High Sensitivity Troponin T in Marathon Runners, Marathon Runners with Heart Disease and Collapsed Marathon Runners

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Abstract

Endurance exercise is an established cause of cardiac troponin (cTn) elevation, of further interest is whether this rise represents clinical significance. This study compared cTnT rise in three cohorts of marathon runners using a high sensitivity assay; control runners, those with known heart disease and runners who collapsed at the finish line. Control runners (n = 126) and runners with heart disease (n = 12) were prospectively recruited with cTnT levels measured pre-race and at race completion. Collapsed runners (n = 15) were retrospectively recruited. A mixed model ANCOVA was used to compare the three groups. Pre-race median cTnT for the control group and heart disease groups were 3.9 $ng.L^{-1}$ (IQR 3.1 $ng.L^{-1}$) and 4.1 $ng.L^{-1}$ (IQR 3.4 $ng.L^{-1}$). Post-race values for the three groups were; control 45.6 $ng.L^{-1}$ (IQR 42.5 $ng.L^{-1}$), heart disease 41.2 $ng.L^{-1}$ (IQR 36.1 $ng.L^{-1}$) and collapsed 41.9 $ng.L^{-1}$ (IQR 57.8 $ng.L^{-1}$). Post-race cTnT and cTnT change were significantly correlated with pre-race cTnT within the control group (r = 0.38 and 0.30, $p < 0.01$). There was no difference in post-race cTnT (adjusted for pre-race cTnT) between the three groups. None of the runners reported symptoms suggestive of acute myocardial infarction on follow up. These results demonstrate that marathon running is associated with an asymptomatic cTnT rise for all runners and this rise is significantly correlated to baseline cTnT levels, in addition, marathon runners with pre-existing cardiac pathology or who collapse at the finish line do not exhibit an increased cTnT rise compared to healthy runners.

Key words: Marathon, running, cardiac, troponin

1. Introduction

The association between endurance exercise and acutely raised cardiac troponin (cTn) is well established, with post-exercise cTn levels observed that meet the biochemical criteria for acute myocardial infarction (MI) (1,2). The kinetics of post-exercise cTn rise do not however match that of acute MI, with normalisation within 24-48 hours (3,4), as opposed to 7-10 days (5). A comparable transient acute cTn rise of similar kinetics to exercise associated troponin elevation is exhibited in pathological conditions that involve increased physiological stress and/or increased cardiac workload (e.g. acute heart failure, myocarditis,

pericarditis, pulmonary embolism and sepsis) (5). These conditions are thought to represent myocardial stress but through mechanisms that are not sufficiently severe to cause the significant cellular necrosis exhibited in myocardial infarction. Such damage has been termed myocardial injury and is thought to be caused by factors such as subcritical ischaemia, increased chamber wall stress, oxidative stress and inflammatory processes (6,7). The mechanism and clinical significance underlying cTn elevation following exercise remains under investigation and it is yet to be determined if the rise exhibited represents a benign process or if there are associated negative health consequences (1).

The cTn complex is composed of three protein molecules (cTnC, cTnI and cTnT), cTnI or cTnT are measured in clinical practice to quantify cTn elevation. Four prior studies have investigated cTnT rise in a field of healthy marathon runners using the Roche Elecsys fifth generation high-sensitivity cTnT assay that is in common diagnostic use (4,8–10), with all studies demonstrating rise from a pre-race baseline. There has been considerable inter-individual variation in the degree of cTnT rise, with no runner characteristic consistently correlated and there is no established explanation for the variation. Baker et al. (10) explored cTnT changes in a control group of healthy runners (n = 57), runners with known heart disease (HD) and runners who collapsed at the finish line, with a with a hypothesis that runners with underlying HD or who collapse will experience greater myocardial stress and therefore exhibit higher post-race cTnT levels. No significant difference was found between the three runner groups, although small number of runners with HD (n = 5) and collapsed runners (n = 14) were included.

This study expands on prior studies investigating cTnT rise in marathon running using a larger cohort of healthy runners, establishing the most comprehensive reference range to date for marathon associated cTnT increase and thus provides a more robust comparison of cTnT levels in healthy runners, HD runners and collapsed runners.

2. Materials and Method

2.1 Participants

The study recruited runners at the 2017 Brighton Marathon (9th April 2017). One hundred and thirty five runners were recruited to the control (CON) group (eighty two males, fifty three females), fifteen into the HD group (nine males, six females) and fifteen into the collapsed (COL) group (twelve males, three females). Runners were prospectively recruited into the CON or HD group with advertising to all marathon entrants via email and also through social media channels. All runners were eligible for enrolment into the CON group providing they did not meet the inclusion criteria for the HD or COL group. The inclusion criteria for HD was defined as a self-reported history of valvular heart disease, atrial fibrillation, ischaemic heart disease, cardiomyopathy, transplanted heart and/or hypertension with left ventricular hypertrophy. The COL group of runners were retrospectively recruited at the finish line medical tent. Collapse was defined as those runners unable to stand unaided upon completing the marathon (11) and who required emergency medical treatment involving diagnostic biochemistry tests.

