Left Ventricular Function and Cardiac Biomarker Release – The Influence of Exercise Intensity, Duration and Mode: A Systematic Review and Meta-Analysis

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Abstract

Objective: We performed a systematic review, meta-analysis and meta-regression of exercise studies that sought to determine the relationship between cardiac troponin (cTn) and left ventricular (LV) function. The second objective was to determine how study-level and exercise factors influenced the variation in the body of literature.

Data Sources: A systematic search of Pubmed Central, Science Direct, SPORTDISCUS, and MEDLINE databases.

Eligibility Criteria: Original research articles published between 1997-2018 involving >30mins of continuous exercise, measuring cardiac troponin event rates and either LV ejection fraction (LVEF) or the ratio of the peak early (E) to peak late (A) filling velocity (E/A ratio).

Design: Random-effects meta-analyses and meta-regressions with four a priori determined covariates (age, exercise heart rate [HR], duration, mass).

Registration: The systematic search strategy was registered on the PROSPERO database (CRD42018102176).

Results: Pooled cTn event rates were evident in 45.6% of participants (95% CI = 33.6 – 58.2%); however, the overall effect was non-significant ($P>0.05$). There were significant ($P<0.05$) reductions in E/A ratio of – 0.38 (SMD = -1.2, 95% CI [-1.4, -1.0]), and LVEF of -2.02% (SMD = -0.38, 95%CI [-0.7, -0.1]) pre to post-exercise. Increased exercise HR was a

significant predictor of troponin release and E/A ratio. Participant age was negatively associated with cTn release. There was a significant negative association between E/A ratio with increased rates of cTn release ($P < 0.05$).

Conclusions: High levels of statistical heterogeneity and methodological variability exist in the majority of EICF studies. Our findings show that exercise intensity and age are the most powerful determinants of cTn release. Diastolic function is influenced by exercise HR and cTn release, which implies that exercise bouts at high intensities are enough to elicit cTn release and reduce LV diastolic function. Future EICF studies should 1) utilise specific echocardiographic techniques such as myocardial speckle tracking, 2) ensure participants are euhydrated during post-exercise measurements, and 3) repeat measures in the hours following exercise to assess symptom progression or recovery. It is also recommended to further explore the relationship between aging, training history, and exercise intensity on cTn release and functional changes.

Key Points:

- The magnitude of exercise induced reductions in diastolic function is related to troponin event rate.
- Higher average exercise heart rates are associated with an increased troponin event rate and greater reductions in diastolic function.
- Increased age leads to a lower troponin event rate and reduced average exercise heart rates. This may have important implications for older/veteran athletes participating in prolonged endurance events.

List of Abbreviations

CI – Confidence intervals

CS – Circumferential strain

cTn – Cardiac troponin

E/A Ratio – Early to late diastolic filling velocity ratio

EICF – Exercise induced cardiac fatigue

HR – Heart rate

LS – Longitudinal strain

LV – Left ventricle

LVEF – Left ventricular ejection fraction

PSE – Prolonged strenuous exercise

RS – Radial strain

RV – Right ventricle

$\dot{V}O_2$ – Oxygen consumption

hs-cTnT – High-sensitivity cardiac troponin T

hs-cTnI – High-sensitivity cardiac troponin I

cTnT – Cardiac troponin T assay

cTnI-Beckman - Cardiac troponin I assays manufactured by Beckman Coulter

cTnI-Siemens - Cardiac troponin I assays manufactured by Siemens

1. Introduction

Prolonged strenuous endurance exercise (PSE) is associated with altered cardiac physiology, that often manifests as both transient alterations in cardiac function and detectable levels of biomarkers, most commonly cardiac troponin (cTn) in the peripheral circulation (1). In some instances, acute measurements of systolic and diastolic left ventricular (LV) function following PSE measured via echocardiography are transiently reduced compared to resting values (1-32). This exercise induced cardiac fatigue (EICF) typically persists for 12-48 hours post-exercise before the heart recovers and functional measures return to baseline levels (2-4). Similarly, immediately post-exercise cTn levels in the blood of endurance athletes have been reported to exceed clinical detection thresholds for the diagnosis of acute myocardial infarction (5-8), but typically return to baseline within 72 hours post-exercise (9). Currently, there is no consensus on whether the process of biomarker release and transient reductions in ventricular function is a benign, pathological or adaptive response. The inclusion of follow-up measurements during the recovery process from exercise may elucidate the nature of EICF; however, this is not always included in study design. Frequently, only single measurements immediately post-exercise are performed and progression to the restoration of normal cardiac function following exercise warrants investigation. While often measured together (1, 8, 10-28), the extent of a possible relationship between cTn release and cardiac function is unclear, with the majority of studies that measure both variables reporting no correlations between the two (5, 6). It is also still unclear from individual studies whether the release of cTn indicates persistent functional alterations to the myocardium following exercise (9), and how the time course of exercise-induced cTn release differs from coronary events.

