  
154Sciences at Canterbury Christ Church University (CCCU) in the UK. This study was  
155performed with approval from the Ethics Committee of CCCU in accordance to the  
156Declaration of Helsinki. All participants recruited provided signed informed consent and the  
157CONSORT guidelines were followed during the course of the research (Schulz et al. 2010).

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## 159**Participants**

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161Forty-four physically inactive males and females (aged  $23\pm 2.7$  years) volunteered for the  
162study. Resting arterial blood pressure (BP) was recorded in a temperature controlled room pre  
163and post the HIIT intervention and control condition using a validated automated device  
164(Dinamap Pro 200 Critikon; GE Medical Systems, Freiburg, Germany), according to recent  
165guidelines (Williams et al. 2018). Participant height was recorded at baseline using a  
166stadiometer (Seca 217 Stadiometer, Hamburg, Germany), weight was measured pre and post  
167the HIIT intervention and control condition using column scales (Seca 700 Mechanical  
168Column Scales, Hamburg, Germany), and body surface area was calculated according to  
169Mosteller's formula (Mosteller, 1987). All participants had no prior medical history and  
170completed a physical activity readiness questionnaire prior to recruitment. Participants were  
171randomised using stratified randomisation for gender to the HIIT or control group, in order to  
172avoid gender bias in each group (Good 2006). All participants were advised to adhere to the  
173same dietary and physical activity habits, refrain from alcohol and caffeine intake 24 hours  
174before each visit and to avoid food intake at least 4 hrs prior to the laboratory visits to avoid

175postprandial haemodynamic changes. Any participants presenting with any  
176cardiovascular/metabolic disease or taking any medication was excluded from the study.

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### 178**High intensity interval training intervention**

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180The HIIT intervention was comprised of twelve sessions over a 4-week period (3  
181sessions/week), with each session consisting of three Wingate tests separated by a 2-minute  
182active (unloaded) recovery period. Each Wingate test was characterised by 30 seconds of  
183maximal cycling against a resistance equal to 7.5% of each participant's body mass and  
184performed on a Wattbike trainer (Nottingham, England). Each participant performed a 5-  
185minute warm up before and a 5-minute cool down after each HIIT session. Strong verbal  
186encouragement was provided during exercise and participants were unaware of the time  
187remaining in each 30-second sprint.

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### 189**Transthoracic Echocardiography**

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191A standardized transthoracic echocardiogram and Doppler examination was performed using  
192a commercially available Vivid-q ultrasound system (GE Healthcare, Milwaukee, Wisconsin)  
193with a 1.5 – 3.6 MHz phased array transducer. All images were acquired at baseline and post  
194intervention in the HIIT and control group by the same sonographer. The images were stored  
195in raw archive DICOM data for offline analysis and measurements were recorded by an  
196experienced echocardiographer (NJ) who was blinded to participant characteristics and group  
197allocation. Echocardiographic studies were performed and standardized in accordance to  
198current ASE/EACVI guidelines (Evangelista et al. 2008). LV dimension, wall thickness,  
199geometry, mass, and LV systolic and diastolic parameters were assessed. LV ejection fraction



200was estimated using Simpson's rule. LV diastolic function was assessed using the EACVI  
201diastolic guidelines (Nagueh et al. 2016) in the apical 4 chamber view using PW Doppler  
202flow at the tips of the mitral valve to obtain mitral E ( $\text{m}\cdot\text{s}^{-1}$ ), mitral A ( $\text{m}\cdot\text{s}^{-1}$ ) and E wave  
203deceleration time (ms). Using tissue Doppler imaging at the annular level of the mitral valve,  
204the septal and lateral peak early diastolic (E'), late diastolic (A') and peak longitudinal  
205systolic velocity (S') of the myocardium were recorded. LV filling pressure was estimated  
206from the Mitral E/E'.

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### 208Left atrial parameters

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210LA deformation was evaluated from the septal and lateral wall of the left atrium in the apical  
211four chamber view (Figure 1). LA strain imaging was analysed offline using a GE EchoPac  
212workstation. During image acquisition, frame rates between 60-90 frames $\cdot\text{s}^{-1}$  were recorded.  
213The software automatically generates a region of interest (ROI) with a default width of 15mm  
214and tracing of the left atrium was performed. If tracking of the LA myocardium was  
215inadequate, the ROI was manual adjusted to enhance tracking. The automated software  
216generated traces depicting the regional longitudinal strain for each segment and calculated  
217global longitudinal strain. Using P wave onset enabled us to define the first negative peak,  
218which occurred at maximal LA contraction and represented its contractile function  
219(contractile strain), the first positive peak, which occurred at mitral valve opening and  
220represented LA conduit function (conduit strain), and the difference of these peaks, which  
221represented reservoir function (reservoir strain). Global LA strain parameters were assessed  
222as the average of six segmental values. Peak atrial longitudinal strain (PALS) was measured  
223from the onset of the QRS to the positive peak of strain at the onset of the P wave (Mondillo  
224et al. 2011). LA stiffness was estimated using the formula, LA stiffness = (E/E')/PALS.

