Title: IMMEDIATE AND 24h POST-MARATHON CARDIAC TROPONIN T IS ASSOCIATED WITH RELATIVE EXERCISE INTENSITY

Running Head: Cardiac Troponin T and Exercise Intensity in Marathon

Abstract

Purpose: This study aimed to explore whether cardiopulmonary fitness, echocardiographic measures and relative exercise intensity were associated with high sensitivity cardiac troponin T (hs-TNT) rise and normalization following a marathon.

Methods: Nighty-eight participants (83 males and 15 females; 38.72 ± 3.63 years) were subjected to echocardiographic assessment and a cardiopulmonary exercise test (CPET) before the race. Hs-TNT was measured before, immediately after and at 24, 48, 96, 144 and 192 h post-race. Heart rate (HR) was recorded throughout the marathon.

Results: Hs-TNT significantly increased from pre to post-race (5.74 ± 5.29 vs 50.4 ± 57.04 ng/L; $p<0.01$) and 95% of the participants displayed values exceeding the Upper Reference Limit (URL). 24 h post-race, 39% of the runners still displayed concentrations above URL (High hs-TNT group); and until 96 h post-race Hs-TNT values remained significantly different from baseline. Hs-TNT rise was correlated with relative exercise intensity: marathon speed $\%V_{VT2}$ ($r=0.22$; $p<0.05$); mean HR ($r=0.41$; $p<0.01$); mean $HR_{\%VT2}$ ($r=0.30$; $p<0.01$); and mean $HR_{\%MAX}$ ($r=0.32$; $p<0.01$). Moreover, High hs-TNT group performed the marathon at a higher relative speed: Speed $\%V_{VT2}$ (88.21 ± 6.53 vs 83.49 ± 6.54%; $p<0.01$) and Speed $\%V_{VMAX}$ (72 ± 4.25 vs 69.40 ± 5.53%; $p<0.01$).

Conclusion: Post-race Hs-TNT was above URL in barely all of the runners. Magnitude of Hs-TNT rise was correlated with exercise mean HR whereas their normalization kept relationship with marathon speed relative to second ventilatory threshold and CPET peak velocity. Cardiopulmonary fitness, echocardiographic measures and training history were unrelated to Hs-TNT rise and normalization.

Keywords: Cardiopulmonary fitness, cardiac stress, running, echocardiography, heart rate

Abbreviations:

hs-TNT	High-sensitive cardiac troponin T
CPET	Cardiopulmonary exercise test
HR	Heart rate
URL	Upper reference limit
BMI	Body mass index
VO_2max	Maximum oxygen uptake
RER	Respiratory exchange ratio
VT_2	Second ventilatory threshold
RVEDD	Right ventricular end diastolic diameter
LVEDD	Left ventricular end diastolic diameter
LVESD	Left ventricular end systolic diameter
IVS	Interventricular septum at the end of diastole
PW	Posterior wall at the end of diastole
LVEF	Left ventricular ejection fraction
ECLIA	Electrochemiluminescence technology
LoB	Limit of the blank
SD	Standard deviation

1. Introduction

The number of recreational/non-elite athletes participating in marathons is yearly increasing and it is becoming well established that such an strenuous physical effort provokes an acute release of cardiac damage biomarkers (i.e., troponin), making them rise above clinically significant values (levels greater than the 99th percentile of a healthy reference population, Upper Reference Limit, URL) (Gresslien and Agewall 2016; Regwan et al. 2010; Shave et al. 2007). Although a debate exists about the pathological vs. physiological meaning of such cardiac response to exercise, available evidence majorly supports the latter reasoning (Baker et al. 2019; Gresslien and Agewall 2016; Kleiven et al. 2019; Vroemen et al. 2019). In fact, specific algorithms have been proposed for the management of athletes attending emergency departments with clinical symptoms compatible with a cardiac event after exercise (Baker et al. 2019).