Of particular relevance to athletes and coaches is the influence of exercise intensity, mode and duration on EICF and cTn release. Both significant and non-significant effects of exercise have been reported following varied exercise modes at both ends of the intensity/duration spectrum (15, 29). Indeed, there is evidence of EICF and cTn release following exercise bouts as short as 30 minutes at high relative intensities (30), and from exercise bouts lasting as long as 10-24 hours (6, 31, 32). However, the between-study event rate and participant responses are varied, with studies rarely reporting declines in all cardiac functional variables and one hundred percent incidence of biomarker release across all their participants. In terms of exercise and participant factors that play a role, Shave and colleagues reported that cTn event rates were higher with increased participant body-mass and lower with increased exercise duration, and that there was no effect of exercise mode (33). In their meta-analysis of LV function pre to post exercise, Middleton and colleagues (4) observed that increased exercise duration resulted in greater reductions in post-exercise left ventricular ejection fraction (LVEF) and no effects of training history, age or body mass.
Importantly, exercise intensity has not yet been meta-analysed as a moderator variable in the body of EICF research, although the most recent published papers suggest that cTn release and temporarily reduced diastolic function is more readily triggered by short, high-intensity exercise (34). Systolic function appears to be more resilient to exercise and has mostly been reported to decline following long-duration exercise performed at lower relative intensities, such as Ironman triathlon or ultra-marathon races (9).

The collective findings of the body of published studies do not demonstrate a clear link between cTn release and EICF, as the results are largely varied. The variation in the findings may be explained by the influence of study and participant level factors, such as the timing of post-exercise data collection, blinding sonographers to the trial conditions or unaccounted for

participant dehydration. A systematic review of studies measuring both cTn and EICF variables would provide recommendations for future studies of cardiac function and cardiac biomarker release following exercise (4, 33). Additionally, meta-analysis of exercise characteristics (mode, duration and intensity) as moderators in a meta-regression would provide evidence towards a mechanistic explanation of EICF and biomarker release. Therefore, the aim of this study was to conduct a systematic review and meta-analysis of studies that measured both EICF and cTn following endurance exercise, and to elucidate the influence of both exercise and participant factors.

2. Materials and Methods

This meta-analysis was performed according to PRISMA guidelines. As such, we conducted a literature search for peer-reviewed, English-language journal articles examining the effects of exercise on both cTn release and cardiac function, as measured by echocardiography. The search strategy was registered on the PROSPERO database prior to being conducted (registry number: CRD420181021760. The full search strategy is shown in Figure 1.

2.1 Search Strategy

Sources used for this search were SPORTDiscus, PubMed Central, Science Direct and MEDLINE. The key words were *cardiac troponin*, *endurance exercise,* and *echocardiography*. The initial search was undertaken by 2 independent researchers (JD, JOD), who selected the studies according to the search strategy and based on the inclusion

and exclusion criteria shown below. After the initial database search, the titles and abstracts of all studies identified by the database search were screened for suitability. The reference lists from published papers were also searched for relevant studies that did not appear in the database search, as well as papers that cited the selected studies were reviewed for inclusion. The most recent search for current publications was conducted in the month of July, 2018.

2.2 Inclusion and Exclusion Criteria

1) Blood and echo measurements taken prior-to exercise and within 1 hour of cessation of exercise. Studies falling outside of this range were excluded. The majority of studies returned in the initial literature search collected blood as close to immediately after exercise. Cardiac troponin is released in phases following exercise, therefore a 1-hour cut-off was imposed to attempt to standardise the release phase.
2) Two-dimensional echocardiographic measurement of either E/A ratio or LVEF or provided data from which they could be calculated.
3) Taken venous blood samples for cardiac troponin T or I (cTn) or high-sensitivity cTn T or I.
4) Reporting the number of positive cTn tests pre and post-exercise.
5) Studies involving pharmacological or dehydration interventions were excluded.
6) Only studies involving continuous exercise such as running or cycling were chosen.
7) Studies involving team sports were excluded.
8) Available information on exercise mode and participant training status.
9) For inclusion into the regression analysis, studies must have reported average exercise heart rate (HR), exercise duration, participant age, and mass.

2.3 Quality Assessment

The quality of the selected studies was independently rated by JD and JOD, using a modified Cochrane risk of bias table (see Supplementary Table 1). Any disputes on study suitability or quality were discussed with a third researcher (JW). We used selective reporting (C), other bias (D), blinding of participants and personnel (E), and blinding of outcome assessment (F) as the main domains. Random sequence generation (A) and allocation concealment (B) were not assessed due to the nature of the exercise interventions. Studies were given a positive score if accounting for one of the main domains and negative scores were given when the criteria were not met. Full descriptions of the criteria are shown in the supplementary file. Where studies failed to describe any of the details required by the criteria, we assigned a neutral score when the criteria were not relevant to the study design. The total score was summed and the studies were then ranked into groups of low quality (positive score in <2 domains), fair quality (positive score in 2 domains), and good quality (positive score in 2 domains). A further criterion was added that demonstrated whether the study had accounted for volume depletion due to dehydration following the exercise bout(s).