## 225 **Aorta parameters**

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

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231 • Aortic strain (%) = (aortic systolic diameter – diastolic diameter) x 100 / diastolic  
232 diameter.

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

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## 237 **Sample size calculation**

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

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## 245 **Statistical analysis**

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

250continuous variables was confirmed using the Shapiro-Wilk test (Field 2018). Comparison of  
251data collected pre and post intervention between the control and HIIT groups (change scores)  
252was analysed using a one-way analysis of covariance (ANCOVA) with baseline parameters  
253used as covariates to assess whether changes in echocardiographic and BP parameters  
254following both intervention and control periods are influenced by initial baseline values.  
255Stepwise linear regression analysis using LA stiffness as the dependent variable was  
256conducted. Statistical significance was deemed *a priori* as  $p < 0.05$ .

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## 275 **Results**

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277 A total of 41 participants completed the HIIT intervention (n=21, age  $21 \pm 1.7$  years, height  
278  $173.7 \pm 9.5$  cm) and control period (n=20, age  $22 \pm 3.5$  years, height  $172.4 \pm 8.8$  cm). Two  
279 participants dropped out the study at randomisation and 1-participant from the control group  
280 discontinued, without giving a reason. Descriptive characteristics are presented in Table 1.  
281 No differences were apparent between conditions for participant's age, height, or BP at  
282 baseline. Following 4-weeks of HIIT there was a statistically significant reduction in resting  
283 systolic BP ( $-6.86 \pm 8.76$  mmHg) compared to the control condition ( $-1.15 \pm 9.4$  mmHg,  
284  $p=0.041$ ).

285

### 286 **Conventional cardiac structural and functional parameters**

287

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

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### 294 **Left atrial mechanics and aortic function**

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

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

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324 **Discussion**

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326The present study is the first randomised controlled study to investigate the effect HIIT has  
327on LA deformation and aortic mechanics in a cohort of physically inactive individuals. The  
328results of the study demonstrate that HIIT significantly improved LA mechanics and aortic  
329distensibility compared to a control condition. Reductions in aortic bioelasticity and LA  
330performance negatively effects LV systolic and diastolic function (Pandey et al. 2017). As  
331such, these findings may have wider health and clinical implications in not only individuals  
332who are unable to meet current PA guidelines, but clinical groups, such as hypertensive,  
333diabetic and heart failure patients with preserved ejection fraction.

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### 335**Left atrial performance**

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337During each cardiac cycle, the left atrium deforms such that during systole the left atrium  
338stretches and recoils to its original shape during diastole. It is evident from previous studies  
339that there is a closer interlink between LA stretch and LV global longitudinal strain, LA  
340volume and LA ejection fraction (Russo et al. 2012). All parameters of LA mechanics were  
341significantly improved following HIIT in our study compared to control conditions. In  
342addition, HIIT was associated with a significant improvement in LA compliance, which was  
343estimated using a non-invasive calculation of LA stiffness. When the left atrium is highly  
344compliant, mean LA pressure is lower due to a steady transformation of venous flow into the  
345LV (Suga 1974). Ultimately, our findings suggest these adaptations in LA deformation may  
346improve cardiac performance. Indeed, our study demonstrated significant improvements in  
347markers of cardiac performance, including ejection time, lateral and septal  $S'$ , lateral  $E'$ , and  
348myocardial performance index. These results are also supported by recent research from our  
349groups laboratory, which demonstrated significant improvements in systolic and diastolic LV  
350mechanics (O'Driscoll et al. 2018). In addition, animal studies have shown increased calcium

351reuptake by the sarcoplasmic reticulum up to 30% higher in the myocardium following  
352aerobic interval training (Matsunaga et al. 2007), which determines LV relaxation. A greater  
353calcium reuptake from myofilaments augments active relaxation and improving LV filling  
354(Carrick-Ranson et al. 2012).

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### 356Aortic mechanics

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358Aortic distensibility is a parameter, which is closely related to the bioelastic function of the  
359aorta and which serves as a marker for CVD (Laurent et al. 2006). The results of this study  
360show that aortic distensibility and aortic stiffness index was significantly improved following  
3614-weeks of HIIT. Erol et al. (2002) demonstrated an increase in aortic distensibility and  
362decreased aortic stiffness in elite athletes compared to a control group. Since our study was  
363observational, the underlying mechanisms by which improved ascending aorta compliance  
364are induced is unclear. However, improved arterial compliance following HIIT demonstrated  
365in the present study may be due to local and systemic influences.

