1 **Altered ventricular mechanics after 60 min of high-intensity endurance exercise:**
2 **Insights from exercise speckle-tracking echocardiography.**

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22 **Abstract**

23 Transient reductions in myocardial strain coupled with cardiac-specific biomarker release
24 have been reported following prolonged exercise (>180min). However, it is unknown if: a)
25 shorter duration exercise (60min) can perturb cardiac function; or b) if exercise-induced
26 reductions in strain are masked by hemodynamic changes that are associated with passive
27 recovery from exercise. Left (LV) and right ventricular (RV) global longitudinal strain
28 (GLS), LV torsion (LVT), and high-sensitivity cardiac troponin (hs-cTnT) were measured in
29 fifteen competitive cyclists (Age: 28 ± 3 yr; VO_{2peak} : 4.8 ± 0.6 L·min⁻¹) before and after a 60-
30 min high-intensity cycling race intervention (CRIT₆₀). At both time points (pre- and post-
31 CRIT₆₀) strain and torsion were assessed at rest and during a standardized low-intensity
32 exercise challenge (power output: 96 ± 8 W) in a semi-recumbent position using
33 echocardiography. During rest, hemodynamic conditions were different from pre- to post-
34 CRIT₆₀ (MAP: 96 ± 1 vs 86 ± 2 mmHg, $p < 0.001$) and there were no changes in strain or torsion.
35 In contrast, during the standardized low-intensity exercise challenge hemodynamic conditions
36 were unchanged from pre- to post-CRIT₆₀ (MAP: 98 ± 1 vs 97 ± 1 mmHg, ns), but strain
37 decreased (LVGLS: $-20.3 \pm 0.5\%$ vs $-18.5 \pm 0.4\%$, $p < 0.01$; RVGLS: $-26.4 \pm 1.6\%$ vs -
38 $22.4 \pm 1.5\%$, $p < 0.05$), while LVT remained unchanged. Serum hs-cTnT increased by 345%
39 after the CRIT₆₀ (6.0 ± 0.6 vs 20.7 ± 6.9 ng·L⁻¹, $p < 0.05$). This study demonstrates that exercise-
40 induced functional and biochemical cardiac perturbations are not confined to ultra-endurance
41 sporting events, and transpire during exercise that is typical of day-to-day training undertaken
42 by endurance athletes. The clinical significance of cumulative exposure to endurance exercise
43 warrants further study.

44 **Key words:** Cardiac function; Endurance exercise; Strain; Torsion; Hemodynamics.

45

46 **Abbreviations**

47	A	Late diastolic filling velocity
48	CO	Cardiac output
49	CRIT ₆₀	60-min high-intensity cycling race intervention
50	cTn	Cardiac troponin
51	E	Early diastolic filling velocity
52	E'	Early diastolic myocardial tissue velocity
53	EDV	End diastolic volume
54	ESV	End systolic volume
55	FAC	Fractional area change
56	GLS	Global longitudinal strain
57	LV	Left ventricle
58	RV	Right ventricle
59	S'	Systolic myocardial tissue velocity
60	SV	Stroke volume

61

62 **Introduction**

63 Although regular moderate intensity exercise confers cardiovascular health benefits,
64 prolonged and intense physical activity can provoke temporary autonomic (30), functional (5,
65 9, 13, 26), and biochemical (29) cardiac abnormalities. The term ‘cardiac fatigue’ is often
66 used to describe transient (usually resolving after 24-48 h) perturbations in systolic and/or
67 diastolic function following strenuous endurance exercise and may be coupled with the
68 release of cardiac-specific injury markers (e.g., cardiac troponin – cTn) (14, 23). Whether this
69 phenomenon represents a physiological response to exercise, stimulating healthy cardiac
70 adaptation or, evokes adverse cardiac remodelling with long term consequences in some
71 individuals, is under debate (15, 19).

72 Transient left ventricular (LV) diastolic dysfunction reported following endurance exercise
73 (5, 36) is attributable to, in part, impaired intrinsic LV relaxation (24). In contrast, evidence
74 for LV systolic dysfunction after endurance exercise is equivocal; several studies have
75 reported impaired LV systolic parameters during recovery (25), while others report no change
76 (13). Two-dimensional speckle-tracking echocardiography offers quantitative assessment of
77 myocardial mechanical function, overcoming several limitations of traditional tissue Doppler
78 indices (2, 6), and has recently been used to evaluate LV strain and torsion (8). Ventricular
79 strain is the percent change an area of interest deforms from its original dimension (i.e.,
80 diastolic dimension), and provides a more sensitive measure of contractile function than
81 traditional echocardiographic indices (e.g., ejection fraction) (27, 38). Transient reductions in
82 LV strain in all planes (i.e., longitudinal, circumferential and radial) and LV torsion have
83 been documented following prolonged (> 180 min) exercise (14, 29, 34, 36). However, the
84 effects of shorter duration (~60 min) exercise, often performed at higher relative intensities,
85 on ventricular strain and torsion have not been established. Furthermore, right ventricular
86 (RV) responses to endurance exercise have received considerably less attention than LV

87 responses; the RV– which may be more profoundly affected by high-intensity exercise due to
88 a higher relative pressure overload and a disproportionate increase in wall stress (16) –
89 warrants more extensive examination following such exercise.

90 Previous studies examining exercise-induced perturbations in ventricular strain and torsion
91 have largely evaluated these parameters during supine resting conditions, typically within 1-h
92 of completing an exercise intervention (5, 9, 13, 26, 34). However, the post-exercise recovery
93 period is characterised by persistent sympatho-excitation (resulting in a sustained
94 tachycardia) (30) and peripheral vasodilatation (resulting in a reduced afterload) (20). In this
95 context, exercise-induced perturbations in ventricular strain and torsion may be confounded
96 by altered autonomic and hemodynamic conditions when assessed during passive recovery
97 from exercise (9, 34). The assessment of ventricular strain and torsion *during* a low-intensity
98 exercise stimulus, which provides a functional load on the heart coupled with controlled
99 hemodynamic conditions (4, 31), may provide a means to evaluate strain and torsion under
100 comparable loading conditions following endurance exercise.