Definition of Exercise Intensity. When available, the mean participant exercise heart rate (HR) was the parameter chosen to indicate the overall exercise intensity per study. Maximum HRs were not reported frequently enough in the literature to allow for the calculation of mean relative intensities. As all studies that reported HR data recruited trained participants only, in order to normalise the HR data as all exercise bouts involved either competitive or time-trial settings, we made the assumption that the mean HRs reported were reflective of the intensity demanded by the duration of the exercise bout.

2.4 Statistical Analysis

2.4.1 Derivation of outcome statistics: Data were extracted from the studies independently by the first author. The key variables were E/A ratio and LVEF, with inter-individual SDs, as well as total cTn samples and positive cTn responses in each study. The dichotomous event rate for cTn response was defined as the number of participants exceeding the assay detection limit for the specific assay reported in the study. If available, the average exercise HR, exercise duration, participant age and mass were also extracted. If these data were not available, efforts were made to contact the authors of the paper to obtain them.

2.4.2 Pooling of results: Data were analysed using the statistical software CMA (Biostat, Englewood, NJ). Standardised mean differences (Cohen's *d*) with 95% CI's were computed individually for E/A ratio and LVEF, and event rate was calculated for cTn positive results. The effect sizes were weighted according to the intra-study variability (calculated from reported means and SDs), with larger, more precise studies having a greater weighting on the overall effect size. Separate random-effects meta-analysis were run for each variable using CMA's meta-regression function. This yielded the summary measures, significance levels (*P*), and the between-study heterogeneity (Cochran's *Q* and I^2) and variability (τ^2).

2.4.3 Exploration of publication bias: Publication bias was assessed via funnel plot inspection, with the expectation that studies would be evenly distributed between both sides of the average effect size, with high-precision studies close to the mean. The individual funnel plots are displayed in the supplementary material (Supplementary Figures 1-4).

Quantitative assessments of Kendall's τ and Egger's regression are also reported for all 3 effect sizes alongside the funnel plots.

2.4.4 Exploration of heterogeneity and meta-regression analyses: Heterogeneity of the 3 effect sizes were assessed by Cochran's Q and I^2 values calculated in the random-effects model. Statistical significance for Q was $p<0.01$ and I^2 of 25, 50 and 75% were interpreted as small, medium and large degrees of heterogeneity. In the event of significant levels of heterogeneity in any of the meta-analyses, exploratory meta-regression analyses were conducted to determine how participant and exercise characteristics accounted for heterogeneous effect sizes. The residual plots were inspected for suitability before reporting the R^2 value of the fitted models. In the event of non-random residual plots, further variables were added to the model to capture possible significant interactions. All covariates were analysed separately and then together, to assess the individual contribution of each variable. A method of moment's estimator for the between-study covariance matrix in the random effect models meta-regression was used. Two sub-group analysis were conducted, the first assessed troponin assay type vs. troponin event rates and five groups were formed for assay types: high-sensitivity cardiac troponin T and I (hs-cTnT and hs-cTnI; respectively), cardiac troponin T assays (cTnT), and cardiac troponin I assays manufactured by Beckman Coulter and Siemens (cTnI-Beckman and cTnI-Siemens; respectively). The effect of study exercise-mode was also assessed, and three groups were formed, which were running, cycling and multisport. Following the meta-analysis of cTn event-rate, we matched the event rate from each study as a separate continuous moderator variable in the meta-analysis of E/A ratio and LVEF.

2.4.5 Sensitivity analysis: We conducted a sensitivity analysis by removing outlying studies. The duration of exercise in the study by Passaglia et al (32) was twice that of the next longest study and was removed from the analysis during the sensitivity analysis. However, no changes were noted following its exclusion, so it was left in the final analysis.

3. Results

The database search yielded 223 potential studies and after duplicates were removed 222 remained. Studies involving chemical interventions, animal studies or *in vivo* methods were excluded, leaving 63 potential studies, which were further refined via the inclusion and exclusion criteria to 23 studies with 32 data sets (see PRISMA flow chart).

3.1 Findings of the Systematic Review

With the exceptions of the two studies by Chan-Dewar et al. (19, 20), all studies reported that exercise lead to a significantly reduced LVEF, E/A ratio, or both variables. There were five studies in total that reported significant reductions in both E/A ratio and LVEF (6, 10, 25, 26, 27) and the study quality amongst these ranged from fair to good. For the detailed breakdown of the level of control applied in each study see Table 2 in the Supplementary file.

It was apparent that only half of the studies in our data set made use of serial measurements of cardiac function and biomarker release into the recovery stages, with the remaining half relying upon single measurements taken immediately post-exercise to draw their conclusions. Of the studies that took serial measurements, three studies (1, 17, 28) performed repeated

measures for cTn and echocardiography at 6 hours post; three studies (17, 23, 31) only collected cTn samples at 24 hours, and six studies (1, 10, 11, 14, 24, 35) took both cTn and echocardiography at 24 hours; the study by Whyte et al. (6) took post-exercise blood and echo measurements at 48 hours post-exercise. The longest follow-up measurements were in the study of La Gerche et al., (27) who collected blood and LV functional data one-week post-exercise. Of the 24-hour follow-up measurements, all studies reported participants echocardiographic and cTn values returning to pre-exercise levels in all but one study (31), that reported elevated cTn in nine participants at the 24-hour point. Of the studies that took follow-up measurements at 6 hours post-exercise, E/A ratio and cTn remained elevated above pre-exercise values in three studies (1, 17, 28). Nie et al (26) reported that LV function had returned to baseline within 6 hours post-exercise but cTn remained elevated in the cohort.