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367Any proposed mechanism must be consistent with structural and functional changes in the  
368vascular system. Structurally, arterial compliance/distensibility is primarily determined by the  
369composition of the arterial media such as vascular smooth muscle (VSM) and connective  
370tissue (elastin and collagen fibres) (MacDonald and Nichols 2011). The elastin/collagen ratio  
371in the proximal thoracic aorta determines the physical properties and the degree of VSM tone  
372determines the functional properties. Relaxation of the VSM transfers less stress from  
373collagen to elastin, which increases aortic compliance as a result of the active adaptation  
374(Belz 1995). It is reasonable to assume that short term HIIT influences active adaptation of  
375the aorta locally and systemically in improving arterial compliance. The significant reduction

376in resting systolic blood pressure supports this concept. There is also suggestion that exercise  
377can suppress sympathetic-adrenergic tone which increases arterial compliance (Tanaka et al.  
3782000). However, several studies have shown conflicting results regarding the role of arterial  
379compliance modulated by sympathetic-adrenergic tone of smooth muscle in the arterial wall  
380(Raper and Peterson 1969; Boutouyrie et al. 1994). It has been known for a long time that  
381aortic diameter and compliance are influenced by vasoactive receptors such as Angiotensin II  
382and noradrenaline, which exist within the large arteries (Bolton 1979; Vanhoutte et al. 1981).  
383It seems reasonable to speculate that release of vasoactive substances may exert autocrine and  
384paracrine influences on vascular tone and be a potential modulator for aortic compliance  
385secondary to HIIT. It is also conceivable that, episodic shear stress on the endothelium of the  
386arteries during exercise due to enhanced blood flow, releases nitric oxide (NO) thereby  
387supporting flow dependant dilatation (Endo et al. 1994). Nonetheless, the present findings  
388indicate that compared to control conditions, short term HIIT in a sedentary population  
389significantly improves aortic elastic properties.

390

391In this study, stepwise linear regression analysis revealed that aortic distensibility, which is  
392an aortic bioelastic parameter, was significantly ( $p=0.002$ ) associated with LA stiffness. In  
393addition, LA reservoir strain was significantly associated with LA stiffness ( $p<0.001$ ), which  
394reflects the LA active relaxation. These findings are important since a reduction in aortic  
395distensibility can impair LV active relaxation, through increased LA afterload that ultimately  
396leads to LA myocardial fibrosis, which is key in LA systolic and diastolic dysfunction  
397(Mondillo et al. 2011; Morris et al. 2011). Previous studies have shown increased LA  
398stiffness is secondary to LA fibrosis in parallel with LV and large artery stiffening, secondary  
399to subendocardial fibrosis (Morris et al. 2011) and medial degeneration (Jacob 2003)  
400respectively. Miyoshi et al (2011) study demonstrated that LA function is related to arterial



401compliance, suggesting increased arterial stiffness impairs early active relaxation (LA  
402reservoir function), which is an early form of LA-LV-arterial decoupling.

403

404Previous studies have attempted to study the association between LV diastolic dysfunction  
405and arterial stiffness (Cauwenberghs et al. 2016; Kaess et al. 2016; Kim et al. 2017). Our  
406study findings support the hypothesis that a four-week HIIT intervention improves aortic and  
407LA mechanics and may provide some mechanistic basis for reduced cardiovascular risk in at-  
408risk groups who undertake increased levels of exercise and consequent improved fitness. We  
409postulate that this improved atrio-ventricular and ventriculo-arterial function after HIIT  
410exercise may, if continued, have important health implications in cardio-metabolic diseases  
411such as hypertension, diabetes and heart failure with preserved ejection fraction in the  
412medium to longer term. Further studies are required to prove this in outcome driven trials of  
413HIIT.

414

#### 415**Strengths and limitations**

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417This was a small, single-centre study design which recruited a Caucasian-only population.  
418Our study does not allow the determination of a causal effect. A causal link in improving  
419aortic and LA function following HIIT can be hypothesized; however, further longitudinal  
420studies are needed to confirm this hypothesis. LA deformation analysis was performed using  
421strain imaging in the apical 4 chamber view only and we used non-invasive imaging methods  
422to analyse aortic mechanics similar to Stefanadis et al. (1990) technique, which has shown  
423good correlation with invasive techniques. For the calculation of aortic distensibility, brachial  
424arterial BP was used instead of aortic root pressure as there may not be any significant  
425variation between both in healthy volunteers. Measurement of pulse wave velocity is

426considered as the gold standard method for assessing arterial stiffness; however, our study  
427focussed on utilizing transthoracic echocardiography in analysing aortic and LA function.  
428Notwithstanding these limitations, our study was randomised and image analysis was  
429performed by a single skilled operator blinded to participant characteristics and group  
430allocation.

431

### 432**Conclusion**

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434Our study demonstrated that a four-week HIIT intervention was associated with significant  
435improvement in LA mechanics and aortic stiffness compared to non-exercise control  
436conditions. The present study also suggests close interaction between aortic distensibility and  
437LA stiffness. These adaptations may have important health implications and contribute to the  
438improved LV diastolic and systolic mechanics, aerobic capacity and reduced arterial BP  
439previously documented following HIIT. In light of the positive impact on the left atrium and  
440aorta, HIIT is a promising exercise strategy for improving cardiometabolic health with  
441minimal time commitment. Further investigation is warranted to identify the potential risks  
442and benefit of long term HIIT and the optimal level of HIIT for cardiovascular protection.

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452

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## 608 **Figure legends**

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

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

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

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