Cardiac autonomic and left ventricular mechanics following high intensity interval training: A randomised cross-over controlled study.

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Abstract

Physical inactivity and sedentary behaviour is associated with increased cardiovascular disease risk. Short duration high intensity interval training (HIIT) has been shown to improve important health parameters. The aim of the present study was to assess the combined adaptations of the cardiac autonomic nervous system and myocardial functional and mechanical parameters to HIIT. Forty physically inactive and highly sedentary males completed 2-weeks of HIIT and control period. The HIIT protocol consisted of 3x30-second maximal cycle ergometer sprints against a resistance of 7.5% body weight, interspersed with 2-minutes of active recovery. Total power spectral density (PSD) and associated low-frequency (LF) and high-frequency (HF) power spectral components of heart rate variability were recorded. Conventional and speckle tracking echocardiography recorded left ventricular (LV) structural, functional and mechanical parameters. HIIT produced a significant increase in total ln PSD and ln HF, and significant decrease in LF/HF ratio (all $p<0.05$) compared to the control period. HIIT produced significant improvements in LV diastolic function, including lateral E', estimated filling pressure (E/E' ratio), E deceleration time, and isovolumetric relaxation time ($p<0.05$ for all). Fractional shortening was the only conventional marker of LV systolic function to significantly improve ($p<0.05$). In this setting, there were significant improvements in global peak systolic strain rate, early and late diastolic strain rate and early to late diastolic strain rate ratio, as well as apical rotation, apical systolic and diastolic rotation velocity, apical radial and circumferential strain and strain rate, LV torsion and LV systolic and diastolic torsion velocity (all $p<0.05$). A short-term programme of HIIT was associated with a significant increase in cardiac autonomic modulation, demonstrated by a residual increase in cardiac vagal activity as well as significantly improved cardiac function and mechanics. This study demonstrates that HIIT

may be an important stimulus to reduce the health implications associated with physical inactivity and sedentary behaviour.

New & Noteworthy

This is the first study to measure the combined adaptations of the cardiac autonomic nervous system and myocardial function and mechanics following HIIT. This study demonstrates that a 2-week high intensity interval training (HIIT) intervention provides significant improvements in cardiac autonomic modulation and myocardial function and mechanics in a large cohort of young physically inactive and highly sedentary individuals. HIIT may be a powerful stimulus to reduce the health implications associated with physical inactivity and sedentary behaviour.

Introduction

Physical inactivity and a highly sedentary behaviour is associated with premature morbidity and mortality worldwide (10, 49). International guidelines recommend a minimum of 150-minites of moderate intensity or 75-minutes of vigorous intensity physical activity, or an equivalent combination per week (49). Despite substantial health benefits observed when meeting these guidelines, adherence to physical activity is <50% and as low as 5% when measured objectively (17). In the general population, lack of time is often cited as a common barrier and recent evidence suggests that as little as 15-minutes of daily moderate intensity exercise is sufficient to provide significant health benefits, with a 14% reduction in all-cause mortality and extended life expectancy (47). In addition, physical activity patterns characterised by one or two sessions per week significantly reduce mortality (31). At a population level, it is therefore of high importance to ascertain a minimum volume/dose of physical activity and precise intensity sufficient to improve markers of cardiovascular disease (CVD) risk and encourage adoption for health benefits.

High intensity interval training (HIIT) is a time efficient exercise intervention that has been demonstrated to provide equal to or superior health benefits when compared to moderate intensity continuous training (MICT). A number of recent meta-analytical studies provide evidence for improved cardiovascular health as measured by increased cardiorespiratory fitness following HIIT in healthy (48) and in those with increased CVD risk (35). There is strong evidence supporting peripheral adaptations as potential mechanisms for improving health following HIIT; with increased oxidative potential of skeletal muscle (39) as a result of increased mitochondrial gene transcription augmenting mitochondrial biogenesis (12), as