Only four of the 22 studies reported correlations with biochemical data and functional cardiac measurements. However, it is important to note that no studies reported any correlations between standard echocardiographic measurements and cTn release. Aagard and colleagues (21) reported that participants who demonstrated the greatest reductions in resting heart-rate variability also released the most cTn. La Gerche et al. (27) found significant ($P<0.05$) correlations between cTn release and myocardial deformation ($R=0.45$) and wall motion abnormalities ($R = 0.77$). Nie and colleagues (26) reported that endocardial strain reductions correlated with the magnitude of cTn release ($R=0.7$), and Tulloh and colleagues (31) reported immediate post-exercise resting cardiac output attenuated the greatest in the participants with the greatest post-exercise cTn release.

3.1.1 Fluid Loss. The monitoring of body mass loss during exercise did not appear to influence the echocardiographic or cTn data. Significant reductions in echocardiographic parameters were found in both monitored and non-monitored studies, and the detection of E/A ratio and LVEF changes was not influenced by weight loss monitoring.

3.1.2 Blinding. The majority of studies did not blind the sonographer or technician, but these studies were not more likely to report reductions in the echocardiographic parameters after exercise. Three studies (10, 20, 35) reported the previously obtained intra-individual CV of their echocardiographic measurements to demonstrate reliability.

3.1.3 Strain Imaging. There were six studies (1, 15, 19, 20, 23, 27) that reported LV or RV strain and strain rates. These variables were reported in limited and insufficient quantities across the 22 studies to facilitate a meta-analysis of the strain data. Exercise was shown to significantly reduce RV longitudinal strain (LS) in two studies (1, 27) that involved >60 minutes of exercise, whereas RV LS was maintained in the study of Stewart et al (15), which involved <60 minutes of exercise. Longitudinal LV strain was significantly reduced in three studies (1, 19, 27), and unaffected following a 6 hour triathlon in the study of Leetmaa et al (23). The participants in this study were elite national-level triathletes and it is worth noting that the reported values were substantially higher than in all other studies (27.5% pre-exercise, 26.8% post). Longitudinal strain was increased following the low-intensity exercise bout in Chan-Dewar et al (20), and maintained following <60 minutes of moderate intensity cycling in the studies of Stewart et al. (15) and Chan-Dewar et al. (19). Stewart and colleagues (15) reported large reductions in radial strain (RS) and a small, significant reduction in circumferential strain (CS), with no concomitant change in RS or CS rates. In

contrast, RS and CS rates were increased following the lower intensity exercise in the two studies of Chan-Dewar et al (19, 20). It would appear from these findings that cycling exercise of up to 60 minutes duration at low to moderate-intensities does not affect myocardial strain but high intensity cycling exercise of >60 minutes may negatively impact radial, circumferential and longitudinal strain.

3.2 Results of the Meta-Analysis

3.2.1 Tests of Heterogeneity: All three meta-analyses reported evidence of significant heterogeneity between the studies, justifying our use of the random-effects model. Additionally, in each analysis there were significant Tau squared values that indicated real differences in effect sizes, ruling out the likelihood of sampling or random errors and subsequent meta-regressions were carried out in each case (Table 1).

3.2.2 Publication Bias Investigation: There was no sign of publication bias among the 3 separate meta-analyses that were conducted. For each variable the funnel plot demonstrated a symmetrical distribution of SE about the mean that closely followed along the guidelines printed by the CMA software. The funnel plot highlighted the absence of clustering around the mean shown in more precise studies, and we can therefore infer an absence of publication bias among the studies meta-analysed. Further tests to explore publication bias also confirmed this was absent; Egger's regression intercepts were non-significant and Kendall's Tau reported a non-significant negative correlation of study size on logit event rate in each case.

3.2.3 Subgroup Analyses: There was no significant effect of exercise mode on the magnitude of effect sizes or event rates of the 3 variables. Subgroup analysis for each variable demonstrated significant heterogeneity when using the fixed-effects models therefore the findings of the mixed-effects model were used. The second subgroup analysis for cTn assay types found there was a significant effect of assay type on troponin event rate. The overall test of between subgroup heterogeneity was significant for the 5 assay groups (Q = 11.8, P = 0.019).