All study participants provided written informed consent and institutional ethical approval (SSCERC 0217) was issued by the University of Brighton in accordance with the Helsinki declaration 1975 (revised 2008).

2.2 Study Design

At the pre-race exhibition occurring on the two days prior to the marathon, the CON and HD runners attended the research stall. A venous blood sample was taken and a questionnaire on their anthropometrics, health and training history completed. Following marathon completion the CON and HD runners presented to the finish line medical tent where a further venous blood sample was taken within ten minutes of marathon completion. All venepuncture was performed at the antecubital fossa in a seated position, 5 ml blood was collected into a Vacuette® Z Serum Separator Clot Activator tube (Greiner Bio-One International, Austria) tube using a 21G Vacuette® needle (Greiner Bio-One International, Austria). Blood was analysed within four hours of collection using an electrochemiluminescence fifth generation high-sensitivity cTnT assay (Elecsys, Roche Modular E170; Roche, Basel, Switzerland) (7). This had a limit of blank of 3ng.L^{-1}, limit of detection of 5ng.L^{-1}, upper limit of normal based on the 99th percentile of 14ng.L^{-1}, coefficient

of variation at URL of <8%. Recruited runners that failed to finish or who provided a haemolysed blood sample were excluded from the analysis.

All runners were asked about symptoms suggestive of acute MI upon marathon completion and provided with an information leaflet regarding post-race symptoms that should prompt urgent self-referral for medical assessment. The European Society of Cardiology 2015 biochemical diagnostic threshold for MI of a cTnT rise from baseline of > 5 $ng.L^{-1}$ when using the Elecsys cTnT assay (2) was noted, however given the high frequency of post-exercise cTnT elevations in prior studies only those runners who reported symptoms suggestive of acute MI or who had a post-race cTnT over 50 $ng.L^{-1}$ were proactively followed up. The 50 $ng.L^{-1}$ threshold was adopted given the noted low positive predictive value of such elevations in diagnosing the likelihood of acute MI (2,12,13).

The medical treatment of runners who collapsed at the finish line was supervised by a Consultant from Emergency Medicine or Anaesthetics. Diagnostic tests performed on these runners included intravenous access and blood sampling for point of care blood glucose and electrolyte assessment. At the time of the diagnostic blood tests an additional 5 ml of blood was collected in a Vacuette® Z Serum Separator Clot Activator tube (Greiner Bio-One International, Austria). This blood was analysed for cTnT if the runner subsequently consented for enrolment into the study following their recovery. Mechanism of collapse was established from review of the medical notes.

2.3 Statistical Analysis

Data was assessed for normality and sphericity and adjusted where necessary using the Huynh-Feldt method. Troponin measurements below the limit of blank (<3$ng.L^{-1}$) were assigned a value of 3 $ng.L^{-1}$, values between the limit of blank and limit of detection (3 to 5 $ng.L^{-1}$) were used in the analysis. Both Pearson's or Spearman's rank correlation were used where appropriate to determine the relationship between baseline anthropometrics, training history, marathon experience, finishing time and baseline cTnT (where available) with cTnT change. A mixed model ANCOVA was used to assess the pre and post-race cTnT between the CON and HD groups with the only covariate in the model being the pre-race cTnT (as no other variables had strong and significant correlations). An additional ANCOVA was performed including the COL group using the CON group pre-race median as an estimated

pre-race median for the COL group. All statistical tests were completed using SPSS Statistics 22 (IBM, New York). The alpha level was set at 0.05. Values are reported as mean or median with standard deviation (SD) or interquartile range (IQR) unless otherwise indicated.

3. Results

Baseline anthropometrics, training history and marathon experience for the included runners are reported in table 1. Nine CON runners were excluded (7%); seven runners failed to finish and two blood samples haemolysed. Three HD runners failed to finish and were excluded. Therefore, one hundred and twenty six CON runners and twelve COL runners were included in the primary analysis. The proportion of runners who failed to finish race amongst the entire marathon population was 8%. Within the included twelve HD runners there were six with valvular disease, three with paroxysmal cardiac arrhythmias, two with ischaemic heart disease and one with a closed patent foramen ovale (endovascular repair).

Fifteen COL runners were recruited, with a variety of collapse aetiology; seven cases of hyperthermia (core temperature > 38.5^{o}C), four cases of exhaustion, two cases of hypoglycaemia, two cases of dehydration and one case of hypothermia (core temperature < 35.0 ^{o}C). None of the COL runners had a history of cardiovascular disease. Eighteen marathon runners collapsed prior to the marathon completion and required diagnostic biochemistry (eight cases of hyperthermia, two cases of hypothermia, two cases of hypoglycaemia, three cases of dehydration, three cases with unknown aetiology) however these were not considered appropriate for inclusion within the study due to the variable workload completed at time of collapse.