well as evidence of improved vascular function, glycaemic control and insulin sensitivity and reduced oxidative stress and inflammation reported (35, 39). Until recently, evidence of central adaptations was limited and equivocal (24); however, Kiviniemi et al. (20) demonstrated improvements in cardiac autonomic modulation following 2-weeks of HIIT compared to aerobic endurance training in middle aged men, and Astorino and colleagues (1) demonstrated that improvements in functional capacity following HIIT were due to improved maximal cardiac output. Recently, Grace et al. (14) demonstrated improved left ventricular diastolic function following HIIT in sedentary men, but reported no significant changes in cardiac mechanics as measured by tissue Doppler imaging (TDI) of the apical 4-chamber view. However, TDI derived myocardial deformation is angle dependent, not highly reproducible (7) and current guidelines now recommend that measurements should be made in the apical 2, 3, and 4-chamber views and averaged (22). Few studies have attempted to measure the combined adaptations of the cardiac autonomic nervous system and myocardial function and mechanics following HIIT, in addition to functional capacity and arterial blood pressure. Therefore, the aim of the present study was to perform a randomised cross-over controlled study in a large cohort of physically inactive (<2.5 MET-h/week) and highly sedentary (≥8 h/day sitting time) young adults following 2-weeks of HIIT and record alterations in functional capacity, arterial blood pressure, non-invasive cardiac autonomic modulation and a comprehensive assessment of cardiac function and mechanics. We hypothesis that improvements in cardiac autonomic modulation and myocardial mechanics will parallel improvements in peripheral haemodynamics and aerobic capacity.

Method

Study population and ethical approval

Forty-four physically inactive Caucasian males (age 21 ± 1.7 years; height 179.5 ± 5.4 cm, body mass 82 ± 11.9 kg), volunteered to participant in this randomised cross-over controlled study. Participants reported no history of cardiac or metabolic disease, were non-smokers and currently taking no medication. We aimed to study a physically inactive (<2.5 MET-h/week) and highly sedentary (>8 h/day sitting time), but otherwise healthy population for four main reasons; first, the homogenous population reduces the impact of other comorbidities on autonomic and cardiac responses, second, adaptations in response to HIIT appear to favour the least fit (48), thirdly, <2.5 MET-h/week and ≥8 h/day sitting time has been shown to have a significantly elevated risk of CVD (10) and fourth, autonomic and cardiac mechanical responses in this group may provide important mechanistic information for health improvements in clinical populations. All procedures for this investigation conformed to the Declaration of Helsinki principles and Canterbury Christ Church Universities Ethics Committee approved the study. Signed, informed written consent was obtained from all participants.

Experimental protocol

Participants visited the laboratory on five occasions for physiological assessment. The first visit included study enrolment, a familiarisation maximal aerobic exercise test and study randomisation. The second and third visit included baseline and post intervention measures for the HIIT and control groups, respectively. Both groups had a 4-week wash-out period, after which group conditions were crossed over. The fourth and fifth laboratory visit consisted of the same pre and post-testing, respectively, for the crossed over HIIT and control groups (see Figure 1). Participants were blinded to physiological measures and all laboratory visits occurred at the same time of day. All cardiovascular and haemodynamic measures were performed ≥48 hours after the final HIIT training session. Participants maintained an abstinence from food for at least 4-hours prior to each visit, and did not consume caffeine or alcohol for 24-hours before each visit. All participants were instructed to maintain normal daily living activities during the control and HIIT condition. Participants were asked to verbally confirm their adherence to these requirements at the start of each testing session.

Functional capacity

Aerobic capacity was measured using the Cosmed Quark CPET (Quark CPET 10.0e) online gas analysis system. The incremental exercise test to exhaustion was conducted using an SRM Ergometer with integrated SRM Training System (SRM, Julich, Germany). Before each test, the gas cylinder was calibrated to gases of known concentration (15% O_2; 5% CO_2), and a three-litre syringe was used to calibrate flow (Cosmed, Rome, Italy). Expired volume was