101 Accordingly, this study evaluated LV and RV strain, and LV torsion – in response to 60-min
102 of high-intensity exercise – while at rest and during a standardized exercise challenge.
103 Furthermore, indices of cardiac autonomic activity (heart rate variability) and biomarkers of
104 cardiac injury (serum cTn T & I) were examined before and after exercise. It was
105 hypothesized that 60-min of high-intensity cycling would induce an autonomic imbalance,
106 increase serum cTn concentrations and perturb ventricular strain and torsion parameters.
107 Furthermore, it was hypothesized that perturbations in ventricular strain and torsion would be
108 exacerbated when assessed under a controlled functional load (i.e., during a low-intensity
109 exercise stimulus).

110 **Methods**

Subjects: Fifteen highly-trained male cyclists participated in the study. Cyclists were considered highly-trained if they attained a peak oxygen uptake above $60 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ during an incremental cycling test, and were currently training $>8 \text{ h}\cdot\text{week}^{-1}$ (quantified using a self-guided training diary). Pre-participation health screening, in accordance with the American College of Sports Medicine (1), ensured subjects were apparently healthy non-smokers, had no history of cardiopulmonary, metabolic or neuromuscular disorders, and were not taking any medications. Experimental procedures were approved by the Griffith University Human Research Ethics Committee and all subjects provided written and witnessed informed consent.

Study design: All subjects visited the laboratory on two separate days after abstaining from exercise for a minimum of 24 h. During the first visit, subjects underwent pre-participation health screening and performed an incremental cycling test for the determination of peak exercise values (oxygen uptake and heart rate). On a subsequent visit subjects attended the laboratory for 1.5 h before (Pre-) and after (Post-) a 60-min high-intensity cycling race intervention (CRIT₆₀), where blood samples were collected and electrocardiograph and echocardiograph measurements were performed under two conditions: 1) at rest, and 2) during a standardized low-intensity exercise challenge (Figure 1). The standardized exercise challenge served to control for any changes in blood pressure that typically manifests during acute recovery from exercise (i.e., post-exercise hypotension), and thus “normalized”, to some extent, the loading conditions on the heart for Pre- and Post-CRIT₆₀ comparisons. Post-CRIT₆₀ measurements began within 15 min of cessation of the cycling race intervention and were completed within an hour of finishing the CRIT₆₀.

Incremental exercise test: Incremental exercise tests were performed on an electronically-braked cycle ergometer (Excalibur Sport, Lode BV, Groningen, Netherlands) and comprised 6 min of warm-up at 80 W, before the workload was increased by 15 W every 30 s until the

subject reached volitional fatigue. Peak heart rate and oxygen uptake, measured via 12-lead ECG and indirect calorimetry (Ultima Cardio₂, MGC Diagnostics, St Paul, MN), were calculated as the average of the highest two consecutive 30-s bin-averaged values attained during the test.

High-intensity cycling race intervention (CRIT₆₀): The CRIT₆₀ comprised 60-min of cycling performed under competitive conditions on a dedicated paved outdoor circuit. Participants were fitted with GPS-enabled heart rate monitors during the session to measure heart rate, speed, distance and environmental conditions. Transit time between the cycling venue and the testing laboratory was a maximum of 10 min.

Electrocardiography: Cardiac rhythm was monitored continuously during experimental trials using a 12-lead electrocardiogram (Mortara X-Scribe, Mortara Instruments, WI, USA). Lead II electrocardiograph signals were simultaneously synchronised to an echocardiograph machine and recorded at 1000 Hz using a data acquisition system (MP100, BIOPAC Systems, Goleta, CA, USA). Beat-by-beat cardiac intervals (RR interval) were subsequently extracted from the raw electrocardiograph traces for designated time periods (5-min of quiet supine rest before and after the CRIT₆₀), and heart rate variability parameters were derived to estimate cardiac autonomic activity Pre- and Post-CRIT₆₀ (30).

Time- and frequency-domain characteristics of the RR intervals were calculated using custom designed Matlab software (version 7.7.0 The Mathworks Inc. R2008b). Time-domain parameters included the mean interval and root mean square of successive differences in intervals. Frequency-domain parameters were derived from the power spectral density data of RR interval signals using autoregression techniques. Low frequency (LF: 0.04-0.15 Hz) and high frequency (HF: 0.15-0.4 Hz) parameters were normalised (nu) to total power (21), and the LF:HF ratio was calculated.

Echocardiography: All 2-dimensional echocardiography (GE Vivid E9 and Imaging System, GE Healthcare, WI, USA) was performed by the same cardiac sonographer in accordance with the American Society of Echocardiography guidelines (18). A minimum of three cardiac cycles were captured and all echocardiograph data was analyzed offline on a commercially available workstation (EchoPac, version 11, GE Healthcare, WI, USA) by a single cardiologist (A.Y.) with specialist training in speckle-tracking analysis, and reproducibility data reported previously (37). All images (during rest and the standardized exercise challenge; see Figure 2) were acquired with the subject semi-supine (30°) and oriented in a partial left decubitus position (30°) on a recumbent cycle ergometer (E-Bike EL, GE Healthcare, WI, USA). Resting images were acquired 10 min after adopting the semi-supine position. The standardized exercise challenge commenced immediately after the resting images were acquired, and required subjects to cycle at individualised power outputs to achieve a target heart rate of $\sim 100 \text{ beats} \cdot \text{min}^{-1}$ when cycling at a cadence of $60 \text{ rev} \cdot \text{min}^{-1}$. A target heart rate of $100 \text{ beats} \cdot \text{min}^{-1}$ was selected to stimulate vagal withdrawal and allow optimum frame rate requirements for speckle-tracking analysis. The power output for each individual during the standardized exercise challenge was held constant before and after the CRIT₆₀, and exercise-echocardiograph images were acquired after at least 3 min of cycling to ensure subjects had reached a steady-state heart rate.

