Individual variability of high-sensitivity cardiac troponin levels after aerobic exercise is not mediated by exercise mode

Alejandro Legaz-Arrese¹, Isaac López-Laval¹, Keith George², Juan José Puente-Lanzarote³, Carlos Castellar-Otín¹, Joaquín Reverter-Masià⁴, Diego Munguía-Izquierdo⁵

¹Section of Physical Education and Sports, University of Zaragoza, Zaragoza, Spain; ²Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK; ³Service of Biochemistry, Lozano Blesa University Hospital, Zaragoza, Spain; ⁴Research Group Human Movement, University of Lleida, LLeida, Spain; ⁵Section of Physical Education and Sports, University Pablo de Olavide, Sevilla, Spain

Corresponding author
Address: Alejandro Legaz Arrese. Departamento de Fisiatría y Enfermería. C/Domingo Miral S/N. 50009. Zaragoza (Spain).
Phone: 0034976761000
e-mail: alegaz@unizar.es

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Abstract

We compared the response of high-sensitivity cardiac troponin T (hs-cTnT) after 60 min of swimming, running, and cycling in well trained triathletes. The maximal increase in hs-cTnT was similar in all exercise bouts (swimming 453%, cycling 349% and running 471%) although there was substantial individual variability in peak hs-cTnT. The post-exercise kinetics for hs-cTnT were consistent. The change in hs-cTnT was correlated between trials. In all trials hs-cTnT had largely returned to baseline levels 24 h post-exercise. In summary, an increase in hs-cTnT was apparent in all triathletes independent of exercise mode and despite variable peak data the consistent kinetics over 24 h post-exercise would suggest this represents a physiological phenomenon.
Introduction

The troponin complex of the myocardial sarcomeric (cTn) unit is composed of troponin T (cTnT) (37 kDa), troponin C (cTnC) (18 kDa), and troponin I (cTnI) (22.5 kDa) (Shave et al., 2010a). Whilst there are some differences among these biomarkers, the quantification in serum of both cTnI and cTnT are used as highly specific markers of cardiomyocyte insult and damage (Thygesen et al., 2012). Exercise has been documented as a potential stimulus for substantial changes in cTn levels (Carranza-Garcia et al., 2011; George et al., 2012; Shave et al., 2007) but the clinical implications, mechanisms, and mediating factors of exercise-related cTn appearance are not well known.

The majority of exercise-related studies of cTn appearance have employed (ultra)endurance exercise often in a field setting with limited blood draws post-exercise (Shave et al., 2010a). The impact of shorter, more intense bouts of exercise upon cTn appearance has received less attention (Shave et al., 2010b), despite the fact that this likely represents a more common exercise stimulus for the general population than ultra-endurance event. It is worthy of note that in spite of the limited volume of exercise (a single 30 min all-out treadmill run) cTnI was elevated during recovery in 75% of athletes (Shave et al., 2010b).

One element of the work by Shave et al. (2007; 2010b) and others (Legaz-Arrese et al., 2015; Tian et al., 2012) is that the individual cTn response to exercise is quite disparate. The percentage of participants whose post-exercise cTn exceeds the upper reference limit (URL) varies significantly between studies (Middleton et al., 2008; Shave et al., 2007). This variability is likely due, at least in part, to considerable methodological differences, including the nature of the cTn assay (Mingels et al., 2009), sampling frequency (Middleton et al. 2008) as well as the exercise stimulus (Shave et al., 2007). A meta-analysis showed that the elevation of cTnT in endurance athletes was greater after running than cycling (Shave et al., 2007). This theory has not been evaluated in a controlled, repeated measures exercise design. Further, the effect of other continuous aerobic modes, including swimming, on cTn levels is unknown. The “kinetics” of cTn appearance and clearance after exercise has been limited to a small number of recent studies (Carranza-Garcia et al., 2011; Legaz-Arrese et al., 2015; Middleton et al., 2008; Tian et al., 2012). Of these studies only Legaz-Arrese et al. (2015) and Tian et al. (2012) assessed hs-cTnT over a 24 h period post-exercise. Whilst this data demonstrated a consistent time to peak hs-cTnT after 60-90 min, there was evidence of heterogeneity in peak responses with the URL exceeded in 71-88% of participants. A comparative study of individual hs-cTnT kinetics in subjects engaging in different types of exercise could add valuable information in this regard.
Therefore, the aim of the present study was to determine the individual hs-cTnT response to 3 different bouts (swim, cycle and run) of 60 min of high intensity aerobic exercise in a controlled, repeated measures study of male triathletes. We hypothesize that the magnitude of hs-cTnT responses to a controlled bout of prolonged exercise is independent of the type of continuous aerobic activity and is marked by high inter- and intra-subject variability.