measured using a Hans Rudolph pneumotach flowmeter connected via a Hans Rudolph Mask and Headgear. Each participant completed a 2-minute warm-up on the SRM ergometer, then performed an incremental exercise test to exhaustion maintaining a pedal cadence between 70-80 $r \cdot min^{-1}$. The saddle and handle bar height configuration was recorded and reproduced in subsequent tests. Each participant began at 50 watts resistance and then ramped at 20 $W \cdot min^{-1}$. Breath-by-breath pulmonary gas-exchange data was collected continuously during the incremental tests and averaged over consecutive 10-second periods. All participants underwent the test until volitional exhaustion or until cadence could not be maintained, upon which all participants underwent a cool down period. All participants were unaware of the exercise time, peak aerobic capacity (VO_{2peak}) or work rate. Participants were always verbally encouraged to ensure a maximal effort was achieved.

Cardiac autonomic and haemodynamic assessment

All testing was conducted in a controlled laboratory environment. Upon arrival at the laboratory, height was meaured using a SECA 213 stadiometer and weight was measured using SECA 700 mechanical collumn scales (SECA gmbh & co, Germany).

The Task Force® Monitor (TFM) is a validated non-invasive monitoring system (11), which was used for the continuous beat-to-beat monitoring and automatic online calculation of all cardiac autonomic and haemodynamic parameters. Cardiac autonomic modulation was assessed by the oscillating fluctuations in the frequency and amplitude of each R-R interval using power spectral analysis and applying an autoregressive model. The algorithm enables

the QRS complex to be distinguished from high P or T waves, noise, baseline drift and artefacts. All ECG traces were also manually screened to confirm traces were clear of any erroneous data. Total heart rate variability (HRV), as well as high and low frequency domain parameters (HF and LF, respectively) were automatically calculated by the TFM as a measure of autonomic control of HR 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 (25). The ratio of LF-to-HF (LF:HF ratio) is an accepted measure of cardiac sympathovagal balance (9).

Continuous measurement of BP (sBP, dBP and mBP) was recorded by use of the vascular unloading technique at the proximal limb of the index or middle finger, which was automatically corrected to oscillometric BP values obtained at the brachial artery of the contralateral arm. HR was recorded through a 6-channel electrocardiogram and rate pressure product (RPP) was calculated as HR x sBP. 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.

Conventional echocardiographic image acquisition

Transthoracic echocardiography was performed using a portable ultrasound system (Vivid-q, GE Healthcare, Milwaukee, Wisconsin) with a 1.5 – 3.6 MHz phased array transducer (M4S-RS Matrix cardiac ultrasound probe). The same sonographer acquired all images, with the participant examined in the left lateral decubitus position. Cardiac structural and functional measurements were recorded as recommended by current guidelines (22). Three consecutive cardiac cycles were recorded and stored for offline analysis using commercial software on a

proprietary workstation (EchoPAC; V.113.0.x, GE Healthcare), with the results averaged. Images were acquired in parasternal long-axis and short-axis (level of mitral valve and apex), and apical 2-, 3-, 4-chamber views. Interventricular septal and posterior wall thickness, fractional shortening, and LV internal dimensions were recorded and relative wall thickness was calculated as (2 x LV posterior wall thickness)/LV internal diameter. LV mass was calculated according to Devereux et al. (8) and indexed to body surface area. LV ejection fraction was determined by the modified biplane Simpson's rule. Pulsed-wave Doppler recordings were obtained to assess transmitral early (E) and late (A) diastolic filling velocities from the apical 4-chamber view, with the sample volume placed at the tips of the mitral valve. Isovolumic relaxation time was measured from the start of aortic valve closure to mitral valve opening. Tissue Doppler imaging was acquired 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 (33). Stroke volume was calculated from LV end diastolic and LV end systolic volumes and cardiac output as the product of HR and SV (22). Total peripheral resistance was calculated according to Ohm's law.