3.2.4 Troponin Event Rates: The overall event rate, as calculated by the random-effects meta-analysis, for the detection of cTn was 45.6%, but not significant (95% CI [33.6, 58.2%], P = 0.494) (Figure 2). By assay type, the mean event rate for cTnT was 40% (95% CI [23.3, 57.2], P = 0.21, *n* = 28); 87.9% for hs-cTnT (95% CI [79.0, 96.7%], P = 0.01, *n* = 4), 49.2% for hs-cTnI (95% CI [26.6, 71.9%], P = 0.96, *n* = 3), 71.4% for cTnI-Beckman (95% CI [51.3, 91.5%], P = 0.58, *n* = 2), and 31.5% for cTnI-Siemens (95% CI [19.3, 43.7%], P = 0.048, *n* = 5).

3.2.5 E/A Ratio: Post-exercise E/A values were significantly ($P < 0.001$) reduced over pre-exercise levels, the mean difference was –0.38 (SE = 0.041, 95%CI [-0.376, -0.307]) and the SMD (Cohen's *d*) was -1.197 (95% CI [-1.401, -0.993]) (Figure 3).

3.2.6 Left Ventricular Ejection Fraction: The mean difference in LVEF between pre and post-exercise values was -2.02% (SE = 0.568, 95%CI [-3.14, -0.91]), d = -0.44 (95%CI [-0.74, -0.14]) (Figure 4).

373 **3.3 Results of the Meta Regression**

374

375 **3.3.1 Troponin Event Rate:** Of the 32 data sets, 22 contained exercise HR and duration data,
376 allowing for comparisons of exercise intensity and duration, as well as participant age and
377 mass for inclusion into the regression analyses. For the reduced sample size of *n*=22, between
378 study variance was similar to the original data set (see Table 1). Following univariate
379 regression analyses, we found that post-exercise positive cTn response rate was influenced by
380 increased exercise HR (intensity) and reduced age. The regression coefficient for HR
381 predicted a 0.12 increase in logit event rate per 1 $b \cdot min^{-1}$ increase in HR (Figure 5A).
382 Participant age was negatively associated with logit event rate (Figure 5B). The regression
383 coefficient was -0.10 per increased year of age. Tests for remaining unexplained variance
384 were significant for each covariate ($P < 0.001$), highlighting that cTn event rate still differed
385 among studies reporting similar participant age and HR (Table 1). Using the 22 data sets that
386 reported HR and duration, there was a significant effect of exercise on event rate despite a
387 reduced overall event rate (logit event rate [95%CI] = 0.64 [-1.25, 0.01], $P < 0.05$).

388

389 **3.3.2 E/A Ratio:** Of the 28 data sets containing E/A ratio data, 18 reported participant mass,
390 age, exercise HR, and duration. Additionally, cTn event rate (%) was included as a covariate
391 in the regression analyses. The results of the single covariate analyses can be seen in Table 1.
392 We found that post-exercise positive cTn response rate was influenced by increased exercise
393 HR and increased cTn event rate. The regression coefficient for HR predicted a 0.03
394 reduction in E/A ratio SMD per 1 $b \cdot min^{-1}$ increase in HR (Figure 5C). Troponin event rate
395 was negatively associated with E/A ratio, the regression coefficient was -0.01 for every 1
396 percent increase in event rate ($p < 0.05$) (Figure 5D).

3.3.3 Left Ventricular Ejection Fraction: For the reduced sample size of $n = 20$, between study variance was similar to the original data set (see Table 1). We found no significant interaction of any of the moderator variables on effect size, despite there being potentially a large proportion of the variance explainable by study-level covariates, as indicated by I^2 of 80.3.

406 Table 1. Univariate and multivariate meta-regression analysis for cardiac troponin and E/A ratio.

	Troponin Event Rate (logit)						*E/A Ratio*					
Model	*n*	*ß (95% CI)*	*Q*	I^2	τ^2	R^2	*n*	*ß (95% CI)*	*Q*	I^2	τ^2	R^2
Univariate	22		85.6***	75.5	1.43	-	18	-	35.6***	52.2	0.20	-
HR	22	0.118 (0.061, 0.175)***	59.4***	66.3	0.98	0.31	18	-0.029 (-0.054, 0.004)*	27.67*	42.17	0.13	0.33
Age	22	-0.104 (-0.202, -0.005)*	80.3***	75.1	1.46	0.02	18	0.015 (-0.028, 0.059)	34.55**	53.69	0.21	-0.08
Duration	22	0.0003 (-0.006, 0.007)	84.8***	76.4	2.00	0.00	18	-0.002 (-0.006, 0.002)	34.00	52.94	0.21	-0.06
Mass	22	-0.054 (-0.125, 0.018)	80.83***	75.3	1.49	0.00	18	0.011 (-0.020, 0.042)	34.24*	53.27	0.21	-0.05
Troponin	22						18	-0.010 (0.018-0.002)*	26.80*	40.3	0.12	0.37
Multivariate	18	-22.82 (-33.90,-11.75)	20.60*	36.88	0.51	0.80	18	2.32 (-6.3, 10.95)	23.82	49.63	0.19	0.04
HR		0.16*** (0.08, 0.19)						0.01 (-0.09, 0.1)				
Age		-0.15* (-0.29, -0.04)						-0.02 (-0.07, 0.03)				
Duration		0.02 (0.007, 0.010)						0 (-0.06, 0.06)				
Mass		0.11 (-0.01, 0.17)						-0.01 (-0.02, 0.01)				