However, whether the magnitude of post-exercise elevation in troponin concentration is related or not with relative intensity at which a marathon is performed is still a relevant and open-to-debate question (Brzezinski et al. 2019; Donaldson et al. 2019). Indeed, several studies have attempted to identify predictors of exercise-induced troponin release (Eijsvogels et al. 2015; Fortescue et al. 2007; Kleiven et al. 2019; Kosowski et al. 2019; Mehta et al. 2012; Neilan et al. 2006; Paana et al. 2019; Richardson et al. 2018), but as far as we are aware only one investigation included objectively-measured marathon relative intensity (i.e., speed and HR as percentages of maximums attained at a cardiopulmonary exercise test) (Richardson et al. 2018). On the other hand, no previous investigation have checked whether normalization of high sensitivity cardiac troponin (hs-TNT) levels is associated with either baseline echocardiographic and fitness variables or relative intensity at which the race has been performed. Measurement using high sensitivity analysis now allows improved accuracy, reliability and identification of those above reference limits compared to second and third-generation assays (Giannitsis et al. 2010; Vilela et al. 2014). Peak hs-TnT release is usually observed within 3 to 6h following a marathon (Baker et al. 2019) and its concentration falls under the URL within 24h among most of the runners;

notwithstanding, a percentage of athletes still display values exceeding the URL at this time point (between 22% and 27%) (Baker et al. 2019; Scherr et al. 2011).

Therefore, the aim of this study was twofold. Firstly, we were interested in assessing whether the degree of post-exercise hs-TNT rise was associated with any of the following variables: baseline echocardiographic, cardiovascular fitness and training variables; or relative intensity at which a marathon is performed. Secondly, we wanted to explore if any of the abovementioned variables was different among those runners who normalize hs-TNT within the initial 24 h post-exercise and those who do not. Our study hypothesis was that relative exercise intensity derived from a cardiopulmonary exercise test would be related to both immediate and 24h post-race hs-TNT concentration. We also hypothesized that baseline echocardiographic and cardiovascular fitness variables would be associated with hs-TNT rise and normalization.

2. Methods

2.1. Participants

All participants of the Valencia Fundacion Trinidad Alfonso EDP 2016 Marathon received an invitation email to participate in the study. Two information seminars were organized in order to fully explain the study design (aims, measurements, etc.) to those individuals who accepted the invitation (N = 456). A total of 98 runners (83 males and 15 females) were selected to participate in this study, according to the following inclusion criteria: age between 30 and 45 years; body mass index (BMI) between 16 and 24.99 $kg \cdot m^{-2}$; previous marathon experience; having a performance best time in marathon between 3 and 4 hours for males and 3:30 and 4:30 hours for females; and individuals who were free from cardiac or renal disease and from taking any medication on a regular basis. Participant characteristics are presented in **Table 1**. All individuals included in the current study were fully informed and gave their written consent to participate. The research was conducted according to the Declaration of Helsinki and it was approved by the Research Ethics Committee of the Jaume I University of Castellon. This study is enrolled in the ClinicalTrails.gov database, with the code number NCT03155633 (www.clinicaltrials.gov).

**** Insert Table 1 near here ****

2.2. Cardiopulmonary exercise test

Cardiopulmonary exercise tests (CPET) were performed on a treadmill (H/P/cosmos pulsar, H/P/cosmos sports & medical GmbH, Nussdorf-Traunstein, Germany) between 2 to 4 weeks prior to the marathon. Pulmonary VO_2 and VCO_2 were measured breath-by-breath using an automated online system (Oxycon Pro system, Jaeger, Würzburg, Germany). Gas analysis system was calibrated for ambient temperature and humidity, air flow and VO_2 and VCO_2 concentrations (with a 4.96% CO_2 – 12.10% O_2 gas mixture) before each testing session according to manufacturer instructions (Rietjens et al. 2001). CPET protocol consisted of 3 min warm up at 6 $km \cdot h^{-1}$ and 1% slope followed by ramp speed increases of 0.25 $km \cdot h^{-1}$ every 15s until volitional

exhaustion. A 3-min constant speed stage at 11 $km \cdot h^{-1}$ for women and 12 $km \cdot h^{-1}$ for men was included in the protocol so as to enable running economy measurements. Maximum oxýgen uptake (VO_2max) values were accepted when a plateau (an increase of <2ml/kg/min) or a decline in VO_2 was reached despite increasing workloads and a respiratory exchange ratio (RER) above 1.15 was achieved. If this criteria was not met, a VO_2peak value was taken, defined as the highest VO_2 measured over a 30 seconds period. Second ventilatory threshold (VT_2) was estimated from gas exchange data by two independent researchers following a validated standard methodology as previously described (Lucia et al. 2000).