All 2-dimensional and tissue Doppler images were acquired from standard parasternal and apical windows, with all system settings adjusted to ensure optimal signal-to-noise ratio and endocardial delineation. LV end-diastolic (EDV) and end-systolic (ESV) volumes were determined using the Simpson biplane method and ejection fraction quantified as the percent change between LV EDV and ESV volumes. Stroke volume (SV) was derived from Doppler waveforms acquired at the LV outflow tract, and cardiac output (CO) calculated. Systemic vascular resistance was estimated from mean arterial blood pressure divided by CO. Peak

early (E) and late (A) LV filling velocities were assessed from apical long-axis views at the level of the mitral valve leaflets and the E-to-A ratio was derived. Wall motion velocities of the LV were assessed during early filling (E') from apical four-chamber views at the level of the mitral valve annulus, with values averaged for the septal and lateral walls. RV end-diastolic and end-systolic areas were traced on the apical four-chamber image (focused on the RV), and the fractional area change (FAC) was derived. Wall motion velocity of the RV during ejection (S') was determined for the lateral free-wall at the level of the tricuspid annulus.

Ventricular strain and rotation were analyzed using semi-automated speckle-tracking techniques (6) for three parasternal short-axis (at the level of the mitral valves, papillary muscles and apex) and three apical (four-chamber, two-chamber and long-axis) images. LV global longitudinal strain (GLS) was determined by averaging longitudinal strain for apical four-chamber, two-chamber and long-axis images (27). RV GLS was determined by averaging strain for 6 RV segments from an apical four-chamber image focused on the RV (3). LV longitudinal, circumferential and radial strain were determined by averaging 18 LV segments (32), and RV longitudinal strain was determined as the average of 3 RV free wall segments (33). LV torsion was determined using parasternal short-axis images at the levels of the mitral valves and at the apex. Basal and apical rotation were determined, and LV torsion calculated as the maximum difference between basal and apical rotation (11). The time integral for strain (strain rate) and rotation (rotation rate) parameters were derived and peak strain and rotation rate was calculated during systole and early diastole.

Blood sampling: Blood samples were collected before the CRIT₆₀ and within 30 min of completing the CRIT₆₀ for the assessment of hematocrit, serum electrolytes (calcium, magnesium, potassium and sodium), and high-sensitivity cardiac troponin T and I (hs-cTnT/I) concentrations. Blood samples were always drawn after the resting

electrocardiograph recordings to eliminate any affects of venipuncture on heart rate variability. Hematocrit was determined from fresh whole blood via an automated blood cell counter (Coulter Counter, Coulter Electronics, Luton, UK). Serum was isolated from whole blood via centrifugation at 1,000 g for 10 min and stored at -80° C for subsequent analysis. An Abbott Architect ci16200 (Abbott Diagnostics, IL, USA) was employed for determination of electrolyte concentrations. High sensitivity cardiac troponin T (cTnT) analyses were performed using the adjusted hs-cTnT assays on a Roche E411 analyser (Roche Diagnostics, Sydney, Australia). High sensitivity cardiac troponin I (cTnI) analyses were performed using the Abbott ARCHITECT *STAT* hs-cTnI assay on the Abbott ci16200 analyser.

Statistical analyses: Statistical analysis was performed using SPSS 21.0 (SPSS Inc, Chicago, IL, USA). Normality of the data was determined using the Shapiro-Wilk test. Paired t-tests were performed to determine any differences in heart rate variability parameters, serum electrolytes and hs-cTn concentrations from Pre- to Post-CRIT₆₀. Two-way analyses of variance with repeated measures were performed to determine any differences in echocardiograph parameters assessed at rest and during a low-intensity exercise challenge before and after the CRIT₆₀. Chamber-specific strain (left and right ventricles) was included as a within subject factor to examine differences between ventricles. Pair-wise comparisons using Bonferroni adjustments were used to further examine differences between time periods (Pre- and Post-CRIT₆₀). Pearson's correlations were performed to examine relationships between exercise intensity (heart rate), training volume history, hs-cTn release and changes in echocardiograph parameters. Significance was accepted at $p < 0.05$. All data are presented as mean $\pm$ SEM.

Results

233 *Subject characteristics:* Fifteen highly-trained male cyclists (19-44 yr) completed the study.

234 Subject characteristics and baseline echocardiographic data are presented in Table 1.

235 *High-intensity cycling intervention:* Heart rate during the CRIT₆₀ (168 ± 4 beats·min⁻¹) equated

236 to 88% of maximum heart rate (range: 85–93%), with an average race time of 59 ± 2 min.

237 Average speed and distance covered during the CRIT₆₀ was 39.5 ± 1.2 km·h⁻¹ and 39.0 ± 0.8

238 km. Ambient temperature during the CRIT₆₀ was 24.3 ± 0.9 °C. Body mass decreased by

239 $\sim 1.4\%$ after the CRIT₆₀ (80.4 ± 2.8 vs 79.3 ± 2.7 kg, $p < 0.01$).

240 *Cardiac autonomic activity and hemodynamics:* During resting conditions, all heart rate

241 variability parameters were significantly different from Pre- to Post-CRIT₆₀ (Table 2).

242 Resting arterial blood pressure (MAP: 96 ± 1 vs 86 ± 2 mmHg, $p < 0.001$) and systemic vascular

243 resistance (Table 3) were reduced after the CRIT₆₀. During the standardized exercise

244 challenge (normalised loading condition), arterial blood pressure (MAP: 98 ± 1 vs 97 ± 1

245 mmHg, ns) and systemic vascular resistance were unchanged from Pre- to Post-CRIT₆₀.