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408 *ß* = meta-regression coefficient, I^2 = percentage of between study variation that is due to heterogeneity, τ^2 = between study variance, *Q-total* = weighted sum of squared
409 differences between individual study effect size and pooled effect size, R^2 = Proportion of total variance explained by covariate model, negative values analogous to zero. * =
410 $P < 0.05$, ** = $P < 0.01$, *** = $P < 0.001$

411

4. Discussion

This is the first systematic review and meta-analysis to focus on the relationship between functional and biochemical indices of cardiac fatigue and damage. We exclusively analysed studies using the mixed methods of echocardiography and cardiac biomarkers to attempt to elucidate the relationship between them, and whether cTn release results in transient functional decrements (28, 34). To better inform endurance athletes, coaches and sports physicians, we also aimed to explore the relationship between exercise duration, mode and intensity in eliciting EICF and cTn release. The results of this study demonstrate that there is an overall reducing effect of prolonged, strenuous exercise on LV diastolic and systolic function, and confirm Shave and colleagues' finding of a ~50% event rate of cTn release (33). Endurance exercise of durations ranging from 45 to 1440 minutes caused significant reductions in E/A ratio of -0.34 (d =-1.20, $P < 0.001$), and LVEF of -2.0% (d = -0.44, P = 0.004). These findings agree with the previous meta-analysis performed by Middleton et al (4), who reported mean reductions in E/A ratio of 0.45 (-0.39, -0.51) and LVEF of -1.95% (-1.03, -2.88%) immediately following endurance exercise of similar durations.

4.1 Systematic Review

The systematic review of the literature aimed to address the influence of study design on the reported outcome measures and to summarise the general findings of the previous works. A key finding was that very few total studies reported LVEF changes across the 22 studies and this may be a factor of the varied time course of systolic and diastolic functional alterations. In pathological conditions, diastolic functional changes occur before systolic (37) and it is

possible that following exercise, any systolic functional changes are realised later and potentially missed by the timing of testing protocols.

Of relevance to future research is the finding that only ten of the studies took echocardiographic measurements immediately prior to exercise. To account for variations in loading conditions and hydration status that influence echocardiographic measurements, it is recommended that pre-exercise measurements be taken as close as possible to the start of exercise (34). Our finding that over half of the sampled studies made inferences about post-exercise cardiac function from potentially inaccurate pre-exercise values should be a future consideration and may assist in explaining the dearth of previously reported correlations between cTn concentration and functional cardiac parameters. Furthermore, only half of the 22 studies performed serial follow-up measurements to assess the recovery of the participants. The remaining eleven studies performed echocardiographic and cTn measurements immediately after exercise, which may have influenced the post-exercise readings through mechanisms such as post-exercise tachycardia, hypotension and volume depletion. Although, to account for such factors a level of control was applied in each study that performed only immediate post-exercise measures, either statistically or via fluid replacement to attempt to restore loading conditions. A single post-exercise blood sample may have missed the peak cTn values, which was reported to occur at 6 hours post-exercise in three of the studies that performed follow-up measures. Two studies (1, 17) also examined the time course of LV functional changes across several time points during the acute recovery period, and only the study by Tian et al. (17) reported significant reductions in LVEF at the 6-hour post-exercise time point, that were not evident immediately after exercise. Therefore, it is apparent that the quality of half of the reviewed studies suffered from not incorporating

multiple time points during the post-exercise data collection periods and by not performing echocardiographic assessments closer to the beginning of exercise.

4.2 Meta-Analysis

4.2.1 Effect of Exercise Intensity

We found that exercise HR was the strongest predictor of cTn event rate (R^2 = 0.31). This current finding of increased cTn event rates with increasing exercise HR supports the theory that cTn release is intensity-dependent and the notion that the rate and force of myocyte contraction influences cTn release. It has been suggested that post-exercise cTn release occurs due to membrane damage caused by increased mechanical force of cardiac myofibrillar contraction (34). In the absence of ischaemia, the transport of intact cTn molecules is potentially mediated by excessive stretch of myofibrils stimulating integrin-mediated transport (38). Troponin I degradation in the absence of ischaemia has been shown to increase with LV preload in the rat model (39). Additionally, increased membrane permeability resulting from oxidative damage and inflammation subsequent to intense exercise may allow cTn release (40). Whether this cTn is bound to the myocardium or stored in the cytoplasm remains to be determined. Figure 6 presents a plausible mechanism for troponin transport from the myocardium to the peripheral circulation. It is therefore plausible that both intact and degraded cTn products found in serum post-exercise originate from viable cardiomyocytes, due to the increased preloads generated during exercise.

If thresholds of exercise intensity, rather than duration exist at which cTn is released, these may be altered following positive cardiac adaptations that establish improved fitness levels. Unfortunately, it was not possible to separate the cases based on training status in the present study owing to a lack of data. Whether cTn release following exercise is an adaptive response that elicits improved cardiac function and a reduced threshold for future cTn release remains to be thoroughly examined.