Left ventricular longitudinal mechanics

Speckle tracking imaging was used to obtain global LV longitudinal strain and the time-derivative strain rate from the apical 2-, 3-, and 4-chamber views. The average value of peak systolic longitudinal strain and peak systolic strain rate from all three views was then calculated as global strain and strain rate (44). Similarly, peak global strain rate during early and late diastole and their ratio as indices of diastolic function was calculated as proposed previously (45). LV radial and circumferential strain and strain rate, and LV rotation and

rotational velocity were obtained from parasternal short axis views obtained from the LV base at the level of the mitral valve (mitral valve leaflets on view) and the LV apex (circular LV cavity with no papillary muscle visible), as described previously (23, 30, 43, 46). For speckle tracking analysis, the highest quality digital images were selected and the endocardium was traced. A full thickness myocardial region of interest was selected. The observer readjusted the endocardial trace line and/or region of interest width to ensure an acceptable tracking score. Since basal and apical rotation are not acquired from the same cardiac cycle and to enable comparison between and within subjects, raw frame-by-frame rotation and rotation rate data was normalised to the percentage duration of systole and diastole using cubic spline interpolation (GraphPad Prism 6 Software, California, USA) (4, 5, 40). Subtraction of the basal data from the apical data at each time point was undertaken to calculate LV torsion (4, 5, 40). Images were optimised for sector width and scan depth in order to obtain high frame rates (>60 Hz) and kept constant for repeat examinations. All images were examined to validate quality and those that did not meet the required level of optimisation and standardisation were excluded. The sonographers reproducibility of speckle tracking indices have been previously reported (32). All echocardiography results were analysed by an investigator blinded to participant order and condition.

HIIT protocol

The HIIT intervention comprised of 6 sessions over a two-week period (3-sessions per 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 participant 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.

Data analysis

Continuous variables are expressed as mean ± standard deviation. A two-way repeated measures ANOVA was performed with a Bonferroni post hoc test, for comparison of outcome measures between (HIIT vs control condition) and within groups (pre vs post intervention) for cardiac autonomic, haemodynamic, echocardiographic and functional capacity variables. Spectral measures of HRV were positively skewed and therefore 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

Of the forty-four participants recruited, forty completed the entire study. Four participants (9.1%) were withdrawn from the study due to missing an exercise session (n=1), no longer wanting to take part in the study (n=1) or failure to attend all data collection visits (n=2). Functional capacity, haemodynamics, cardiac autonomic function, and echocardiograpic images were successfully acquired on all forty subjects. Importantly, there were no significant differences between measurements at time points 1 and 3 between or within groups, which suggests that the 4-week washout period was long enough for those participants who initially performed HIIT to return to baseline.

Functional capacity and haemodynamics

As shown in Table 1, peak VO_2 in absolute and relative units significantly increased post HIIT (both $p<0.001$) with no significant change post control ($p=0.942$ and $p=0.732$, respectively). This difference was significant between condition ($p=0.013$ and $p=0.011$, respectively). In addition, peak minute ventilation significantly increased post HIIT ($p=0.009$), with no significant change ($p=0.292$) post control. This change was significant between conditions ($p=0.007$). The slope of the V_E/VCO_2 significantly increased post HIIT ($p=0.034$), with no change post control ($p=0.126$) and no significant difference between conditions ($p=0.545$).

Table 1 also documents that there were significant reductions in systolic and mean arterial blood pressure and rate pressure product post HIIT ($p<0.001$, $p=0.029$, $p<0.001$, respectively), with no significant change post control period ($p=0.837$, $p=0.721$, $p=0.415$, respectively). These reductions were significantly different between conditions ($p<0.001$, $p=0.022$, $p=0.001$, respectively). There was a significant reduction in diastolic blood pressure post HIIT ($p=0.038$), with no significant change post control ($p=0.72$). However, there was no significant difference between conditions ($p=0.124$). Resting stroke volume significantly increased post HIIT ($p<0.001$) with no significant change post control ($p=0.22$). This difference was significant between condition ($p<0.013$). However, there was no significant change in resting cardiac output in control or HIIT conditions. Conversely, there was a significant reduction in TPR post HIIT ($p=0.03$) with no significant change post control ($p=0.69$). This difference was significant between condition ($p=0.001$; see Table 1).