246 *Echocardiography during resting conditions:* Conventional and speckle-tracking

247 echocardiographic data before and after the CRIT₆₀ are presented in Tables 3 and 4. During

248 resting conditions, conventional (e.g., LV EDV, E', and E/A) and speckle-tracking

249 (e.g., LV early diastolic circumferential strain rate) diastolic parameters were reduced after

250 the CRIT₆₀, while estimates of left atrial pressure (E/E') were unchanged. All conventional

251 LV systolic parameters were unchanged from Pre- to Post-CRIT₆₀. With the exception of LV

252 circumferential strain, all strain and rotation parameters at rest were unchanged from Pre- to

253 Post-CRIT₆₀. During rest, RV FAC decreased from Pre- to Post-CRIT₆₀, while S' and RV

254 GLS were unchanged.

255 *Echocardiography during a standardized exercise challenge:* Conventional (e.g., E' and E/A)

256 and speckle-tracking (e.g., LV and RV early diastolic strain rates) diastolic parameters were

reduced after the CRIT₆₀ when assessed during the standardized exercise challenge. Despite no change in LV and RV GLS from Pre-to Post-CRIT₆₀ when assessed under resting conditions, LV and RV GLS both decreased after the CRIT₆₀ when assessed during the standardized exercise challenge (Figure 3). During the standardized exercise challenge, SV, LV strain in all planes (i.e., longitudinal, circumferential and radial) and RV longitudinal strain were also reduced after the CRIT₆₀ (Table 3 and 4). Augmentation of longitudinal strain (from rest to the standardized exercise challenge) was significantly different ($p<0.01$) for the LV and RV Post-CRIT₆₀. Attenuated augmentation was observed in the LV after the CRIT₆₀, while RV augmentation was completely abolished after the CRIT₆₀ (Table 4). Changes in apical rotation and LV torsion (acquired during the standardized exercise challenge) Post-CRIT₆₀ correlated with training history (Figure 4), with reduced apical rotation and LV torsion observed in individuals who accumulated relatively lower training volumes ($r=0.79$ & 0.93 , respectively, $p<0.01$). Conventional (e.g., RV FAC and S') and speckle-tracking parameters calculated for the RV were reduced after the CRIT₆₀ during the standardized exercise challenge. No correlations between exercise intensity (heart rate during the CRIT₆₀) and changes in echocardiographic parameters were observed.

Hematological responses: Hematocrit, serum albumin and serum electrolyte concentrations were unchanged after the CRIT₆₀ (Table 5). Both cTnT and cTnI increased significantly by $>350\%$ after the CRIT₆₀. The magnitude of cTnT and cTnI release (Post-CRIT₆₀ - Pre-CRIT₆₀) correlated with exercising heart rate ($r=0.77$, $p<0.01$ and 0.68 , $p<0.05$, respectively, Figure 5). No correlations between serum troponin concentrations and echocardiographic parameters were observed.

Discussion

This study is the first to demonstrate that a relatively short-duration (60-min) bout of high-intensity exercise, that is typical of routine cycling training, significantly perturbs ventricular function and provokes substantial release of cardiac-specific biomarkers. In a cohort of well-trained cyclists, echocardiography performed during a standardized low-intensity exercise challenge provided a means to evaluate ventricular strain and torsion under comparable loading conditions, before and after endurance exercise. Perturbations in ventricular strain and torsion following high-intensity exercise were particularly evident during the standardized exercise challenge. Furthermore, functional and biochemical abnormalities were most evident in the least-trained individuals and those with the highest exercising heart rate.

Evidence of reduced diastolic function when assessed during passive recovery

Despite a maintained blood volume (based on stable hematocrit Pre- to Post-CRIT₆₀) and unchanged estimates of preload (E/E'), several conventional diastolic parameters were reduced post-race (Table 3), suggesting 60-min of high-intensity exercise induced LV diastolic dysfunction during passive recovery (5, 14, 24, 36). Previous studies have reported impaired LV relaxation during supine recovery from ultra-endurance exercise (23, 24, 36). Our findings highlight the potential for routine exercise undertaken by endurance athletes as well as recreationally active individuals to evoke alterations in cardiac function that are similar to that observed with prolonged exercise. Additionally, despite evidence supporting transient LV systolic dysfunction during supine recovery from strenuous exercise (23), impaired systolic function following exercise was not confirmed under resting conditions in the present study (with the exception of reduced LV circumferential strain and RV FAC), which is consistent with other work (13). The current results may be a reflection of the relatively 'short' duration of the CRIT₆₀ exercise intervention, or perhaps more pertinently, the altered autonomic and hemodynamic perturbations observed following exercise. Indeed, sustained sympatho-excitation and peripheral vasodilatation during supine recovery from

exercise may provoke favorable cardiac autonomic and loading conditions, masking any intrinsic systolic dysfunction (34).

In the present study, parameters of heart rate variability reflected an altered cardiac autonomic tone during passive recovery Post-CRIT₆₀, which is consistent with previous studies reporting an autonomic imbalance following strenuous exercise (7, 12, 30). Furthermore, resting arterial blood pressure and systemic vascular resistance were reduced Post-CRIT₆₀, which is indicative of sustained post-exercise vasodilatation (20). The current heart rate variability and hemodynamic results indicate that exercise-induced perturbations in cardiac autonomic tone and loading conditions were evident during supine recovery and may confound comparisons of ventricular function before and after endurance exercise (34). Indeed, such post-exercise perturbations are ubiquitous to most individuals who undertake even moderately-intense exercise (20). In contrast, arterial blood pressure and systemic vascular resistance were unchanged from Pre- to Post-CRIT₆₀ during the standardized low-intensity exercise challenge. Thus, a low-intensity exercise challenge serves to provide comparable loading conditions following relatively high-intensity exercise. Given that strain is load-dependent, this technique offers, in general, a controlled method for pre- to post-exercise comparisons of ventricular strain and torsion.

