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

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Key words: Cardiac mechanics, High intensity interval training, Heart rate variability.

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.

1 **Introduction**

2

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

16

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

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

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47

48

49 **Method**

50

51 **Study population and ethical approval**

52

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

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70

71 **Experimental protocol**

72

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

86

87 **Functional capacity**

88

89 Aerobic capacity was measured using the Cosmed Quark CPET (Quark CPET 10.0e) online
90 gas analysis system. The incremental exercise test to exhaustion was conducted using an
91 SRM Ergometer with integrated SRM Training System (SRM, Julich, Germany). Before each
92 test, the gas cylinder was calibrated to gases of known concentration (15% O₂; 5% CO₂), and
93 a three-litre syringe was used to calibrate flow (Cosmed, Rome, Italy). Expired volume was

94 measured using a Hans Rudolph pneumotach flowmeter connected via a Hans Rudolph Mask
95 and Headgear. Each participant completed a 2-minute warm-up on the SRM ergometer, then
96 performed an incremental exercise test to exhaustion maintaining a pedal cadence between
97 70-80 r·min⁻¹. The saddle and handle bar height configuration was recorded and reproduced
98 in subsequent tests. Each participant began at 50 watts resistance and then ramped at 20
99 W·min⁻¹. Breath-by-breath pulmonary gas-exchange data was collected continuously during
100 the incremental tests and averaged over consecutive 10-second periods. All participants
101 underwent the test until volitional exhaustion or until cadence could not be maintained, upon
102 which all participants underwent a cool down period. All participants were unaware of the
103 exercise time, peak aerobic capacity (VO_{2peak}) or work rate. Participants were always verbally
104 encouraged to ensure a maximal effort was achieved.

105

106 **Cardiac autonomic and haemodynamic assessment**

107

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

111

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

117 the QRS complex to be distinguished from high P or T waves, noise, baseline drift and
118 artefacts. All ECG traces were also manually screened to confirm traces were clear of any
119 erroneous data. Total heart rate variability (HRV), as well as high and low frequency domain
120 parameters (HF and LF, respectively) were automatically calculated by the TFM as a
121 measure of autonomic control of HR and expressed in absolute (ms^2) and normalised units
122 (nu). Normalisation of the frequency components of HRV has proven crucial to the
123 interpretation of these data (25). The ratio of LF-to-HF (LF:HF ratio) is an accepted measure
124 of cardiac sympathovagal balance (9).

125

126 Continuous measurement of BP (sBP, dBP and mBP) was recorded by use of the vascular
127 unloading technique at the proximal limb of the index or middle finger, which was
128 automatically corrected to oscillometric BP values obtained at the brachial artery of the
129 contralateral arm. HR was recorded through a 6-channel electrocardiogram and rate pressure
130 product (RPP) was calculated as $\text{HR} \times \text{sBP}$. Following 15 minutes of supine rest, baseline
131 autonomic and haemodynamic function were recorded continuously for 5 minutes. All
132 biological signals were recorded with a sample frequency of 1000Hz and 16-bit resolution.

133

134 **Conventional echocardiographic image acquisition**

135

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

142 proprietary workstation (EchoPAC; V.113.0.x, GE Healthcare), with the results averaged.
143 Images were acquired in parasternal long-axis and short-axis (level of mitral valve and apex),
144 and apical 2-, 3-, 4-chamber views. Interventricular septal and posterior wall thickness,
145 fractional shortening, and LV internal dimensions were recorded and relative wall thickness
146 was calculated as $(2 \times \text{LV posterior wall thickness})/\text{LV internal diameter}$. LV mass was
147 calculated according to Devereux et al. (8) and indexed to body surface area. LV ejection
148 fraction was determined by the modified biplane Simpson's rule. Pulsed-wave Doppler
149 recordings were obtained to assess transmitral early (E) and late (A) diastolic filling
150 velocities from the apical 4-chamber view, with the sample volume placed at the tips of the
151 mitral valve. Isovolumic relaxation time was measured from the start of aortic valve closure
152 to mitral valve opening. Tissue Doppler imaging was acquired at the lateral and septal mitral
153 annulus to assess peak longitudinal (S'), peak early diastolic (E') and peak late diastolic (A')
154 velocities, with values averaged. LV filling pressure was estimated from the mitral E/E' ratios
155 (33). Stroke volume was calculated from LV end diastolic and LV end systolic volumes and
156 cardiac output as the product of HR and SV (22). Total peripheral resistance was calculated
157 according to Ohm's law.