2.3. Echocardiography

Transthoracic echocardiography was performed at baseline with a Philips HD5 Diagnostic Ultrasound System (Philips Ultrasound, Bothell, Washington USA 98021). All two-dimensional images were acquired from standard parasternal and apical windows by the same experienced echocardiographist following international recommendations for chambers quantification (Mitchell et al. 2019). The study included the following two-dimensional measures: Right Ventricular End Diastolic Diameter (RVEDD), Left Ventricular End Diastolic Diameter (LVEDD), Left Ventricular End Systolic Diameter (LVESD), Interventricular Septum at the end of diastole (IVS) and Posterior Wall at the end of diastole (PW). Left Ventricular Ejection Fraction (LVEF) was assessed according to Teichholz Method. Finally, Left Ventricular Mass was calculated using Devereux modified method and Penn modified method.

2.4. Blood sampling and analysis

Blood samples were collected at baseline (the day before the race), after finishing the marathon and at 24, 48, 96, 144 h and 192 h post-race. Samples were collected from antecubital veins by venipuncture using BD Vacutainer PST II tubes, centrifuged at 3500 rpm for ten minutes and transported at 4°C within 2 hours after their extraction to the Vithas 9 de Octubre Hospital (Valencia), as previously published (Bernat-Adell et al. 2019). Hs-TNT was measured quantitatively with the new high-sensitive enzyme immunoassay based on

electrochemiluminescence technology (ECLIA), using a Cobas e411 analyzer (Roche Diagnostics, Penzberg, Germany). Detailed descriptions of this assay have been previously published (Giannitsis et al. 2010). The Limit of the Blank (LoB) of this assay is 3 ng/L and the URL, defined as the 99th percentile of a healthy population, 14 ng/L. The approximate hs-TnT equivalent to the upper limit of 30 ng/L for the 4th generation cardiac troponin T assay is 50 ng/L (Giannitsis et al. 2010). For the blood sample obtained immediately after the race, values were corrected due to changes in plasma volume and the hemoconcentration caused by dehydration using Dill and Costill formula (Dill and Costill 1974).

2.5. Exercise intensity monitoring

On the morning of the marathon, participants were given a Polar M400 HR monitor (Kempele, Finland) and a GENEActiv accelerometer (Activinsights, Ltd., Kimbolton, Cambridgeshire, United Kingdom). Mean and peak HR (highest HR maintained for at least 1 min) during the marathon (both in absolute values and expressed as percentage of HR at VT_2 and maximum HR reached at the CPET) were retained for statistical analyses. Time above HR at VT_2 and time at extremely vigorous intensity derived from accelerometer data were also considered (Hernando et al. 2018). Finally, marathon finish time was obtained using the ChampionChip time registration (ChampionChip®, MYLAPS, The Netherlands), out of which mean running speed was calculated (both in absolute values and expressed as a percentage of the velocity at VT_2 and the peak velocity reached at the CPET) and retained for statistical analyses.

2.6. Statistical analysis

Statistical analyses were carried out using the Statistical Package for the Social Sciences software (IBM SPSS Statistics for Windows, version 22.0, IBM Corp., Armonk, NY). Normal distribution of the variables was *a priori* verified through the Kolmogorov Smirnov test, obtaining values of $p<0.05$ for all Troponin related variables. This result motivated the usage of nonparametric tests. Friedman and Wilcoxon tests were used to assess differences in Hs-TNT between pre-race and post-race values (finishing line, 24, 48, 96 and 144 and 192 h post-race). Spearman correlations

were employed to analyze possible relationships between baseline echocardiographic and cardiopulmonary test variables (i.e., VO_2max, maximal speed and speed attained at VT_2), training-related variables, exercise intensity and post-race change in Hs-TNT. To that purpose, post-race Hs-TNT values for each subject were related to the individual baseline level (values below the LoB were set to 3 ng/l) to calculate delta scores (Δ): Δ (fold increase) = (post-race value – pre-race value)/pre-race value.

Additionally, 24h post-race hs-TNT data set was splitted into two groups based on the URL for this biomarker (High hs-TNT and Low hs-TNT groups) and possible differences in baseline echocardiographic and cardiopulmonary test variables, training-related variables and exercise intensity variables were assessed using a Mann-Whitney U test. The meaningfulness of the significant outcomes was estimated through Cohen's *d* effect size: a $d<0.5$ was considered small; between 0.5-0.8, moderate; and greater than 0.8, large (Thomas et al. 2005). Likewise, correlations >0.5 were considered strong, 0.3-0.5, moderate and <0.3, small. The significance level was set at $p<0.05$ and data are presented as means and standard deviations (±SD).