Evidence of reduced diastolic and systolic function when assessed during exercise

Recent work suggests myocardial strain imaging exceeds the predictive value of conventional echocardiograph-derived LV systolic indices (e.g., LV ejection fraction), and may be a more sensitive measure of subclinical changes in myocardial function (38). Indeed, when strain (Figure 3) was assessed during the standardized exercise challenge, LV GLS decreased by 8.9% after the CRIT₆₀ (despite no change in ejection fraction), and RV GLS decreased by 15.2%. Furthermore, both conventional (Table 3) and speckle-tracking (Table 4) parameters

of diastolic function were reduced Post-CRIT₆₀ when assessed during the standardized exercise challenge, while estimates of pre-load were unchanged. These results suggest impaired ventricular relaxation and an attenuated contractile reserve following 60 min of high intensity exercise (4, 9, 34).

Interestingly, while reductions in LV and RV strain were ubiquitous across the cohort, the magnitude of reduction in strain was greatest in the RV; indeed, RV augmentation was much more severely impaired than the LV following 60 min of exercise, and in fact appears to be completely abolished. Given that high-intensity exercise induces a disproportionate rise in RV wall stress (4, 17), these results suggest that intense exercise induces a much greater ‘over-load’ on the RV than the LV. Thus, modest post-exercise reductions in left ventricular strain (particularly when assessed during a standardized exercise challenge) may reflect bi-ventricular interactions, whereby acute increases in RV compliance/volume may impinge on the LV (13). Studies have reported an increased incidence of ‘septal bounce’ following endurance exercise (14, 26).

Changes in LV torsion (Pre- to Post-CRIT₆₀) during the standardized exercise challenge were predominantly a result of altered apical rotation, with basal rotation unchanged. This suggests increased apical responsiveness to an acute exercise stimulus, and may reflect acute changes in adrenergic sensitivity of the apical myocardium (9). Furthermore, perturbations in apical rotation and LV torsion correlated with historical training volume (Figure 4), whereby those with the lowest training volume experience the greatest reduction in apical rotation and LV torsion Post-CRIT₆₀. Interestingly, LV torsion tended to be enhanced (i.e., positive values for change in torsion) after the race in individuals with the greatest training volume. Augmented LV torsion after exercise in athletes undertaking higher training volumes suggests a training-induced adaptation (31, 35), potentially resulting in a greater torsional reserve which can be recruited post-exercise to maintain contractile function. Indeed, Stöhr et al., 2012 have shown

that during exercise, individuals with high aerobic fitness generate lower LV torsion (as well as heart rate) for a given cardiac output, when compared to moderately fit individuals.

Exercise-induced biomarker release

Transient elevations in serum cardiac-specific troponin have been widely observed following endurance exercise (22, 29), however the clinical significance of this phenomenon remains unclear. Whether exercise-induced troponin release is a physiological phenomenon, potentially leading to adaptation, or reflects acute myocardial injury (29) is debated. In the present study, 60-min of high-intensity cycling induced significant increases in cTnT and cTnI concentrations (~3.5-fold increase from pre-exercise). Interestingly, individuals with relatively lower training volumes and higher exercising heart rates recorded the largest increases in cTnT and cTnI concentrations (Figure 5), suggesting that habitual exercise and myocyte contraction rate may influence the mechanisms of cTn release. Indeed, extraordinary cardiac loading and a high rate of contraction could increase cell membrane stress, provoke inflammation and alter myocyte metabolism (28), consequently resulting in the release of cTn from cardiomyocytes. While cardiac troponin within the myocyte is largely bound to tropomyosin, a small amount of unbound troponin resides in the cytosol. In contrast to troponin release induced by tissue necrosis, often secondary to a myocardial infarct, exercise-induced cTnT and cTnI release may be a result of increased cell membrane permeability and leakage of unbound cytosolic troponin (22).

Although elevations in cTnT and cTnI were observed in all individuals, no significant correlations were observed between cardiac biomarker release and echocardiographic measures. Our findings are in contrast with others who have reported positive relationships between cardiac-specific troponin release and echocardiographic measures of systolic RV function following ultra-endurance exercise (13). The time-course of exercise-induced

cardiac-specific troponin release is highly individual, with potentially multiphasic onset and recovery kinetics during and after exercise (22). Given that we obtained a blood sample at a fixed time point post-CRIT₆₀, the cTnT and cTnI data presented may not reflect each individual's peak release, and may explain why relationships between changes in serum cardiac-specific troponin concentrations and ventricular strain were not observed.

Methodological considerations

During the study, cardiac loading conditions were modulated with a standardized low-intensity exercise challenge so as to provide a functional cardiac challenge and controlled metabolic requirements. While this exercise stimulus provided comparable LV afterload before and after the CRIT₆₀ (Table 3), estimates of RV afterload were not successfully obtained due to the low incidence of observed tricuspid regurgitation (n = 2). In these participants, estimates of RV systolic pressure agree with previous work (17), and were similar Pre- and Post-CRIT₆₀, both at rest (19.8 vs. 20.0 mmHg) and during the standardized exercise challenge (41.1 vs. 39.4 mmHg).

It is important to note that changes in autonomic tone and heart rate (i.e., a post-exercise tachycardia) can independently influence strain, and may therefore confound pre-to-post exercise comparisons of cardiac function assessed at rest (34). While an exercise-induced cardiac autonomic imbalance was identified during resting conditions using heart rate variability analysis, estimates of autonomic tone were not performed during the standardized exercise challenge – the assessment of heart rate variability during exercise is problematic and negates the assumption of stationarity (21). Furthermore, respiratory patterns (e.g., frequency and depth) were not controlled during the experimental trials and may influence parameters of heart rate variability (10). To minimize vagal influence on cardiac function during the study, a target heart rate of 100 beats·min⁻¹ was selected during the standardized

exercise challenge. Although a Post-CRIT₆₀ cardiac drift was observed during the low-intensity exercise challenge, the increase in heart rate was minimal (12 ± 3 beats·min⁻¹). This may represent a compensation for a reduction in stroke volume to maintain cardiac output, which remained unchanged, during the standardized exercise challenge (Table 3).