Cardiac autonomic parameters

As shown in Figure 2A, there was a significant reduction in HR (62.2±8.6 to 57.7±8.3 $b \cdot min^{-1}$; $p<0.001$) in the HIIT condition and no significant change (64.7±10.6 to 64.3±10.8 $b \cdot min^{-1}$; $p=0.479$) during the control period. This response was significantly different ($p=0.011$) between conditions. There was a significant increase in HRV expressed as R-R PSD (ln) (3.53±0.27 to 3.67±0.26; $p<0.005$) in the HIIT condition and no significant change (3.51±0.24 to 3.51±0.25; $p=0.532$) during the control period. There was a significant difference ($p=0.04$) in R-R PSD (ln) between condition (Figure 2B). As shown in Figure 2C and 2D, there was a significant reduction in R-R LFnu (61.4±11.5 to 57.6±11.6; $p<0.001$) and significant increase in R-R HFnu (38.6±11.5 to 42.4±11.6; $p<0.001$) following HIIT and

no significant change during the control condition (59.6±11.8 to 59.5±12.5; p=0.583 and 40.4±11.8 to 40.5±12.5; p=0.583, respectively). However, these changes were not significantly different between conditions (p=0.389 for both).

There was no significant changes in the HIIT or control condition for R-R LF(In). However, HIIT produced a significant increase in R-R HF(In) (2.96±0.37 to 3.05±0.33; p<0.005), with no change in the control condition (2.99±0.34 to 2.97±0.37; p=0.162). This change was significantly different (p=0.048) between conditions. These data are presented in Figure 3A and 3B. These cardiac autonomic responses resulted in a significant decrease in the R-R LF/HF ratio in the HIIT condition (2.00±1.04 to 1.47±0.77; p<0.001) with no change in the control condition (1.90±0.97 to 1.92±1.01; p=0.661) and a significant difference (p=0.007) between conditions (Figure 3C).

Cardiac function and structure: conventional and tissue Doppler parameters

As shown in Table 2, there were significant improvements in parameters of diastolic function, with a significant reduction in mitral E deceleration time (181±24.5 to 163±22.1 ms*;* p=0.009) in the HIIT condition and no significant change (179±23 to 178±22.7 ms*;* p=0.67) during the control period. This response was significantly different (p=0.003) between conditions. There was a significant reduction in isovolumetric relaxation time (78.8±9 to 70.3±7.1 ms*;* p=0.01) in the HIIT condition and no significant change (78.2±9 to 78.1±8.1 ms*;* p=0.92) during the control period. This response was significantly different (p<0.001) between conditions. After adjustment for HR and mBP, E deceleration time

(*p*=0.019 and *p*=0.02; respectively) and isovolumetric relaxation time (*p*=0.006 and *p*=0.008; respectively) remained significantly different between conditions. There was also a significant improvement in lateral E' following HIIT (0.18±0.03 to 0.2±0.03 $m \cdot s^{-1}$*; p*=0.001), with no change in the control period (0.17±0.03 to 0.17±0.03 $m \cdot s^{-1}$*; p*=0.21). This response was significantly different (*p*<0.001) between conditions. As a result, there was a significant reduction in estimated LV filling pressure as measured by lateral E/E' and average E/E' following HIIT (3.94±0.73 to 3.49±0.68*; p*=0.001 and 4.38±0.67 to 4.07±0.64*; p*=0.002, respectively), with no change in the control period (4.03±0.87 to 4.07±0.68*; p*=0.65 and 4.36±0.79 to 4.3±0.7*; p*=0.68, respectively). These differences were significant between conditions (*p*<0.001 and *p*=0.021, respectively). Fractional shortening was the only systolic parameter that significantly improved following HIIT (29.1±3.1 to 31.2±2.3*; p*=0.002), with no change in the control period (29±2.5 to 30±3*; p*=0.83). This response was significantly different (*p*<0.001) between conditions. After adjustment for HR and mBP, lateral E' (*p*=0.001 and *p*=0.001; respectively), lateral E/E' (*p*=0.001 and *p*=0.011; respectively), average E/E' (*p*=0.039 and *p*=0.04; respectively) and fractional shortening (*p*=0.002 and *p*=0.003; respectively) remained significantly different between conditions.