Weather conditions over the day of the marathon were unusually hot and sunny for the UK in April (18-23°C, 40-50% relative humidity).

Table 1 details marathon finishing time and cTnT data for the three groups. Seven runners in the CON group had a pre-race cTnT above the upper reference limit of 14 ng.L^{-1} with no runners in the HD group having a pre-race cTnT above 14 ng.L^{-1}. All runners had a cTnT rise from baseline with 12/12 HD runners and 123/126 CON runners exhibiting a post-race

cTnT above the 99th percentile value of 14 ng.L^{-1}. None of the runners reported post race symptoms suggestive of acute MI and none of the runners with a post-race cTnT > 50 ng.L^{-1} reported any symptoms on follow up that warranted further medical assessment.

No significant or strong (r > 0.3) correlations were found between baseline anthropometrics, training history, marathon experience or marathon completion time and post-race cTnT or cTnT change (Δ cTnT) for the CON group. Pre-race cTnT was significantly correlated with post-race cTnT (r = 0.38, p < 0.01) and Δ cTnT (r = 0.30, p < 0.01) (table 1). There was no difference in post-race cTnT (adjusted for pre-race cTnT) between the CON and HD groups (F = 0.026, df = 1, p = 0.873) and CON, HD and COL groups using the estimated pre-race COL cTnT value of 5.4 ng.L^{-1} (F = 0.015, df = 2, p = 0.985).

4. Discussion

This study is the largest study to date investigating cTnT rise in marathon running using the Roche Elecsys fifth generation high sensitivity cTnT assay that is in common medical diagnostic usage. It also incorporates the largest number of runners with heart disease or who collapsed at the finish line as a means of investigating the clinical significance of cTnT rise. The results provides compelling evidence that marathon running always causes a rise in cTnT; and that the magnitude of this rise, while variable, is almost always likely to result in a cTnT level required for the biochemical diagnosis of acute MI. However, the results also demonstrate no difference in cTnT rise when compared across the CON, HD and COL groups (figure 1) with a similar marathon finishing time across the three groups (table 1).

Four prior studies have investigated cTnT rise in marathon runners utilising the same high-sensitivity cTnT assay with an average post-marathon value of between 31.1 to 47.0 ng.L^{-1} (4,8–10). The median cTnT rise of 45.6 ng.L^{-1} observed in the CON group is at the higher end of the range seen in prior studies. Peak post-exercise cTnT value is not achieved immediately upon exercise completion with peak post-exercise cTnT and cTnI values reported 1-4 hours following exercise completion (14,15). As our study was sampled closer to race completion than previous studies, the higher cTnT rise exhibited is unlikely related to differences in sample timing. Of note the 2017 Brighton Marathon conditions were unseasonably warm and the majority of runners would not have been acclimatised for such conditions. Un-acclimatised runners are known to be less tolerant of higher temperatures

with comparatively reduced thermoregulation mechanisms and therefore experiencing a greater physiological strain and increased cardiac workload when exercising in unfamiliarly warm temperatures (16,17). The literature exploring the effect of exercise temperature on cTnT is limited to a single study; Shave et al. performed 100 mile cycling trials in $0^{o}C$ and $19^{o}C$ temperatures on 8 highly trained male athletes, 2 of the athletes in the $19^{o}C$ condition demonstrated a measurable post-exercise cTnT level but none at $0^{o}C$ (18). It is likely that exercising temperature has some influence on TnT rise given its contribution to the physiological stress of exercise, however further research is required to establish this potential relationship.

The lack of strong and significant correlations between baseline anthropometrics, training history, marathon experience or marathon completion time and cTn rise is in contrast to earlier smaller studies investigating cTn rise and exercise. These studies have identified associations with younger age (19,20), endurance exercise inexperience (21,22), endurance exercise experience (8) marathon intensity (23) and marathon time (4,20) with cTn rise. However no variables have been consistently correlated with cTn rise across a number of studies and there remains no consensus regarding predictors of cTn rise despite significant variation between individuals (1). The observation that baseline cTnT was correlated to post-race cTnT is in agreement with an earlier marathon study (9) and laboratory based exercise trials (24,25). In addition, our study identified a correlation between baseline cTnT and the magnitude of exercise associated cTnT increase (Δ cTnT). Given the recent work demonstrating an association between baseline cTnI and future cardiovascular events in healthy individuals (26,27), it may be that these baseline and post exercise cTnT associations reflect a predisposition to future cardiac disease or existing subclinical cardiac pathology.