Physiological/Clinical Perspectives

While this study did not include recovery time-course measures, the current results (with some speculation) suggest that exercise-induced functional and biochemical perturbations in response to routine day-to-day endurance training most likely reflects a transient event that may constitute the physiological stimulus for adaptation rather than significant cardiac damage with long term consequences. Indeed, previous data using prolonged ultra-endurance exercise suggests that this response is transient and returns to baseline within 24-48 h post-exercise (14, 26). Furthermore, none of the subjects presented with any indications of pathological remodeling, nor did they experience any acute cardiac events during the study. Nonetheless, given the ambiguity in the dose-response relationship between exercise and cardiac health/function, clarification of the ‘cardiac recovery’ timeline in response to routine day-to-day endurance training would be valuable, particularly given that recreationally active individuals do engage in high-intensity exercise and many athletes undertake multiple training sessions per day.

Conclusion

High-intensity endurance exercise transiently increases ventricular wall stress – causing acute functional and biochemical cardiac abnormalities – with ambiguous long-term consequences. Exercise-induced functional cardiac perturbations were particularly evident when assessed using speckle-tracking echocardiography under controlled hemodynamic conditions (i.e., during a standardized low-intensity exercise challenge). This study highlights that exercise-

426 induced cardiac dysfunction and biomarker release is not unique to ultra-endurance sporting
427 events, and transpires during shorter-duration, high intensity exercise that is a common and
428 routine component of day-to-day training regimes undertaken by endurance athletes. The
429 results of this study emphasise the need for additional studies to clarify the cardiovascular
430 consequences of acute and chronic participation in high-intensity endurance exercise.
431 Whether this phenomenon reflects a positive, negative or neutral process with regards to
432 cardiac adaptation is unclear.

433 **Disclosures**

434 None.

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Figure captions

Figure 1. Schematic of the experimental procedures performed before (Pre-CRIT₆₀) and after (Post-CRIT₆₀) 60-min of high-intensity cycling (CRIT₆₀). ECG: Electrocardiography; Blood: Blood sample; Rest & Exercise Echo: Echocardiography performed during passive rest and during a standardized low-intensity recumbent cycling exercise challenge.

Figure 2. Representative image of the left and right ventricles analyzed for longitudinal strain at Rest and during a standardized exercise challenge (Exercise challenge). AVC: Aortic valve closure; GS: Global strain.

Figure 3. Left (LV) and right (RV) ventricular global longitudinal strain measured at Rest and during a standardized exercise challenge (Exercise challenge) before (closed circles) and after (open circles) a 60-min high-intensity cycling race (CRIT₆₀). Data are mean and SEM. *significantly different to Pre-CRIT₆₀ ($p < 0.05$).

Figure 4. Change in left ventricular torsion (Post-CRIT₆₀ – Pre-CRIT₆₀) and apical rotation (Post-CRIT₆₀ – Pre-CRIT₆₀) after a 60-min high-intensity cycling race (CRIT₆₀) plotted against historical training volume.

Figure 5. Magnitude of cTnT (Post-CRIT₆₀ – Pre-CRIT₆₀) and cTnI release (Post-CRIT₆₀ – Pre-CRIT₆₀) after a 60-min high-intensity cycling race (CRIT₆₀) plotted against average exercising heart rate. Hs-cTnT: high-sensitivity cardiac troponin T. Hs-cTnI: high-sensitivity cardiac troponin I.

Table 1. Subject characteristics

<i>Demographic and functional measures</i>	
Age (yr)	28 ± 3
BMI ($\text{kg} \cdot \text{m}^2$)	23.5 ± 0.7
MAP (mmHg)	95 ± 1
HR_{peak} ($\text{beats} \cdot \text{min}^{-1}$)	194 ± 3
VO_{2peak} ($\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	65.2 ± 2.7
Power_{peak} (W)	467 ± 20
Training (yr)	7 ± 2
Training ($\text{h} \cdot \text{wk}^{-1}$)	13 ± 5.0
<i>Echocardiographic measures</i>	
IVSd (cm)	0.9 ± 0.1
LVOT (cm)	2.4 ± 0.2
LVIDd (cm)	5.5 ± 0.4
LVIDs (cm)	3.8 ± 0.5
LVEDV (mL)	169 ± 6
LVESV (mL)	66 ± 3
LVEF (%)	61 ± 1
LVGLS (%)	-17.3 ± 0.5
RVEDA (cm^2)	20.6 ± 0.8
RVESA (cm^2)	10.7 ± 0.7
RVFAC (%)	48 ± 1
RVGLS (%)	-24.3 ± 0.8

Data are mean $\pm$ SEM. BMI: Body mass index; MAP: Mean arterial pressure; HR: Heart rate; VO₂: Oxygen uptake; IVSd: Inter-ventricular septum diastole; LVOT: Left ventricular (LV) outflow tract; LVIDd: LV internal dimension diastole; LVIDs: LV internal dimension systole; LVEDV: LV end diastolic volume; LVESV: LV end systolic volume; LVEF: LV ejection fraction; LVGLS: LV global longitudinal strain; RVEDA: Right ventricular (RV) end diastolic area; RVESA: RV end systolic area; RVFAC: RV fractional area change; RVGLS: RV global longitudinal strain.