Higher exercise HRs increased the magnitude of the post-exercise alteration in LV diastolic filling. In most cases, this was due to a reduction in peak early (E) and maintenance of peak late (A) transmitral filling velocity, which is associated with increased heart rates and reduced ventricular filling times (34). Potential mechanisms responsible for altered LV relaxation, in addition to prolonged elevated HRs, include downregulation of cardiac ß-adrenoceptors mediated by elevated catecholamines during exercise (42). In fact, circulating catecholamines are responsible for maintaining tachycardia during endurance exercise and Breuer et al. (41) have shown that concentrations of plasma catecholamines increase with exercise HR. Alterations in adrenergic responsiveness following exercise were reported by Eysmann and colleagues (42) in both Ironman athletes and healthy sedentary individuals, and these changes were correlated with declines in LV function. However, it remains to be seen how differential modulation of the autonomic nervous system, prolonged heart rates, and substrate circulation factor in the development of EICF (36, 42, 43). Our data support the hypothesised relationship between altered myocardial relaxation and decreased sensitivity of ß-adrenoceptors induced by increasing circulating catecholamines ubiquitous to higher exercise HRs during prolonged strenuous exercise (44, 45).

4.2.2 Effect of Exercise Mode

Our sub group analyses did not identify any differences between exercise mode in contrast to the findings of Shave et al. (33) who reported that running stimulated greater cTn release compared to cycling. While the fixed effects model returned a significant effect of exercise mode, our accompanying tests of heterogeneity did not fulfil the assumptions of the model. It has been hypothesised that running exercise elicits higher HRs than cycling due to greater $\dot{V}O_2$ requirements, recruitment of the upper body musculature and accessory muscles, and the lack of postural support during cycling (46). Additionally, modal differences in cTn release may be explained by attaining higher absolute cardiac and metabolic work rates during running (46, 47). In our data, average cycling HR was 150 vs. 156 $b \cdot min^{-1}$ in running. It is not possible to compare with the previously published meta-analysis as HR data were unavailable in the studies analysed by Shave and colleagues (33).

4.2.3 Effect of Exercise Duration

We found no significant effect of exercise duration on either cTn release, LV systolic or diastolic function. When the exercise protocols employed in PSE studies typically involve a maximal race-effort, exercise duration dictates exercise intensity. Previous meta-analyses have failed to investigate the role of exercise HR and have concentrated on duration; therefore, no comparable data exists. The absence of a significant effect of exercise duration on either cTn release or EICF contradict the meta-analyses by Shave et al. (33) and Middleton et al. (4) despite inclusion of a similar amount of studies, cases and participant

characteristics. The previous meta-analysis of cTn event rates did not report regression coefficients for significant moderators and also used a fixed-effects meta-regression. This may not have been appropriate, depending on the level of heterogeneity between studies in the model as we encountered significant heterogeneity at the study level in all 3 meta-analyses. In our review, this meant that the true effect size likely differed between studies at similar levels and use of the fixed-effects model would not be appropriate.

4.2.4 Participant Age

We found that participant age was negatively associated with troponin event rate and we also observed a significant ($P<0.05$) negative correlation between age and HR, indicating that older participants do not achieve higher HRs during exercise. The attainment of higher levels of cardiac work during exercise may therefore be a crucial role in the development of exercise troponin release, as previously indicated. Conversely, the level of training previously achieved may be responsible for reduced cTn event rates with increased age, and it may be that lifelong athletes develop greater thresholds to cTn release than younger, less-trained counterparts. Without training history data, this phenomenon cannot be investigated *via* meta-analytical methods.

4.2.5 Troponin Event Rate Affects Diastolic Function

Our data demonstrated a significant relationship between the E/A ratio and cTn release, wherein the reduction in E/A ratio was related to the magnitude of cTn positive event rates.

This finding is contradictory to the majority of research as few individual studies have reported correlations between any LV functional indices and cTn release. When loading conditions such as resting heart rate and plasma volume are controlled for, exercise induced diastolic functional changes are likely to be caused by reductions in myocardial relaxation. While the mechanistic basis for altered relaxation are yet to be fully determined, increased cardiomyocyte membrane permeability has been suggested as a factor in this, as well as cTn release (9). Although individual studies rarely find significant correlations between the two (12), it may be the case that this was due to insufficient sample sizes to bear out the underlying relationships and the larger sample sizes meta-analysed in this study addressed this limitation.