Methods

Participants

Fifteen amateur male triathletes (age 35 ± 9 years, height 177 ± 5 cm, weight 71 ± 4 kg) were recruited from three local triathlon clubs through an open invitation. All triathletes had a minimum of 4 years of experience (7 ± 3 years) and competed in sprint ($N = 15$, result: 71 ± 8 min) and/or Olympic triathlons ($N = 7$, result: 140 ± 12 min). The month before the study, the participants trained 8 ± 1 h per week. None of the participants had any clinical evidence or personal history of cardiovascular disease. All had a normal 12-lead electrocardiogram (ECG). All triathletes provided informed written consent. All procedures conformed to the Declaration of Helsinki and were approved by the local ethics committee.

Research design and protocols

The study employed a repeated measures design with four visits to the “laboratory”. During the first laboratory visit, a baseline ECG was taken along with anthropometric measurements and data from a personal questionnaire, which included information on personal characteristics, level of athletic performance, training history, and cardiac symptoms history. Initially, subjects exercised at maximum intensity for a brief period (Ayalon et al., 1974) to determine a peak heart rate (HR) response while swimming, cycling, and running in a random order. In the final three visits, subjects performed, in a randomized order, 60-min “all out” swimming, cycling, and running exercise trials. The three trials occurred at the same time of day (11:00 am) and were separated by at least 72 h, during which the subjects were instructed to abstain from all training activities. The swimming test took place in a 20-m indoor pool (water temperature 24°C, air temperature 27°C, relative humidity 77%). The cycling test took place on a cyclo-ergometer (Model M3, Keiser, USA) and the running test on a treadmill (Run Excite 700, Technogym, Italia) in an air-conditioned sports hall with the temperature and relative humidity set at 20°C and 50%, respectively. Prior to the tests, the triathletes completed a self-
paced 5-min warm-up (HR<130 beats min⁻¹). Pairs of triathletes competed side-by-side to mimic regular competition and coaches provided verbal encouragement. Subjects were constantly aware of the time and distance covered. Water consumption was permitted *ad libitum*. HR was continuously recorded during the tests (Polar Electro Oy, Kempele, Finland). Exercise intensity was established as the percentage of peak HR determined from prior high intensity exercise tests. The distance covered on each test was recorded every 10 min. Immediately after the test was completed, the participants rated the test for perceived exertion (RPE) (Borg and Kaijser, 2006).

Venous blood samples were taken before, immediately after (5 min), and 1, 3, 6, 12, and 24 h after exercise to assess serum hs-cTnT. Blood samples were drawn by repetitive venipuncture from an antecubital vein and quickly centrifuged. The serum and plasma were drawn off and stored at −80°C for later analysis. hs-cTnT was measured quantitatively with the new high-sensitive enzyme immunoassay based on electrochemiluminescence technology using the Cobas E 601 analyzer (Roche Diagnostics, Penzberg, Germany). This assay has a range from 3 to 10,000 ng L⁻¹ with a lower limit of the blank of 3 ng/L. The intra-assay coefficient of variation at a mean hs-cTnT level of 13.5 ng L⁻¹ is 5.2%. Precision was determined by 2 cycles daily in duplicate, each for 21 days. The URL for hs-cTnT, defined as the 99th percentile of healthy participants, was 14 ng L⁻¹ (Giannitsis et al., 2010).

**Statistical analysis**

Statistical analyses were performed using Statistical Package for the Social Sciences (IBM SPSS Statistics, v.20.0 for Windows). Cohort data are presented as the mean ± standard deviation unless otherwise stated. After Kolmogorov-Smirnov analysis raw data for hs-cTnT were log-transformed to achieve a normal distribution prior to inferential statistical testing. Baseline data before each trial and exercise data were compared using repeated-measures analysis of variance (ANOVA). To determine the impact of sampling time (before, 5 min, 1 h, 3 h, 6 h, 12 h, and 24 h after exercise) and type of exercise (swimming, cycling, and running) on hs-cTnT, we employed a fully repeated measures 2-way ANOVA with post-hoc Bonferroni tests when appropriate. The associations between the increase in hs-cTnT (peak post-exercise value minus the baseline value) in the three exercise bouts as well as with other relevant variables (e.g., baseline biomarker concentration, mean exercise HR and percentage of peak HR) were assessed using bivariate Pearson’s product-moment correlation coefficients. The values were considered significant if *p* < 0.05.
Results