Left ventricular mechanics

Table 2 also indicates that there was no significant change in average global longitudinal peak systolic strain following HIIT (19.82±2.1 to 20.61±2.1%*; p*=0.42) or control period (19.87±2 to 19.8±2.1%*; p*=0.88). However, there was a significant improvement in average global longitudinal strain rate following HIIT (0.97±0.1 to 1.11±0.1% $\cdot s^{-1}$*; p*=0.014), with no change in the control period (0.98±0.1 to 0.97±0.1% $\cdot s^{-1}$*; p*=0.87). This response was

significantly different (p=0.04) between conditions. After adjustment for HR and mBP, global longitudinal strain rate (p=0.04 and p=0.044; respectively), remained significantly different between conditions. There was also a significant improvement in average global early diastolic strain rate following HIIT (1.56±0.3 to 1.89±0.3%·s^{-1}; p=0.016), with no change in the control period (1.53±0.3 to 1.54±0.3%·s^{-1}; p=0.34). This response was significantly different (p=0.04) between conditions. Although there were no differences in global late diastolic strain rate following HIIT, there was a significant increase the global early to late diastolic strain rate ratio following HIIT (2.4±0.3 to 3.3±0.3; p=0.001), with no change in the control period (2.4±0.3 to 2.5±0.4; p=0.89). This response was significantly different (p=0.003) between conditions.

There was no significant change in basal rotation, basal systolic rotation velocity, basal diastolic rotation velocity, basal radial strain or basal circumferential strain following HIIT or control period. However, there was a significant improvement in apical rotation (5.6±3.1 to 7.6±3.7º; p=0.004), apical systolic rotation velocity (45.8±18.1 to 61±22.8º·s^{-1}; p=0.001), apical diastolic rotation velocity (-45.2±17.6 to -59.8±25.1º·s^{-1}; p=0.004), apical radial strain (35.5±14.7 to 47.5±19.9%; p=0.005), apical circumferential strain (-21.8±5.7 to -26.4±8.8%; p=0.02), apical circumferential strain rate (-1.55±0.8 to -1.89±0.9º·s^{-1}; p=0.004), LV torsion (9.27±4.1 to 12.2±4.5º; p=0.001), systolic torsion velocity (55.3±20.9 to 74.7±37.2 º·s^{-1}; p=0.01) and diastolic torsion velocity (-60.1±19.1 to -79.4±32.4 º·s^{-1}; p=0.001) following HIIT, with no change in the control period. These responses were significantly different (all p<0.05) between conditions. Figure 4 displays the composite torsion, basal and apical rotation and rotational velocity curves with annotations indicating key findings.

Discussion

The present study is the first to demonstrate that a 2-week HIIT intervention provides significant improvements in cardiac autonomic modulation and myocardial function and mechanics in a large cohort of young physically inactive and highly sedentary individuals. Our results also confirm the widely reported improvements in functional capacity and arterial blood pressure following HIIT.

HRV is a non-invasive and reproducible measure of cardiac autonomic modulation. Traditional aerobic exercise training has been shown to improve autonomic function, indicated by a significant increase in cardiac vagal modulation and decrease in sympathetic activity in healthy (42) and clinical populations (26). The significant increase in the total power spectrum of HRV (ln PSD) indicates an improvement in cardiac autonomic modulation or specifically, the sino-atrial nodes dynamic responsiveness to maintain homeostasis (36). The significant reduction in heart rate, significant increase in the HF component of HRV and significantly reduced LF/HF ratio in the present study, indicates a potential mechanistic shift towards increased parasympathetic and decreased sympathetic activity. These responses compare favourably with prior research in middle-aged men following HIIT (20). Furthermore, these responses are generally associated with reduced risk of adverse cardiac events (36) and have been demonstrated in higher risk patients following HIIT (28).