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Table 2. Heart rate variability parameters Pre- and Post-CRIT₆₀

	Pre-CRIT₆₀	Post-CRIT₆₀
Mean interval (ms)	1067 ± 43	807 ± 36*
RMSSD (ms)	62.7 ± 12.0	26.1 ± 6.9*
HFnu	53.8 ± 5.1	29.0 ± 3.9*
LFnu	46.2 ± 5.1	71 ± 3.9*
LF:HF	1.3 ± 0.5	4.3 ± 1.7*

Data are mean ± SEM. CRIT₆₀: 60-min high-intensity cycling race; RMSSD: Root mean square of successive differences; HF: High frequency; LF: Low frequency; nu: normalized to total power.

*significantly different to Pre-CRIT₆₀ (p<0.05).

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Table 3. Hemodynamic and echocardiographic parameters measured at Rest and during a standardized exercise challenge (Exercise challenge) Pre- and Post-CRIT₆₀

	Rest		Exercise challenge		Rest to Exercise challenge Δ	
	Pre-CRIT ₆₀	Post-CRIT ₆₀	Pre-CRIT ₆₀	Post-CRIT ₆₀	Pre-CRIT ₆₀	Post-CRIT ₆₀
<i>Hemodynamic parameters</i>						
HR (beats·min ⁻¹)	56 ± 2	70 ± 3*	94 ± 1	106 ± 4*	38 ± 2	35 ± 3
SBP (mmHg)	123 ± 2	112 ± 3*	144 ± 4	142 ± 3	18 ± 4	27 ± 4*
DBP (mmHg)	82 ± 1	73 ± 2*	76 ± 1	74 ± 1	-7 ± 1	1 ± 2*
SVR (mmHg·min·L ⁻¹)	18.2 ± 1.0	13.3 ± 0.9*	8.2 ± 0.4	7.6 ± 0.4	-10 ± 0.8	-5.7 ± 0.9*
<i>Left ventricular parameters</i>						
EDV (mL)	169 ± 6	162 ± 6*	170 ± 6	164 ± 6	1 ± 4	1 ± 2
ESV (mL)	66 ± 3	61 ± 3	57 ± 4	55 ± 4	-8 ± 2	-5 ± 2
EF (%)	61 ± 1	63 ± 1	67 ± 1	66 ± 1	6 ± 1	4 ± 1
E/A	1.97 ± 0.14	1.56 ± 0.19*	1.53 ± 0.09	1.27 ± 0.06*	-0.44 ± 0.12	-0.40 ± 0.28
E' (m·s ⁻¹)	0.16 ± 0.00	0.14 ± 0.01*	0.21 ± 0.01	0.19 ± 0.01*	0.05 ± 0.01	0.03 ± 0.02
E/E'	5.1 ± 0.2	5.3 ± 0.3	6.2 ± 0.3	5.8 ± 0.3	1.16 ± 0.23	0.53 ± 0.30
SV (mL)	98 ± 4	95 ± 4	128 ± 4	121 ± 4*	30 ± 3	27 ± 4
CO (L·min ⁻¹)	5.3 ± 0.3	6.6 ± 0.4	12.3 ± 0.5	12.9 ± 0.6	7.0 ± 0.5	6.5 ± 0.5
<i>Right ventricular parameters</i>						
EDA (cm ²)	20.6 ± 0.8	20.9 ± 0.7	21.2 ± 0.7	20.8 ± 0.8	0.6 ± 0.3	0.0 ± 0.4
ESA (cm ²)	10.7 ± 0.6	11.3 ± 0.17	10.1 ± 0.4	10.5 ± 0.5	-0.6 ± 0.4	-0.8 ± 0.3
FAC (%)	48 ± 1	46 ± 1*	52 ± 1	49 ± 2*	4 ± 2	3 ± 1
S' (m·s ⁻¹)	0.16 ± 0.01	0.16 ± 0.01	0.22 ± 0.01	0.20 ± 0.01*	0.06 ± 0.01	0.05 ± 0.01

Data are Mean ± SEM. HR: CRIT₆₀, 60-min high-intensity cycling race; Heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial pressure; SVR: Systemic vascular resistance; EDV: End-diastolic volume; ESV: End-systolic volume; EF: Ejection fraction; E/A: Ratio of early to late diastolic mitral inflow velocities; E': Mean septal and lateral early relaxation velocity; SV: Stroke volume; CO: Cardiac Output; EDA: End-diastolic area; ESA: End-systolic area; FAC: Fractional area change; S': Peak systolic tissue velocity; Δ : Change score. *significantly different to Pre-CRIT₆₀ (P<0.05).

Table 4. Speckle-tracking derived echocardiograph parameters measured at Rest and during a standardized exercise challenge (Exercise challenge) Pre- and Post-CRIT₆₀