3. Results

From the initial sample of 98 participants, 88 runners finished the marathon and we could obtain whole data from 77 athletes, 64 men (83%) and 13 women (17%), who constitute the final sample of the study. Their average finishing time was 3h:35min ± 20min, ranging from 2h:58min to 4h:35min. No signs of ischemia were detected in any athlete in the exercise electrocardiogram performed during the CPET.

The concentration of hs-TNT significantly and largely increased from pre-race to post-race (5.74 ± 5.29 vs 50.4 ± 57.04 ng/L; $p<0.001$; $d=1.08$) (see **Figure 1**). It significantly dropped from immediately post-race to 24 h post-race (50.4 ± 57.04 ng/L vs 15.55 ± 14.29; $p<0.001$; $d=0.84$), and from 24 h post-race to 48 h post-race (15.55 ± 14.29 vs 11.49 ± 14.12; $p<0.001$; $d=0.29$). However, hs-TNT remained largely elevated at 24 h ($p<0.001$; $d=0.86$) and moderately elevated at 48 h post-race ($p<0.001$; $d=0.52$) compared to pre-race values. At 96 h it significantly dropped again from 48 h measurement (5.02 ± 4.53 vs 11.49 ± 14.12; $p<0.001$; $d=0.63$) and then it normalized their values in relation to pre-race ($p=0.347$). At baseline, concentrations of hs-TNT were negative (i.e., below the LoB) in 15 participants (19%) and only 4 runners (5%) displayed a value above the URL. After the race, all of the athletes showed measurable values of hs-TNT; 73 of those runners (95%) displayed values exceeding the URL and 25 participants (32%) surpassed the threshold for suspicion of myocardial injury. The post-race range of concentrations varied from 9.3 to 431.3 ng/L. At 24 h measurement, 30 runners (39%) still displayed values exceeding the URL but only in 3 participants (4%) hs-TNT concentration was above the threshold for suspicion of myocardial injury. The 24 h post-race range of concentrations varied from <3 to 92.8 ng/L.

***** Insert Figure 1 near here *****

The results from correlational analyses are presented in **Table 2 and 3**. No relationship was found between post-race hs-TNT and self-reported training history. Similarly, hs-TNT rise was uncorrelated with cardiopulmonary test variables. Regarding baseline echocardiographic measures, only LVESD showed a significant but small association with post-race hs-TNT (r=-0.26; p=0.018). However, rise in hs-TNT was significantly and moderately correlated with marathon mean HR (r=0.41; p<0.001), marathon mean $HR_{\%VT2}$ (r=0.30; p=0.007) and marathon mean $HR_{\%MAX}$ (r=0.32; p=0.004). It also displayed a significant but small association with marathon speed $\%V_{VT2}$ (r=0.22; p=0.042). On the contrary, no relationships were found between post-race hs-TNT and marathon peak HR, time spent above HR_{VT2} and time at extremely vigorous intensity zone measured by accelerometry. The results from Mann-Whitney U test revealed no differences between High and Low hs-TNT groups in baseline echocardiographic and cardiopulmonary exercise test variables and self-reported training history. Conversely, marathon speed, either relativized by VT_2 or maximum attained at the cardiopulmonary exercise test, were significantly and moderately greater in the High hs-TNT group (p=0.002 and p=0.009 respectively; *d*=0.73 and *d*=0.52 respectively).

***** Insert Table 2 and Table 3 near here *****

4. Discussion

The main purposes of the present study were to identify possible predictors of exercise-induced troponin release and explore whether runners who do not normalize hs-TNT within the initial 24h post-exercise display different values in baseline echocardiographic, cardiovascular fitness and training variables or performed the marathon at a higher relative intensity. As we hypothesized, mean HR during the marathon (both the absolute value and the percentage of the HR in VT_2 and the peak HR reached at the CPET) was directly correlated with post-race rise in hs-TNT; whereas athletes who still displayed a hs-TNT concentration above URL 24h following the race performed the marathon at a significantly higher relative speed (i.e., expressed as a percentage of either the speed at VT_2 or the peak speed reached at the CPET). However, contrary to our expectations, baseline echocardiographic and cardiovascular fitness variables were not associated with hs-TNT rise and normalization, except for a small association between LVESD and post-race hs-TnT, which seems clinically unimportant.