Exercise test data

One triathlete was injured during the running trial and was excluded from the study. No subjects reported cardiac symptoms during or after exercise. The principal performance results are reported in Table 1. Mean HR was lowest during swimming. There was no exercise mode difference in the percentage of peak HR ($p = 0.131$) or RPE reached ($p = 0.085$).

hs-cTnT appearance

No significant difference was observed in baseline hs-cTnT across the exercise trials ($p = 0.887$). A significant effect of sampling time was observed for hs-cTnT, with increases (swimming 453%, cycling 349% and running 471%) compared to pre-exercise at 0, 1, 3, 6, 12, and 24-h post-exercise ($p = 0.000$ for each) (Table 2).

There was no main effect of exercise mode on hs-cTnT appearance ($p = 0.102$) with an increase, post-effort, in hs-cTnT observed in all individuals for all three exercise tests (Figure 1). There was no significant interaction effect between time and mode on hs-cTnT values ($p = 0.090$). There were no significant differences in the post-effort peak hs-cTnT values between the swimming ($20.4 \pm 9.9$ ng L$^{-1}$), cycling ($17.3 \pm 7.5$ ng L$^{-1}$), and running tests ($20.5 \pm 9.9$ ng L$^{-1}$) ($p = 0.503$). In support of this the maximal increase in hs-cTnT (peak-baseline) was similar in swimming ($16.2 \pm 10.3$ ng L$^{-1}$), cycling ($13.0 \pm 8.1$ ng L$^{-1}$), and running ($16.3 \pm 10.4$ ng L$^{-1}$) ($p = 0.167$).

Some individual variability was noted in the magnitude of peak hs-cTnT with the URL being exceeded in 12 triathletes (86%): 8 (57%) in all three exercise tests, 1 (7%) in two tests, and 3 (22%) in one test (Figure 1). In support of this the maximal increase in hs-cTnT was highly variable between subjects in swimming (range: 3.0-37.4; CV = 64%), cycling (range: 1.9-27.1; CV = 62%), and running (range: 3.9-37.8, CV = 64%). The percentage of subjects with hs-cTnT values exceeding the URL was similar for swimming (64%), cycling (71%), and running (71%). Of the 42 individual exercise tests, the maximum post-effort hs-cTnT value was observed at 5 min and 1 h in 1 exercise test, 3 h in 30 exercise tests, 6 h in 6 exercise tests, 12 h in 3 exercise test, and 24 h in 1 exercise test. At 12 and 24 h post-exercise, no subjects had hs-cTnT exceeding the URL, and by 24 h, all values were at or near baseline levels.
The increase in hs-cTnT was not associated with baseline data or any exercise-related parameters. The associations between the increase in hs-cTnT during the exercise tests were positive, of moderate to large magnitude and in 2 out of 3 cases statistically significant (Figure 2). Despite this, some degree of intra-subject variability was noted across exercises in the increase in hs-cTnT (CV = 37%, range: 7-72%) (Figure 1).

**Discussion**

To our knowledge, this is the first controlled, repeated measures study comparing detailed recovery “kinetics” of hs-cTnT where exercise mode was manipulated. Our results provide confirmatory and novel data on the following points; 1) hs-cTnT rose in all participants after all trials, 2) exercise mode did not alter the hs-cTnT response to high intensity aerobic exercise, 3) substantial inter- and intra-individual variability was noted in the magnitude of post-exercise hs-cTnT data, although 4) the kinetics of hs-cTnT increase and recovery during the 24 h post-exercise period was more consistent.