158

159 **Left ventricular longitudinal mechanics**

160

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

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

184

185 **HIIT protocol**

186

187 The HIIT intervention comprised of 6 sessions over a two-week period (3-sessions per week),
188 with each session consisting of three Wingate tests separated by a 2-minute active (unloaded)
189 recovery period. Each Wingate test was characterised by 30-seconds of maximal cycling
190 against a resistance equal to 7.5% of participant body mass and performed on a Wattbike
191 trainer (Nottingham, England). Each participant performed a 5-minute warm up before and a

192 5-minute cool down after each HIIT session. Strong verbal encouragement was provided
193 during exercise and participants were unaware of the time remaining in each 30-second
194 sprint.

195

196 **Data analysis**

197

198 Continuous variables are expressed as mean \pm standard deviation. A two-way repeated
199 measures ANOVA was performed with a Bonferroni post hoc test, for comparison of
200 outcome measures between (HIIT vs control condition) and within groups (pre vs post
201 intervention) for cardiac autonomic, haemodynamic, echocardiographic and functional
202 capacity variables. Spectral measures of HRV were positively skewed and therefore log
203 transformed (ln) prior to analysis. All data were analysed using the statistical package for
204 social sciences (SPSS 22 release version for Windows; SPSS Inc., Chicago IL, USA).

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214 **Results**

215

216 Of the forty-four participants recruited, forty completed the entire study. Four participants
217 (9.1%) were withdrawn from the study due to missing an exercise session (n=1), no longer
218 wanting to take part in the study (n=1) or failure to attend all data collection visits (n=2).
219 Functional capacity, haemodynamics, cardiac autonomic function, and echocardiographic
220 images were successfully acquired on all forty subjects. Importantly, there were no
221 significant differences between measurements at time points 1 and 3 between or within
222 groups, which suggests that the 4-week washout period was long enough for those
223 participants who initially performed HIIT to return to baseline.

224

225 **Functional capacity and haemodynamics**

226

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

235

236 Table 1 also documents that there were significant reductions in systolic and mean arterial
237 blood pressure and rate pressure product post HIIT ($p<0.001$, $p=0.029$, $p<0.001$,
238 respectively), with no significant change post control period ($p=0.837$, $p=0.721$, $p=0.415$,
239 respectively). These reductions were significantly different between conditions ($p<0.001$,
240 $p=0.022$, $p=0.001$, respectively). There was a significant reduction in diastolic blood pressure
241 post HIIT ($p=0.038$), with no significant change post control ($p=0.72$). However, there was
242 no significant difference between conditions ($p=0.124$). Resting stroke volume significantly
243 increased post HIIT ($p<0.001$) with no significant change post control ($p=0.22$). This
244 difference was significant between condition ($p<0.013$). However, there was no significant
245 change in resting cardiac output in control or HIIT conditions. Conversely, there was a
246 significant reduction in TPR post HIIT ($p=0.03$) with no significant change post control
247 ($p=0.69$). This difference was significant between condition ($p=0.001$; see Table 1).

248

249 **Cardiac autonomic parameters**

250

251 As shown in Figure 2A, there was a significant reduction in HR (62.2 ± 8.6 to 57.7 ± 8.3 b·min⁻¹;
252 $p<0.001$) in the HIIT condition and no significant change (64.7 ± 10.6 to 64.3 ± 10.8 b·min⁻¹;
253 $p=0.479$) during the control period. This response was significantly different ($p=0.011$)
254 between conditions. There was a significant increase in HRV expressed as R-R PSD (ln)
255 (3.53 ± 0.27 to 3.67 ± 0.26 ; $p<0.005$) in the HIIT condition and no significant change
256 (3.51 ± 0.24 to 3.51 ± 0.25 ; $p=0.532$) during the control period. There was a significant
257 difference ($p=0.04$) in R-R PSD (ln) between condition (Figure 2B). As shown in Figure 2C
258 and 2D, there was a significant reduction in R-R LFnu (61.4 ± 11.5 to 57.6 ± 11.6 ; $p<0.001$)
259 and significant increase in R-R HFnu (38.6 ± 11.5 to 42.4 ± 11.6 ; $p<0.001$) following HIIT and

260 no significant change during the control condition (59.6 ± 11.8 to 59.5 ± 12.5 ; $p=0.583$ and
261 40.4 ± 11.8 to 40.5 ± 12.5 ; $p=0.583$, respectively). However, these changes were not
262 significantly different between conditions ($p=0.389$ for both).