HIIT significantly improved both systolic and diastolic LV mechanics. This positive effect of HIIT has been documented previously in populations with forms of CVD (14, 27); however, to our knowledge, this is the first time that a comprehensive evaluation of cardiac function and mechanics has been performed in a physically inactive and highly sedentary population. Of the functional measures, our study demonstrated a significant increase in fractional shortening and lateral E', and significant reduction in E-deceleration time, lateral E/E' and average E/E'. E' is a relatively load independent measure of LV relaxation rate. In addition, prior research has demonstrated that cardiorespiratory fitness is associated closely with diastolic function, in particular E/E' (38), which suggests that elevated LV filling pressure is associated with a reduced exercise capacity. These findings are important since slower LV relaxation and increased LV filling pressures are hallmarks of diastolic dysfunction. Prior research utilising 4x4 minute aerobic interval training at >90% maximal heart rate over 12-weeks supports our findings (16, 27). However, our study has now demonstrated these positive functional adaptations are possible with a total training duration of 9-minutes compared to 576-minutes in previous studies (16, 27).

Our results demonstrate that LV longitudinal strain was within normal limits and did not change significantly following HIIT. However, LV longitudinal strain rate, which is a strong index of LV contractility (15), was below the lower threshold for normal myocardial deformation at baseline and control periods (21). HIIT significantly improved LV longitudinal strain rate to within normal thresholds. This finding is important, since it highlights that even in a young healthy population who are physically inactive and highly sedentary, there is evidence of reduced rates of myocardial deformation. Moreover, these markers of adverse physiological function can be reversed with as little as two weeks of HIIT. In a recent study, all-cause mortality patients had significantly lower longitudinal strain

rate compared to surviving patients (37). Early diastolic strain rate has been shown to be a sensitive marker for myocardial diastolic function (45) and the early to late diastolic strain rate ratio has been shown to differentiate between normal LV relaxation and those with diastolic dysfunction (41). Although all participants in the current study had normal early to late diastolic strain rate ratios (>1), the study provides evidence that HIIT significantly improves this parameter, which may delay the age related decline in diastolic function. In addition, HIIT induced a significant increase in LV torsion and systolic and diastolic torsion mechanics, primarily mediated by a significant increase in apical rotation, apical systolic rotational velocity and apical diastolic rotational velocity. This adaptation is a potential mechanism for the increase in resting stroke volume. Furthermore, enhanced LV torsion augments potential energy during the ejection phase and the recoil of this systolic deformation and release of elastic energy (bidirectional spring) may contribute to pressure decay, enhancing LV suction and associated diastolic filling (18). Previous human studies have reported that invasive measure of LV pressure and indexes of LV untwist are related to parameters of early diastolic filling (6). Similar results have been reported previously in young males following 90-days of endurance training (46). Prior research suggests that these cardiac mechanical adaptions occur due to HIIT placing a larger load on the central circulation, inducing greater cardiac adaptations. Alterations in intracellular calcium regulation may contribute to these adaptations. Indeed, an animal study demonstrated that high intensity exercise, but not moderate intensity, improved cardiac myocyte relaxation rate, which was linked to increased re-uptake of calcium into the sarcoplasmic reticulum during diastole (19). In addition, the LV mechanical responses may in part be explained by mechanisms that also result in reduced blood pressure. Increased nitric oxide bioavailability may also exert significant effects on cardiac function, in particular LV relaxation and may modulate fundamental events of myocardial excitation-contraction coupling (34). Together,

these responses reduce peripheral vascular resistance, which reduces cardiac after-load and improves LV haemodynamics. The significant reduction in peripheral vascular resistance following HIIT supports this concept.

A greater aerobic capacity is a strong independent predictor of mortality (3) and reportedly, a stronger predictor of mortality compared with traditional CVD risk factors (29). This study demonstrated that 2-weeks of HIIT significantly increased aerobic capacity, which is strongly supported in the literature (13). Whilst the 0.21 $L \cdot min^{-1}$ increase in oxygen uptake reported in the current study is lower than the mean 0.51 $L \cdot min^{-1}$ change reported from meta-analysis (2), it is pertinent to note that the training duration of the studies included in the meta-analysis ranged from 6-13 weeks, compared to 2-weeks in the present study.