*hs-cTnT appearance*

An increase in cTn after prolonged exercise is well documented (Shave et al., 2010a) and this work extends that by detailing cTn appearance throughout a 24 h recovery period to shorter and intense bouts of aerobic exercise including swimming. Short-duration exercise can be very intense, but the total volume is small compared to (ultra)endurance activities, and the cTn response has been contradictory in previous work. Chan-Dewar et al. (2013) observed a rise in cTnI in only 17% of subjects after 60 min cycling and similar data was observed in relation to the URL of hs-cTnT by Duttaroy et al. (2012). In contrast, our results show an increase in hs-cTnT in all participants after every exercise bout undertaken, with a larger percentage of participants exceeding the URL (64-71%). The discrepancy between studies may reflect differences in the exercise stimulus, sampling time and frequency as well as a potential effect of participant training status (Chan-Dewar et al., 2013; Duttaroy et al., 2012). Shave et al. (2010b) noted an increased cTn in 70% of participants after 30 min of “all-out” running but it is pertinent to note they assessed cTnI and not hs-cTnT. Although Mingels et al. (2009) reported no significant differences in the number of “positives” between cTnI and hs-cTnT levels after a marathon, we cannot discount the possibility that some assay-related differences exist after shorter-duration exercise.
Within the current study we elected to study, in a controlled repeated measures design, one potential confounding factor from past work; exercise mode. Swimming, cycling, and running, although basically aerobic in nature, result in different muscle recruitment patterns as well as divergent HR response to steady-state exercise. The cTn response to cycling and running has been reported independently in several studies with the only comparative comment made in a meta-analysis (Shave et al. 2007) where the positive cTn response to exercise was lower in cycling (27%) compared with running (52%). These results were likely influenced, at least in part, by the different exercise duration (running mean 4 h 46 min; cycling mean 7 h 59 min) and other methodological factors including assay precision, sampling frequency, training status and exercise intensity. The current study compared the impact of similar bouts of cycling and running in a single cohort of triathletes and it was apparent that the mode of aerobic activity had no significant influence on the magnitude and/or kinetics of hs-cTnT levels as well as the percentage of subjects with values exceeding the URL for hs-cTnT. Furthermore, the increases in hs-cTnT in response to swimming, running, and cycling tests were moderately-highly correlated ($r = 0.495-0.802$). The magnitudes of these associations were similar to those recently observed after two identical bouts of prolonged exercise (Legaz-Arrese et al., 2015; Tian et al., 2014). This would suggest that the small differences in exercise HR, pacing, etc. between cycling, running and swimming had very little influence on post-exercise hs-cTnT.

At odds with most field work but confirming three recent controlled studies (Legaz-Arrese et al., 2015; Middleton et al., 2008; Tian et al., 2012), the present data suggest that cTn was elevated in all subjects after exercise. It is important to consider that the magnitude of cTn response across past work has been highly variable (Eijsvogels et al., 2015; Serrano-Ostáriz et al., 2009; Tian et al., 2012). The fact that 8 of our 14 subjects exceeded the hs-cTnT URL in each of the three exercise tests and that 2 subjects did not reach the URL in any bout further supports the hypothesis that individuals are more or less susceptible to a hs-cTnT response to exercise. Despite this, our results also suggest a degree of intra-subject variability in the response of hs-cTnT with exercise. Moreover, this variability differed between subjects (CV = 7-72%). The factors that influence the marked inter- and intra-subject variability in the exercise-associated cTn response are not fully understood but could not be explained in our data by exercise mode, duration, intensity, time of day, environment, or number of blood samples. Several previous studies observed a significant association between peak post-exercise cTnI and baseline level (Legaz-Arrese et al., 2011; Serrano-Ostáriz et al., 2011). This was not the case for hs-cTnT in our study or in others (Legaz-Arrese et
al., 2015; Saravia et al., 2010; Tian et al., 2014). The discrepancy between studies may be associated with the small range in resting cTn concentrations which limit the nature of any association. Further, in our relatively homogenous cohort, we did not observe an influence of age, weight, or training level on hs-cTnT levels. Whilst there is evidence of heterogeneity in the magnitude of hs-cTnT appearance after exercise, there was much more consistency in the overall “pattern” or “kinetics” of hs-cTnT throughout the 24 h recovery period. Visual observation suggests a rapid rise in hs-cTnT in the early hours of recovery, with 71% reaching a peak at 3 h, with close to complete recovery to baseline at 24 h. This was consistent between exercise mode trials and between individuals and largely agrees with the only two others studies of hs-cTnT kinetics over 24 h (Legaz-Arrese et al., 2015; Tian et al., 2012).

**Implications**

The return of hs-cTnT to baseline levels 24 h post-exercise is a pattern that differs substantially from observations in acute coronary syndromes, in which hs-cTnT can remain elevated for days (Thygesen et al., 2012). Furthermore, the hs-cTnT increase was produced in the absence of clinical signs and symptoms suggestive of cardiac disease all continued training and competing in triathlons for more than 8 months after the experiment. The results of the present study provide more support to the hypothesis that post-exercise cTn appearance reflects a physiological process that may indicate transient cytosolic leakage propagated by membrane damage, rather than cardiomyocyte necrosis (Shave et al., 2007). It is hypothesized that this increased membrane permeability is secondary to the physiological stress placed on the cells as a result of exercise (Scharhag et al., 2008). From a clinical perspective, there seems to be no strong rationale for full clinical cardiovascular examination in athletes with elevated cTn in the absence of other clinical signs and symptoms. When evaluating cTn in an emergency setting, detailed information regarding any recent exercise activities should be obtained, especially in the first 24 h post-exercise. It is important to differentiate between what might be a benign “normal” exercise response and what could be clinically relevant in the real-world setting of an athlete presenting to a medical tent after an endurance exercise bout.