263

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

272

273 **Cardiac function and structure: conventional and tissue Doppler parameters**

274

275 As shown in Table 2, there were significant improvements in parameters of diastolic
276 function, with a significant reduction in mitral E deceleration time (181 ± 24.5 to 163 ± 22.1
277 ms; $p=0.009$) in the HIIT condition and no significant change (179 ± 23 to 178 ± 22.7 ms;
278 $p=0.67$) during the control period. This response was significantly different ($p=0.003$)
279 between conditions. There was a significant reduction in isovolumetric relaxation time
280 (78.8 ± 9 to 70.3 ± 7.1 ms; $p=0.01$) in the HIIT condition and no significant change (78.2 ± 9 to
281 78.1 ± 8.1 ms; $p=0.92$) during the control period. This response was significantly different
282 ($p<0.001$) between conditions. After adjustment for HR and mBP, E deceleration time

283 ($p=0.019$ and $p=0.02$; respectively) and isovolumetric relaxation time ($p=0.006$ and $p=0.008$;
284 respectively) remained significantly different between conditions. There was also a
285 significant improvement in lateral E' following HIIT (0.18 ± 0.03 to 0.2 ± 0.03 $\text{m}\cdot\text{s}^{-1}$; $p=0.001$),
286 with no change in the control period (0.17 ± 0.03 to 0.17 ± 0.03 $\text{m}\cdot\text{s}^{-1}$; $p=0.21$). This response
287 was significantly different ($p<0.001$) between conditions. As a result, there was a significant
288 reduction in estimated LV filling pressure as measured by lateral E/E' and average E/E'
289 following HIIT (3.94 ± 0.73 to 3.49 ± 0.68 ; $p=0.001$ and 4.38 ± 0.67 to 4.07 ± 0.64 ; $p=0.002$,
290 respectively), with no change in the control period (4.03 ± 0.87 to 4.07 ± 0.68 ; $p=0.65$ and
291 4.36 ± 0.79 to 4.3 ± 0.7 ; $p=0.68$, respectively). These differences were significant between
292 conditions ($p<0.001$ and $p=0.021$, respectively). Fractional shortening was the only systolic
293 parameter that significantly improved following HIIT (29.1 ± 3.1 to 31.2 ± 2.3 ; $p=0.002$), with
294 no change in the control period (29 ± 2.5 to 30 ± 3 ; $p=0.83$). This response was significantly
295 different ($p<0.001$) between conditions. After adjustment for HR and mBP, lateral E'
296 ($p=0.001$ and $p=0.001$; respectively), lateral E/E' ($p=0.001$ and $p=0.011$; respectively),
297 average E/E' ($p=0.039$ and $p=0.04$; respectively) and fractional shortening ($p=0.002$ and
298 $p=0.003$; respectively) remained significantly different between conditions.

299

300 **Left ventricular mechanics**

301

302 Table 2 also indicates that there was no significant change in average global longitudinal
303 peak systolic strain following HIIT (19.82 ± 2.1 to $20.61\pm 2.1\%$; $p=0.42$) or control period
304 (19.87 ± 2 to $19.8\pm 2.1\%$; $p=0.88$). However, there was a significant improvement in average
305 global longitudinal strain rate following HIIT (0.97 ± 0.1 to $1.11\pm 0.1\%$ · s^{-1} ; $p=0.014$), with no
306 change in the control period (0.98 ± 0.1 to $0.97\pm 0.1\%$ · s^{-1} ; $p=0.87$). This response was