The percentage of runners with post-race hs-TNT values above URL in our study (95%) falls within the range previously reported following a road marathon (between 86% and 100%) (Mingels et al. 2009; Paana et al. 2019; Richardson et al. 2018; Roca et al. 2017; Scherr et al. 2011). Such previous studies unfortunately did not report the percentage of participants who surpassed the threshold for suspicion of myocardial injury (i.e., 50 ng/L), so we can not compare our results at that point. Our finding of a direct relationship between post-exercise rise in hs-TNT and marathon speed $\%V_{VT2}$ suggest that runners who performed the marathon at a higher relative intensity released greater amounts of cardiac troponins. Previous studies assessing the relationship between in hs-TNT response and exercise intensity in endurance competitions have been conflicting: some studies found a direct correlation (Kleiven et al. 2019; Martinez-Navarro et al. 2019), whereas others found an inverse correlation (Eijsvogels et al. 2015; Jassal et al. 2009; Roca et al. 2017; Scherr et al. 2011) or no correlation (Bishop et al. 2019; Kosowski et al. 2019; Mingels et al. 2009; Richardson et al. 2018). However, in all of those studies absolute and not relative

speed (i.e., expressed as a percentage of maximal speed and speed attained at VT_2 in a CPET) was considered. The above suggestion that greater relative intensity is associated with a larger release of cardiac troponin is reinforced in our study by the relationship between post-race hs-TNT and marathon mean HR. Such association agrees with previous results from Richardson et al. (2018) but contrasts with other previous studies, who showed no association between post-exercise hs-TNT and mean HR during either a 91-km mountain bike race or a marathon (Kleiven et al. 2019; Kosowski et al. 2019; Scherr et al. 2011). The fact that in this latter studies participants reported HR data from different personal sportwatches (Kleiven et al. 2019; Scherr et al. 2011) and HR was measured in 1-min intervals (Kosowski et al. 2019) could explain this disagreement.

Additionally, our percentage of runners displaying a hs-TNT value above URL (39%) 24 h post-race is greater than that showed following a road marathon (between 17 and 27%) (Baker et al. 2019; Mingels et al. 2009; Scherr et al. 2011) and a 91-km mountain bike race (18%) (Kleiven et al. 2019). Moreover, we are unaware of previous investigations showing that athletes who still displayed a hs-TNT concentration above URL 24h following the marathon performed the race at a significantly higher relative speed (i.e., expressed as a percentage of either the speed at VT_2 or the peak speed reached at the CPET). In view of these results, athletes who are capable of running the marathon at a greater relative intensity, which it has been largely demonstrated to be a key performance factor (di Prampero et al. 1986), are those who sustain greater cardiac strain. Therefore, it becomes crucial for such higher-performing athletes to precisely balance training and recovery following strenuous competitions such as a marathon.

The absence of any relationship between post-race hs-TNT and self-reported training history coincides with Kleiven et al. (2019) but differs, however, with other previous studies (Fortescue et al. 2007; Kosowski et al. 2019; Mehta et al. 2012; Neilan et al. 2006), where cardiac troponin release was inversely associated with training experience and weekly training mileage. It could be that our sample was more homogeneous in relation to training status compared to previous studies, because of our narrow inclusion criteria. This fact could explain why no relationship was

identified between post-race hs-TNT and self-reported training history. On the other hand, the lack of any association between post-race hs-TNT and baseline CPET variables (i.e., VO_2max, maximal speed and speed attained at VT_2) concurs with previous studies (Kosowski et al. 2019; Richardson et al. 2018; Trivax et al. 2010). Similarly, our results also coincides with preceding investigations where no relationships were showed between echocardiographic measures and hs-TNT release after exercise (Donaldson et al. 2019; Kosowski et al. 2019; Paana et al. 2019).

5. Conclusions

Runners who performed the marathon at a relative higher mean HR sustained a greater post-race hs-TNT rise. Moreover, participants who still displayed values above the URL for this biomarker 24 h post-race, ran the marathon at a higher speed relative to their second ventilatory threshold and the peak speed reached at the CPET. Conversely, neither training history nor cardiopulmonary fitness were related to hs-TNT rise and normalization. These data lead us to suggest that running a marathon closer to each one individual's limits, independently of training background and absolute cardiopulmonary fitness, provokes greater cardiac stress.