4.3 Limitations

Inconsistent timing of the post-exercise echocardiograms and blood samples across the range of studies may have had severe effects on the values we analysed. Mechanisms responsible for this include the time-course of cTn release, which is thought to peak at approximately 3hrs post-exercise (12). To control for this variability, we selected studies that obtained blood values within 1hr of the cessation of exercise, and it was apparent from the findings of the systematic review that only a limited amount of studies performed follow-up measurements beyond 1 hour after exercise. Additionally, an important limitation was the inclusion of studies that measured both troponin I and T. Troponin I is thought to be less sensitive than troponin T due to several manufacturers producing assays for it (33). Our sub-group analysis to determine a significant effect of assay type on troponin event rate found that there were significant differences between all assay types, yet there was significant variation and

heterogeneity among the 5 sub-groups. The intrinsically high levels of variation amongst the sample sizes in terms of study design, exercise characteristics, and participant variables therefore mean that the influence of assay type on event rate prevalence may come secondary to other such factors. Previous studies measuring both high sensitivity troponin T and I have demonstrated the assays to perform comparably in diagnostic performance in a clinical population, and these are currently the recommended assay-type for cardiac damage diagnosis (48). Echocardiographic variables may be influenced by the timing of post-exercise echocardiograms as loading conditions are altered by blood plasma shifts during and after exercise. Further, the influence of post-exercise hypotension and augmented autonomic modulation during the recovery from exercise should not be overlooked. Stewart and colleagues (1) demonstrated by using more sensitive echocardiographic techniques that when loading and functional requirements are equal to pre-exercise levels, demonstrably greater differences in LV and RV function exist post-exercise. Additionally, the lack of availability of RV data is a key limitation to the implications that can be made from our data, as this chamber has shown to be more susceptible to fatigue in athletes (27).

While we found evidence of a significant effect of cTn release with altered diastolic filling, our data are merely correlational. There is insufficient physiological data present in the original studies to determine a causal relationship. In addition, a comprehensive approach in the assessment of diastolic function is required in future research to confirm whether diastolic dysfunction is present in athletes following exercise, including tissue Doppler imaging, left atrial volume, LV twist/untwist velocities, and global strain and strain rate imaging to support this association (1).

4.4 Conclusion

The novel findings of the meta-analysis established exercise intensity, measured *via* average absolute exercise HR, as the predominant factor in causing reduced diastolic function and cTn release. Our finding supports the theory that cTn release and EICF are intensity-dependent as our data did not show a significant effect of duration on any of the cardiac variables. The second novel finding was that increased troponin event rates were positively associated with greater reductions in mitral E/A ratio, which supports the theory that EICF and cTn release are related. The low to moderate R^2 values related to exercise HR and cTn event rate (0.33 and 0.37; respectively. See Table 1) leave a remaining portion of the calculated variance requiring further exploration. Future work should aim to investigate these relationships further, using more specific tissue Doppler measurements of diastolic function, and potentially by employing standardised exercise challenges to normalise cardiac function before and after PSE (1).

Finally, our finding of a significant negative effect of participant age on cTn event rates indicates that longer-term athletes may be less prone to cTn release as a result of cardiac adaptations pursuant to life-time training volumes (49), challenging the theory that cTn release is related to permanent cardiac injury (50). Future research into the effects of aging on cardiac adaptation to exercise may wish to investigate the characteristics of cTn release following exercise in life-long endurance athletes compared to younger, highly-trained athletes.

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Figure Legends

Figure 1: PRISMA flow chart.

Figure 2: Forest plot showing logit event rate (solid squares) and 95%CI limits (solid horizontal lines) for each study. The studies are ranked with ascending magnitude of event rate, by exercise mode sub-groups. The overall random-effects logit event rate is shown in the bottom row (solid diamond). The – symbol indicates data that were unavailable. A logit event rate of 0 corresponds to an event rate of 50%, a negative logit event rate indicates a frequency of troponin release from less than 50% of the participants within the study.

Figure 3: Forest plot showing standardised mean differences (SMD, Cohen's *d*) between pre and post exercise values of the E/A ratio (early to late peak transmitral velocity flow) (solid squares) and 95%CI limits (solid horizontal lines) for each study. The studies are ranked with ascending magnitude of event rate, by exercise mode sub-groups. The overall random-effects SMD is shown in the bottom row (solid diamond). The – symbol indicates data that were unavailable.

Figure 4: Forest plot of standardised mean differences (SMD, Cohen's d) between pre/post exercise ejection fraction (solid squares) and 95%CI limits (solid horizontal lines) for each study. The studies are ranked with ascending magnitude of event rate, by exercise mode sub-groups. The overall random-effects logit event rate is shown in the bottom row (solid diamond). The – symbol indicates data that were unavailable.

Figure 5: Random-effects univariate meta-regression **A)** HR on troponin event rates showing the positive relationship between increased exercise intensity and troponin release, **B)** Participant age on troponin event rates showing the negative relationship between increased age and troponin release, **C)** Average HR on E/A ratio SMD (*d*) showing greater reductions in E/A ratio occur as exercise HR increases, **D)** Percentage of participants per study who exceeded the troponin assay limit of detection vs the standardised differences in E/A ratio (d) following exercise, indicating that E/A ratio is reduced to a greater extent in studies with higher rates of troponin release. Each circle represents a study and the size of the circle reflects the influence of that study on the model. The regression prediction is represented by the solid line.

Figure 6: Exercise intensity and age influence myocardial diastolic function and cardiac troponin release.

Table 1: Univariate and multivariate meta-regression analyses for cardiac troponin and E/A ratio.