Several studies have demonstrated the anti-hypertensive effect of exercise. Despite our population having optimal arterial blood pressure, HIIT produced a significant reduction in systolic (-4.8 mmHg) and mean (-3.5 mmHg) blood pressure. Not surprisingly, the significant reduction seen in heart rate and systolic blood pressure resulted in a significant reduction in rate pressure product, which is strongly related to myocardial oxygen consumption. The mechanisms for the reduction in blood pressure following exercise interventions are complex; however, mean arterial blood pressure is determined by cardiac output and peripheral resistance, therefore a reduction in blood pressure must involve one or both components. Our results support peripheral vascular adaptations for the reduction in blood pressure, due to the significant reduction in peripheral vascular resistance and non-significant change in cardiac output following HIIT.

Clinical implications

Physical inactivity and sedentary behaviour is a significant modifiable risk factor for premature CVD morbidity and mortality. In addition, this lifestyle is associated with a decline in functional capacity, which is known to be associated with reduced cardiac autonomic modulation, a decline in myocardial function and progressive elevations in arterial blood pressure. This study demonstrates that 9-minutes of HIIT over a 2-week period can significantly improve these parameters. Recent research reported that HIIT was more enjoyable than traditional MICT, due to its time efficiency and stimulus. Combined with the favourable responses reported in our manuscript, HIIT may be a powerful stimulus to reduce the health implications associated with physical inactivity and sedentary behaviour. Future research is required to ascertain the long-term benefits of HIIT with regards to continued physiological improvement and importantly programme adherence and behaviour change.

Limitations

These results were documented in healthy male participants, as such the relative transference to female and clinical populations is unclear. The authors also acknowledge the inherent limitations of a cross over design due to the potential carry over effect and bias. However, a 4-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 HIIT. It is also important to acknowledge that a 4-week wash-out period was adequate for participants to lose the favourable physiological adaptations reported. This finding is in keeping with the training principle of reversibility and reiterates the requirement for a continued exercise stimulus in order to sustain the physiological improvements observed.

Conclusion

A short-term programme of HIIT was associated with a significant increase in cardiac autonomic modulation, demonstrated by a residual increase in cardiac vagal activity. HIIT was also associated with significant improvements in cardiac function and mechanics, as well as functional capacity and arterial blood pressure. The results of this study demonstrate that HIIT may be an important exercise stimulus to reduce the health implications associated with physical inactivity and sedentary behaviour. Future research is required to ascertain the long-term benefits of HIIT with regards to continued physiological improvement and importantly exercise adherence and behaviour change.

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Author Contributions

J.O'D, S.M.W, K.A.T, J.D.W., D.A.C., and R.S. conception and design of research; J.O'D, S.M.W, and K.A.T performed experiments; J.O'D, S.M.W, K.A.T. and R.S. analysed data; J.O'D, S.M.W, K.A.T, J.D.W., D.A.C., and R.S. interpreted results of experiments; J.O'D prepared figures; J.O'D, S.M.W, K.A.T, J.D.W., D.A.C., and R.S. drafted manuscript; J.O'D, S.M.W, K.A.T, J.D.W., D.A.C., and R.S. edited and revised manuscript; J.O'D, S.M.W, K.A.T, J.D.W., D.A.C., and R.S. approved final version of manuscript.

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Figure Legends

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 cardiac autonomic modulation, cardiac function and mechanics, resting blood pressure and functional capacity.

Figure 2: Cardiac autonomic responses pre and post control and high intensity interval training periods. A, Heart rate responses; B, Log transformed R-R power spectral density (HRV) response; C, R-R normalized units low frequency; D, R-R normalized units high frequency responses.

Figure 3: Cardiac autonomic responses pre and post control and high intensity interval training periods. A, Log transformed R-R low frequency response; B, Log transformed R-R high frequency response; C, R-R LF/HF ratio.

Figure 4: Sequential representation of left ventricular torsion, basal, and apical rotation pre and post high intensity interval training. Annotations indicate key findings and for clarity, statistical differences have not been displayed; refer to Table 2. Note: AVC = aortic valve closure.