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

317

318 There was no significant change in basal rotation, basal systolic rotation velocity, basal
319 diastolic rotation velocity, basal radial strain or basal circumferential strain following HIIT or
320 control period. However, there was a significant improvement in apical rotation (5.6 ± 3.1 to
321 $7.6\pm 3.7^\circ$; $p=0.004$), apical systolic rotation velocity (45.8 ± 18.1 to $61\pm 22.8^\circ \cdot s^{-1}$; $p=0.001$),
322 apical diastolic rotation velocity (-45.2 ± 17.6 to $-59.8\pm 25.1^\circ \cdot s^{-1}$; $p=0.004$), apical radial strain
323 (35.5 ± 14.7 to $47.5\pm 19.9\%$; $p=0.005$), apical circumferential strain (-21.8 ± 5.7 to $-26.4\pm 8.8\%$;
324 $p=0.02$), apical circumferential strain rate (-1.55 ± 0.8 to $-1.89\pm 0.9^\circ \cdot s^{-1}$; $p=0.004$), LV torsion
325 (9.27 ± 4.1 to $12.2\pm 4.5^\circ$; $p=0.001$), systolic torsion velocity (55.3 ± 20.9 to $74.7\pm 37.2^\circ \cdot s^{-1}$;
326 $p=0.01$) and diastolic torsion velocity (-60.1 ± 19.1 to $-79.4\pm 32.4^\circ \cdot s^{-1}$; $p=0.001$) following
327 HIIT, with no change in the control period. These responses were significantly different (all
328 $p<0.05$) between conditions. Figure 4 displays the composite torsion, basal and apical
329 rotation and rotational velocity curves with annotations indicating key findings.

330

331 **Discussion**

332

333 The present study is the first to demonstrate that a 2-week HIIT intervention provides
334 significant improvements in cardiac autonomic modulation and myocardial function and
335 mechanics in a large cohort of young physically inactive and highly sedentary individuals.

336 Our results also confirm the widely reported improvements in functional capacity and arterial
337 blood pressure following HIIT.

338

339 HRV is a non-invasive and reproducible measure of cardiac autonomic modulation.

340 Traditional aerobic exercise training has been shown to improve autonomic function,

341 indicated by a significant increase in cardiac vagal modulation and decrease in sympathetic

342 activity in healthy (42) and clinical populations (26). The significant increase in the total

343 power spectrum of HRV (ln PSD) indicates an improvement in cardiac autonomic

344 modulation or specifically, the sino-atrial nodes dynamic responsiveness to maintain

345 homeostasis (36). The significant reduction in heart rate, significant increase in the HF

346 component of HRV and significantly reduced LF/HF ratio in the present study, indicates a

347 potential mechanistic shift towards increased parasympathetic and decreased sympathetic

348 activity. These responses compare favourably with prior research in middle-aged men

349 following HIIT (20). Furthermore, these responses are generally associated with reduced risk

350 of adverse cardiac events (36) and have been demonstrated in higher risk patients following

351 HIIT (28).

352

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

368

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

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

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

406

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

414

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

426 **Clinical implications**

427

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

439

440 **Limitations**

441

442 These results were documented in healthy male participants, as such the relative transference
443 to female and clinical populations is unclear. The authors also acknowledge the inherent
444 limitations of a cross over design due to the potential carry over effect and bias. However, a
445 4-week washout period was selected to ensure adequate time for participants to return to
446 baseline. Importantly, no significant difference within and between groups were seen
447 between visit 1 and 3 of the study, indicating sufficient washout. In addition, each participant
448 verbally confirmed that they maintained their usual habits during the study, with the

449 exception of HIIT. It is also important to acknowledge that a 4-week wash-out period was
450 adequate for participants to lose the favourable physiological adaptations reported. This
451 finding is in keeping with the training principle of reversibility and reiterates the requirement
452 for a continued exercise stimulus in order to sustain the physiological improvements
453 observed.

454

455 **Conclusion**

456

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

465

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472 **Author Contributions**

473

474 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,
475 S.M.W, and K.A.T performed experiments; J.O'D, S.M.W, K.A.T. and R.S. analysed data;
476 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
477 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,
478 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,
479 K.A.T, J.D.W., D.A.C., and R.S. approved final version of manuscript.

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652

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.