	Rest		Exercise challenge		Rest to Exercise challenge Δ	
	Pre-CRIT ₆₀	Post-CRIT ₆₀	Pre-CRIT ₆₀	Post-CRIT ₆₀	Pre-CRIT ₆₀	Post-CRIT ₆₀
<i>Left ventricular strain</i>						
LS (%)	-18.6 $\pm$ 0.4	-18.1 $\pm$ 0.2	-21.8 $\pm$ 0.4	-20.3 $\pm$ 0.4*	-3.2 $\pm$ 0.3	-2.2 $\pm$ 0.3*
LSr s (s ⁻¹)	-1.14 $\pm$ 0.03	-1.15 $\pm$ 0.03	-1.52 $\pm$ 0.04	-1.52 $\pm$ 0.06	-0.38 $\pm$ 0.04	-0.37 $\pm$ 0.05
LSr e (s ⁻¹)	1.49 $\pm$ 0.05	1.51 $\pm$ 0.07	1.97 $\pm$ 0.05	1.89 $\pm$ 0.06	0.49 $\pm$ 0.04	0.37 $\pm$ 0.07*
CS (%)	-20.2 $\pm$ 0.6	-19.1 $\pm$ 0.4*	-24.0 $\pm$ 0.7	-21.9 $\pm$ 0.8*	-3.7 $\pm$ 0.6	-2.8 $\pm$ 0.6
CSr s (s ⁻¹)	-1.34 $\pm$ 0.04	-1.35 $\pm$ 0.04	-1.85 $\pm$ 0.07	-1.79 $\pm$ 0.08	-0.52 $\pm$ 0.06	-0.46 $\pm$ 0.07
CSr e (s ⁻¹)	1.65 $\pm$ 0.07	1.50 $\pm$ 0.05*	2.42 $\pm$ 0.13	1.99 $\pm$ 0.11*	0.77 $\pm$ 0.08	0.49 $\pm$ 0.09*
RS (%)	45.7 $\pm$ 2.0	42.6 $\pm$ 2.7	52.1 $\pm$ 2.8	46.8 $\pm$ 2.9*	6.4 $\pm$ 3.4	4.2 $\pm$ 3.2
RSr s (s ⁻¹)	1.66 $\pm$ 0.06	1.69 $\pm$ 0.07	2.12 $\pm$ 0.09	2.10 $\pm$ 0.09	0.46 $\pm$ 0.12	0.45 $\pm$ 0.09
RSr e (s ⁻¹)	-1.68 $\pm$ 0.10	-1.67 $\pm$ 0.09	-2.02 $\pm$ 0.09	-1.74 $\pm$ 0.14*	-0.34 $\pm$ 0.13	-0.07 $\pm$ 0.15*
<i>Right ventricular strain</i>						
LS (%)	-27.3 $\pm$ 1.1	-27.1 $\pm$ 0.8	-28.4 $\pm$ 1.1	-23.5 $\pm$ 1.1*	-1.1 $\pm$ 1.7	3.4 $\pm$ 1.4*
LSr s (s ⁻¹)	-1.54 $\pm$ 0.09	-1.69 $\pm$ 0.12	-2.09 $\pm$ 0.09	-2.06 $\pm$ 0.1	-0.55 $\pm$ 1.0	-0.36 $\pm$ 0.15
LSr e (s ⁻¹)	2.15 $\pm$ 0.06	2.12 $\pm$ 0.13	2.65 $\pm$ 0.13	2.14 $\pm$ 0.14*	0.50 $\pm$ 0.16	0.39 $\pm$ 0.17
<i>Left ventricular rotation</i>						
Apical Rot (°)	7.7 $\pm$ 1.1	7.9 $\pm$ 1.0	11.2 $\pm$ 1.3	10.4 $\pm$ 1.6	3.4 $\pm$ 1.4	1.9 $\pm$ 1.6
Apical Rotr s (°·s ⁻¹)	65.3 $\pm$ 7.2	76.4 $\pm$ 6.3	101.4 $\pm$ 6.0	91.4 $\pm$ 9.3	36.2 $\pm$ 7.6	15.1 $\pm$ 7.6*
Apical Rotr e (°·s ⁻¹)	-67.7 $\pm$ 6.1	-61.5 $\pm$ 6.6	-90.5 $\pm$ 5.6	-88.1 $\pm$ 7.4	-22.8 $\pm$ 7.6	-26.6 $\pm$ 6.8
Basal Rot (°)	-5.0 $\pm$ 0.8	-5.7 $\pm$ 0.5	-5.1 $\pm$ 0.4	-5.7 $\pm$ 0.8	-0.1 $\pm$ 0.9	0.0 $\pm$ 0.9
Basal Rotr s (°·s ⁻¹)	-67.7 $\pm$ 4.1	-63.4 $\pm$ 5.4	-71.4 $\pm$ 4.8	-84.6 $\pm$ 6.7	-3.7 $\pm$ 6.4	-21.2 $\pm$ 6.3
Basal Rotr e (°·s ⁻¹)	56.6 $\pm$ 5.2	50.6 $\pm$ 4.8	62.5 $\pm$ 4.3	60.8 $\pm$ 7.1	5.9 $\pm$ 6.1	10.1 $\pm$ 7.9
Torsion (°)	11.1 $\pm$ 1.5	12.6 $\pm$ 1.5	15.9 $\pm$ 1.5	15.1 $\pm$ 2.1	4.8 $\pm$ 2.0	2.5 $\pm$ 2.6

Data are Mean $\pm$ SEM. CRIT₆₀: 60-min high-intensity cycling race; LS: Longitudinal strain; LSr: Longitudinal strain rate; CS: Circumferential strain; CSr: Circumferential strain rate; RS: Radial strain; RSr: Radial strain rate; Rot: Rotation; Rotr: Rotation rate; s: Systolic; e: Early diastolic; Δ : Change score. *significantly different to Pre-CRIT₆₀ (P<0.05).

Table 5. Hematocrit, and serum electrolyte and high-sensitivity troponin concentrations Pre-and Post-CRIT₆₀

	Pre-CRIT₆₀	Post-CRIT₆₀
Hematocrit (%)	41.6 ± 0.1	41.7 ± 0.1
Albumin (g·L⁻¹)	44.2 ± 0.7	44.6 ± 0.9
Sodium (mmol·L⁻¹)	139.6 ± 0.5	140.5 ± 0.4
Potassium (mmol·L⁻¹)	3.99 ± 0.10	3.95 ± 0.08
Calcium (mmol·L⁻¹)	2.37 ± 0.02	2.39 ± 0.02
Magnesium (mmol·L⁻¹)	0.81 ± 0.01	0.79 ± 0.02
hs-cTnT (ng·L⁻¹)	6.0 ± 0.6	20.7 ± 6.9*
hs-cTnI (ng·L⁻¹)	5.9 ± 1.2	19.7 ± 6.2*

Data are mean ± SEM. CRIT₆₀: 60-min high-intensity cycling race; hs-cTnT: high-sensitivity cardiac troponin T; hs-cTnI: high-sensitivity cardiac troponin I. *significantly different to Pre-CRIT₆₀ (p<0.05).

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5