Practical implications

- Running a marathon induces significant cardiac stress. The magnitude of post-race troponin release is correlated with exercise relative intensity.
- A longer post-race recovery time is recommended for those participants who run the marathon at a harder intensity, relative to their cardiopulmonary fitness.
- Performing a CPET before the race and wearing a HR monitor during the marathon, especially in those participants with any cardiovascular risk factor, is strongly advocated as a means of better regulate race pace.

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Figure legend

Figure 1. Evolution of hs-TNT

* Significantly different from baseline condition ($p<0.05$); # Significantly different from the preceding measuring ($p<0.05$). URL, Upper Reference Limit for hs-TNT

Figure 1

Click here to access/download;Figure;FIGURE 1.PNG

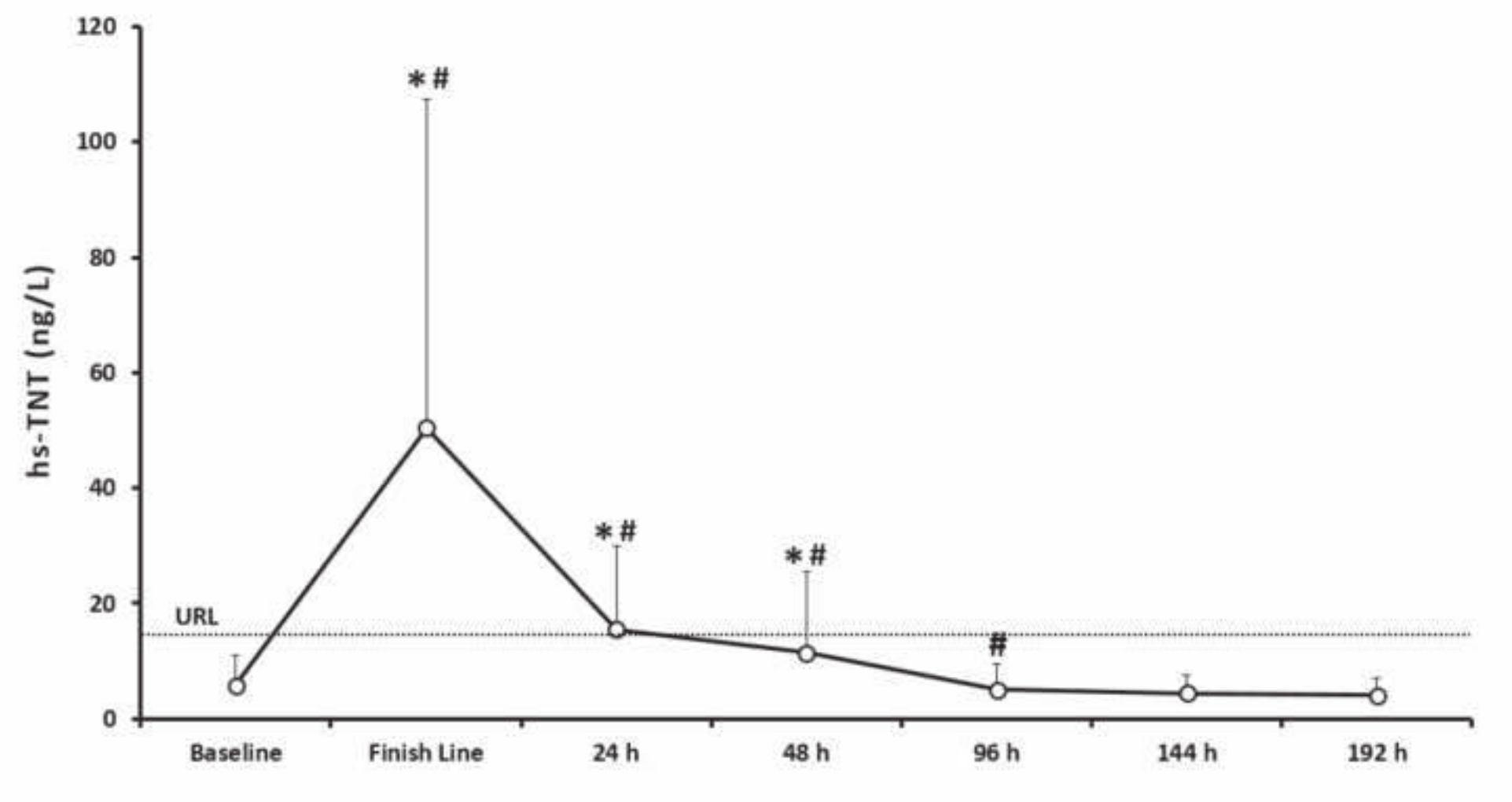

Table 1. Sample main characteristics (mean ± SD)