Our data indicates that there is no difference in cTnT rise between healthy marathon runners, those with HD or COL runners. This finding is in agreement with the only other study assessing these populations (10). Although only a relatively small number of HD runners were recruited, the cohort represented a diverse spectrum of HD pathology. The similarity of the cTnT rise with the CON runners demonstrates that variations in post-marathon cTnT rise cannot be used to reliably identify individuals with undiagnosed cardiac abnormalities. There was also no difference in post-race cTnT values between CON and COL runners, suggesting that post-marathon cTnT rise is not influenced by increased physiological stress. Of useful clinical note is the similar distribution of cTnT rise exhibited

across the CON and COL groups, suggesting that collapsed runners, who do not present with a clinical suspicion of cardiac pathology, are not sustaining significant occult myocardial injury.

The small numbers of HD and COL runners and the heterogeneous nature of the HD group primarily limit the study. The self-reported selection criteria is a pragmatic approach to recruit marathon runners with HD. Unfortunately, we are unaware of any published databases of the incidence of HD within mass participation marathon events to establish if the recruited cohort of HD runners within this study is representative of the spectrum of HD pathology found amongst marathon runners. The pre-race cTnT was comparable between the CON and HD runners suggesting that the clinical severity of disease amongst the HD runners was relatively low. Increased understanding of the functional impact that exercise and cardiovascular disease imposes on the runner, with for example pre and post-marathon echocardiography, blood pressure monitoring and electrocardiography, would benefit future work comparing cTn rise in healthy vs HD runners. The small number of collapsed runners recruited in this study reflects the low incidence of marathon finish line collapse that requires diagnostic biochemistry as part of the initial medical management, expanding the numbers in this cohort would require an aggregate analysis of cTnT changes in collapsed runners across a number of marathons.

5. Perspective

This study demonstrated a quantifiable and variable cTnT rise in a diverse population of marathon runners with no difference between a healthy control group, a group with heart disease and a group that collapsed at the finish line. This work supports the existing literature and consensus that exercise induced cTn rise does not represent significant myocardial necrosis given the asymptomatic nature of the rise, however the question of what influences the variable rise observed between individuals and if there is associated clinical significance remains. If cTnT rise is related to myocardial cell injury or myocardial cell stress, then the correlation with baseline cTnT and post-marathon cTnT rise is of note given the recent work associating baseline cTnI with future cardiac events. The long-term prognostic significance of exercise induced cTn rise is a novel perspective that warrants further investigation.

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Conflicts of Interest

All authors report no relationships that could be construed as a conflict of interest

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Ethics

The protocol for this study was approved by the University of Brighton College Research Ethics Committee (SSCERC 0217).

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Table 1: High-sensitivity cTnT values for CON, HD and COL runners. Anthropometric, training history and marathon experience for CON correlated to troponin change from baseline and post-marathon. Mean or median and standard deviation (SD) or interquartile range (IQR). * indicates statistical significance ($p < 0.01$).

	CON (n = 126)			**HD (n = 12)**	**COL (n =15)**
	Mean (SD)	Correlation with post-cTnT (*r*)	Correlation with Δ cTnT (*r*)	Mean (SD)	Mean (SD)
Age (year)	40 (11)	0.01	-0.02	46 (9)	42 (12)
Height (m)	1.72 (0.09)	0.12	0.04	1.73 (0.09)	1.78 (0.05)
Body mass (kg)	73.9 (11.8)	0.04	0.11	73.4 (16.2)	79.1 (9.4)
Previous marathons completed	7 (17)	-0.25*	- 0.26*	3 (3)	2 (3)
Mean weekly running distance in previous 12 weeks (km)	42.6 (20.1)	0.06	0.05	56.4 (23.7)	40.6 (12.9)
an training velocity (km.hr^{-1})	10.7 (1.7)	0.02	0.02	9.6 (0.8)	10.7 (1.3)
Marathon time (min)	274 (56)	- 0.08	- 0.09	274 (34)	280 (72)
rathon velocity (km.hr^{-1})	9.6 (2.0)	-0.08	- 0.09	9.4 (1.1)	9.4 (1.8)
Me	Median (IQR)	Correlation with post-cTnT (*r*)	Correlation with Δ cTnT (*r*)	Median (IQR)	Median (IQR)
-race cTnT (ng.L^{-1})	3.9 (3.1)	0.38*	0.30*	4.1 (3.4)	
Ma t-race cTnT (ng.L^{-1})	45.6 (42.5)			41.2 (36.1)	41.9 (57.8)
TnT (ng.L^{-1})	40.8 (42.3)			35.1 (35.4)	
% Δ cTnT	1010 (1144)			803 (1112)	
Pre					
Pos					
Δ c					

Figure 1: Box plots demonstrating high-sensitivity cTnT values pre-marathon for CON and HD runners (top) and post-marathon cTnT values for CON, HD and COL runners (bottom).