**Limitations**

We should note, as a limitation, that we only studied a relatively small sample of young adult male athletes and as such generalizability of the data is limited. Likewise, our results, and their clinical impact,
cannot be directly extrapolated to the effects of much more demanding triathlon exercise tests. The evaluation of other cardiac biomarkers, such as cTnI, could be of interest in future studies.

Conclusions

In conclusion, 60 min of high intensity running, cycling, and swimming resulted in the appearance of hs-cTnT in all triathletes during all tests. Our data also suggest that exercise-induced hs-cTnT appearance is likely to display inter- and intra-individual variation that is independent of the aerobic exercise mode. Clinicians should understand that it is possible to observe high levels of hs-cTnT, often exceeding the URL, after intense athletic activity of 1 h duration.

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**Figure legends**

Fig. 1. Individual data points for hs-cTnT (ng L⁻¹) after swimming (a), cycling (b) and running (c) at pre-exercise (PRE), as well as 5 min, 1, 3, 6, 12, and 24 h (0HR, 1HR, 3HR, 6HR, 12HR, 24HR, respectively) after a 60 min maximal exercise test. The horizontal dotted line is the upper reference limit (99th percentile) at 14 ng L⁻¹.

Fig. 2. Association between the increase in hs-cTnT during the swimming, cycling and running test.
Table 1. Performance characteristics by exercise type. Data are mean ± SD

| Exercise   | Velocity (km h⁻¹) | Peak HR (beats min⁻¹) | Mean HR (beats min⁻¹) | Percentage maximum HR (%) | RPE         |
|------------|-------------------|-----------------------|-----------------------|---------------------------|-------------|
| Swimming   | 3.3 ± 0.5         | 171 ± 14              | 150 ± 16              | 88 ± 4.4                  | 8.7 ± 0.8   |
| Cycling    | 29.7 ± 1.4        | 181 ± 13              | 157 ± 10              | 87 ± 1.8                  | 9.4 ± 0.6   |
| Running    | 13.2 ± 1.4        | 184 ± 12              | 164 ± 12              | 89 ± 2.6                  | 8.7 ± 1.1   |

* Significant difference between running and cycling
* Significant difference between swimming and running
* Significant difference between cycling and swimming
Table 2. hs-cTnT (ng L⁻¹) before and after 60 min of swimming, running, and cycling at maximum velocity. Data are mean ± SD (% over URL)

|                  | Pre-exercise | 5 min post | 1 h post | 3 h post | 6 h post | 12 h post | 24 h post | P value |
|------------------|--------------|------------|----------|----------|----------|-----------|----------|---------|
| **Swimming**     | 4.21 ± 1.27  | 7.23 ± 1.92| 11.13 ± 4.11| 18.91 ± 10.17| 16.50 ± 8.03| 9.70 ± 2.99| 5.99 ± 1.96| 0.000   |
|                  | (0)          | (0)        | (21)     | (57)     | (57)     | (0)       | (0)      |         |
| **Cycling**      | 4.31 ± 1.28  | 5.97 ± 1.46| 10.08 ± 3.71| 16.75 ± 8.06| 10.61 ± 4.50| 8.21 ± 2.76| 5.75 ± 2.17| 0.000   |
|                  | (0)          | (0)        | (21)     | (71)     | (21)     | (0)       | (0)      |         |
| **Running**      | 4.13 ± 1.46  | 6.91 ± 2.07| 10.44 ± 2.33| 19.09 ± 9.66| 16.70 ± 7.51| 9.50 ± 3.20| 6.33 ± 2.14| 0.090   |
|                  | (0)          | (0)        | (7)      | (71)     | (57)     | (0)       | (0)      |         |
Fig. 1. Individual data points for hs-cTnT (ng L⁻¹) after swimming (a), cycling (b) and running (c) at pre-exercise (PRE), as well as 5 min, 1, 3, 6, 12, and 24 h (0HR, 1HR, 3HR, 6HR, 12HR, 24HR, respectively) after a 60 min maximal exercise test. The horizontal dotted line is the upper reference limit (99th percentile) at 14 ng L⁻¹.
Fig. 2. Association between the increase in hs-cTnT during the swimming, cycling and running test.

(a) $r = 0.543$, $p = 0.045$
(b) $r = 0.802$
$p = 0.001$

(c) $r = 0.495$
$p = 0.072$