	All sample (n = 98)	Males (n = 83)	Females (n = 15)
Age (years)	38.72 ± 3.63	38.76 ± 3.65	38.50 ± 3.63
BMI (kg/m^2)	22.87 ± 1.71	23.18 ± 1.48	21.32 ± 2.01
VO_{2peak} (ml O_2/kg/min)	54.53 ± 5.63	55.74 ± 5.14	48.27 ± 3.60
V_{MAX} (km/h)	16.89 ± 1.28	17.26 ± 1.01	15.01 ± 0.76
V_{VT2} (km/h)	13.92 ± 0.97	14.14 ± 0.83	12.78 ± 0.88
Number of years running	6.49 ± 2.81	6.58 ± 2.91	5.38 ± 1.80
Number of previous marathons	3.28 ± 3	3.56 ± 3.09	1.92 ± 2.08
Weekly training days	4.81 ± 0.86	4.90 ± 0.85	4.33 ± 0.81
Weekly running volume (km)	63.16 ± 13.42	64.45 ± 13.21	55.66 ± 12.79
Weekly training hours	7.30 ± 2.67	7.46 ± 2.69	6.21 ± 2.27
Strength training (%)	39.8%	42.2%	26.7%

Abbreviations: BMI, Body Mass Index; VO_2peak, peak oxygen uptake; V_{MAX}, peak speed reached at the Cardiopulmonar Exercise Test; V_{VT2}, speed associated with the second ventilatory threshold in the Cardiopulmonar Exercise Test; Strength training (%), percentage of participants who performed at least one weekly strength-training in the previous 3 months

Table 2

Table 2. Correlational results and differences between High hs-TNT and Low hs-TNT groups regarding baseline echocardiographic and cardiopulmonary exercise test variables and self-reported training history.

	All sample Mean ± SD (n = 77)	**Correlation with post-race Δ hs-TNT** (r /*p*)	**High hs-TNT group** Mean ± SD (n = 30)	**Low hs-TNT group** Mean ± SD (n = 47)
RVEDD (cm)	2.11 ± 0.38	0.041 / 0.718	2.15 ± 0.36	2.09 ± 0.39
IVS (cm)	1.06 ± 0.11	-0.132 / 0.237	1.05 ± 0.1	1.05 ± 0.11
LVEDD (cm)	4.96 ± 0.52	-0.208 / 0.061	4.87 ± 0.53	5 ± 0.51
LVESD (cm)	3.05 ± 0.41	-0.261 / 0.018 *	2.98 ± 0.45	3.08 ± 0.38
PW (cm)	1 ± 0.12	-0.14 / 0.211	1 ± 0.11	1 ± 0.12
LVEF (%)	67.8 ± 8.45	0.069 / 0.54	67.99 ± 9.68	67.79 ± 7.71
LVMass_Devereux (g)	104.72 ± 21.15	-0.197 / 0.076	102.78 ± 20.77	105.02 ± 21.11
LVMass_Penn (g)	120.32 ± 26.12	-0.195 / 0.079	117.89 ± 25.65	120.72 ± 26.07
$\mathbf{V_{VT1}}$ (km/h)	11.42 ± 0.85	-0.039 / 0.724	11.42 ± 0.93	11.38 ± 0.81
$\mathbf{V_{VT2}}$ (km/h)	13.99 ± 0.91	-0.142 / 0.193	13.81 ± 1.14	14.02 ± 0.81
$\mathbf{VO_{2peak}}$ (ml O_2/kg/min)	53.9 ± 5.27	-0.086 / 0.432	53.97 ± 5.35	53.39 ± 5.28
$\mathbf{V_{MAX}}$ (km/h)	16.95 ± 1.19	-0.074 / 0.497	16.93 ± 1.5	16.88 ± 1.05
RE (ml O_2/kg/km)	211.25 ± 14.61	-0.01 / 0.931	213.03 ± 14.82	209.95 ± 14.56
RE (kcal/kg/km)	1.06 ± 0.07	-0.035 / 0.753	1.06 ± 0.07	1.05 ± 0.07

Number of years running	6.66 ± 3.13	0.008 / 0.939	6.91 ± 3.07	6.4 ± 3.09
Number of previous marathons	3.49 ± 3.18	0.016 / 0.888	3.41 ± 3.35	3.62 ± 3.1
Weekly training days	4.89 ± 0.85	-0.073 / 0.51	4.88 ± 0.81	4.87 ± 0.82
Weekly running volume (km)	62.52 ± 13.53	-0.019 / 0.86	61.62 ± 13.24	63.83 ± 12.9
Weekly training hours	7.32 ± 2.44	-0.081 / 0.471	6.79 ± 1.82	7.66 ± 2.73

Abbreviations: VO_2peak, peak oxygen uptake; V_{MAX}, peak speed reached at the CPET; V_{VT1}, speed associated with the first ventilatory threshold in the CPET; V_{VT2}, speed associated with the second ventilatory threshold in the CPET; RE, running economy; RVEDD, Right Ventricular End Diastolic Diametrer; IVS, Interventricular Septum at the end of diastole; LVEDD, Left Ventricular End Diastolic Diameter; LVESD, Left Ventricular End Systolic Diameter; PW, Posterior Wall at the end of diastole; LVEF, Left Ventricular Ejection Fraction; LVMass, Left Ventricular Mass.

Table 3. Correlational results and differences between High hs-TNT and Low hs-TNT groups regarding exercise intensity variables

	All sample Mean ± SD (n = 77)	**Correlation with post-race Δ hs-TNT** (r /*p*)	**High hs-TNT group** Mean ± SD (n = 30)	**Low hs-TNT group** Mean ± SD (n = 47)
Marathon Speed (km/h)	11.91 ± 1.13	0.039 / 0.724	12.17 ± 1.14	11.71 ± 1.1
Marathon Speed %V_{VT2} (%)	85.21 ± 6.87	0.22 / 0.042 *	88.21 ± 6.53 #	83.49 ± 6.54
Marathon Speed %V_{MAX} (%)	70.33 ± 5.18	0.207 / 0.056	72 ± 4.25 #	69.40 ± 5.53
Marathon Mean HR (bpm)	161.56 ± 8.5	0.414 / 0.001 **	163.26 ± 6.35	160.82 ± 9.68
Marathon Mean $HR_{\%VT2}$ (%)	96.68 ± 4.66	0.298 / 0.007 **	97.27 ± 4.49	96.41 ± 4.78
Marathon Mean $HR_{\%MAX}$ (%)	89.94 ± 3.82	0.318 / 0.004 **	90.09 ± 3.50	89.67 ± 4.01
Marathon Peak HR (bpm)	177.89 ± 12.47	0.212 / 0.058	181.76 ± 14.95	176.41 ± 11.35
Marathon Peak $HR_{\%VT2}$ (%)	106.44 ± 7.43	0.137 / 0.223	108.33 ± 9	105.71 ± 6.68
Marathon Peak $HR_{\%MAX}$ (%)	98.95 ± 7.07	0.104 / 0.357	100.3 ± 8.48	98.41 ± 6.27
Time at EV Intensity (min)	119.51 ± 82.27	-0.039 / 0.719	121.44 ± 81.05	118.26 ± 85.43
Time above HR_{VT2} (min)	56.62 ± 67.2	0.168 / 0.135	58.42 ± 70.83	58.67 ± 65.22

Abbreviations: Marathon Speed %V_{VT2}, Marathon speed as a percentage of the velocity at VT_2 in the CPET; Marathon Speed %V_{MAX}, Marathon speed as a percentage of the peak velocity in the CPET; Marathon Mean $HR_{\%VT2}$, Marathon mean HR as a percentage of the HR at VT_2 in the CPET; Marathon Mean $HR_{\%MAX}$, Marathon mean HR as a percentage of the peak HR in the CPET; Marathon Peak $HR_{\%VT2}$, Marathon peak HR as a percentage of the HR at VT_2 in the CPET; Marathon Peak $HR_{\%MAX}$, Marathon peak HR as a percentage of the peak HR in the CPET; Time at EV Intensity, Time at Extremely Vigorous intensity

measured by accelerometry; Time above HR_{VT2}, Time at a HR above the HR corresponding to VT_2 in the CPET. * $p<0.05$ ** $p<0.01$ # Significantly different from Low hs-TNT group ($p<0.01$)