The kinetics of cardiac troponin T release during and after 1- and 6-h maximal cycling trials

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Abstract

Objectives: In this study, the effects of short-duration high-intensity exercise and long-duration exercise on high-sensitivity cardiac troponin T (hs-cTnT) levels were compared.

Methods: Twelve male amateur cyclists performed 1- and 6-h cycling trials. In both exercise trials, hs-cTnT was assessed at rest, immediately postexercise and at 1, 3, 6, 12, and 24 h postexercise. Additionally, hs-cTnT levels were assessed every hour during the 6-h trial.

Results: Exercise resulted in an increase in hs-cTnT levels in all subjects. Circulating hs-cTnT levels increased in both exercise trials (p<0.001), with higher peak values occurring after the 1-h trial compared with those of the 6-h trial (p=0.023). The upper reference limit (URL) exceeded 83% of the participants in the 1-h trial and 42% of the participants in the 6-h trial. There was substantial individual variability in peak hs-cTnT in both trials. Values of hs-cTnT were greater after exercise than during exercise for the 6-h trial. For both exercise trials, the maximum postexercise hs-cTnT values correlated with the $\%HR_{MAX}$ (r=0.906 for the 1-h trial, r=0.735 for the 6-h trial). For the 1-h trial, the maximum postexercise hs-cTnT values were observed at 3 hours in all subjects. No significant difference in the hs-cTnT values was observed for the 6-h trial during the first 12 h postexercise.

Conclusions: Our results demonstrated greater hs-cTnT levels in young male participants after a 1-h cycling trial than after a 6-h cycling trial, despite a substantially greater energy expenditure and total external work completed in the 6-h trial. Postexercise hs-cTnT values are associated with relative exercise intensity.

Keywords

Cardiac biomarkers; Exercise duration; Exercise intensity; Amateur cyclists

Introduction

The exercise-induced release of cardiac troponin (cTn) is common in apparently healthy athletes.[1,2] However, an increase in cardiac troponin T (cTnT) or I (cTnI) is often associated with myocardial damage, and cTn is the preferred biomarker for the diagnosis of myocardial injury.[3] The underlying mechanisms responsible for this phenomenon during exercise and the clinical significance of increases in postexercise cTn remain controversial.[1] Exercise-induced increases in cTn have traditionally been interpreted as a benign form of cTn release for the following reasons: the elevations are relatively small, often occur in ostensibly healthy people after exercise of different types, durations, and intensities; and are not related to cardiac symptoms.[1] Available data also demonstrate large but reproducible differences in the magnitude of exercise-induced cTn release between individuals.[4] Whether such variance is associated with future clinical implications is an area of current debate.[5,6,7]

The kinetics of cTn concentrations after acute myocardial infarction (AMI) are well described.[8] In contrast to that of an AMI-related release, the magnitude of exercise-related cTn is believed to be smaller, and the peak is earlier and shorter, with values returning to basal levels after 24–48 hours of recovery in most participants.[1] However, kinetic data for exercise-induced changes in cTn concentrations are not common, and within-group comparative data are rare. A comprehensive understanding of cTn kinetics during exercise is important to further our understanding of potential mechanisms and clinical significance and to differentiate this release from pathophysiological scenarios.

In addition, current evidence has not conclusively determined the importance of exercise intensity and/or duration as important determinants of cTn elevation[9,10]. This relationship is difficult to elucidate because the intensity, duration and volume of exercise can vary considerably in the reports in the literature, and few mechanistic studies have controlled for these factors in the same subjects. We previously observed a significant increase in cTn after short-duration high-intensity exercise (1-h cycling trial) and after long-duration exercise (200-

km road cycling race) in different athletes.[11,12] It is also likely that exercise parameters may be moderators of cTn kinetics, but this has not been established beyond doubt to date.[2] Certainly, information on cTn kinetics during exercise and/or within the first 24 h after completing long-duration exercise is very limited and controversial.[13,14] Consequently, limited data are available to support or refute the previous observation of biphasic cTn release during prolonged exercise.[14] Furthermore, no study has directly compared cTn kinetics after short- and long-duration exercise in the same athletes while exercising at the highest possible intensity that is ecologically similar to competitive performance situations.

In an attempt to generate new data and resolve prior contradictory evidence, we examined hs-cTnT before and after 1- and 6-h cycling trials by obtaining multiple measurements during the 24-h recovery period. For further confirmation, we also evaluated hs-cTnT levels during exercise in the 6-h trial.

Methods

Participants

Twelve amateur male cyclists, aged 26±6 years (range 19-37 years), with a height of 175±5 cm, weight of 71±8 kg, and VO_{2MAX} of 55±9 $ml.kg^{-1}.min^{-1}$ were recruited from two local cycling clubs through an open invitation. Participants had a minimum of 1 year of experience (10±7 years) and trained an average of 13±13 h per week for 1 month before the study. None of the participants had any personal history of cardiovascular disease and all had a normal resting 12-lead electrocardiogram (ECG) results. All of the cyclists provided written informed consent. The procedures used in this study completely 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 three visits to the laboratory. During the first laboratory visit, a baseline ECG (PC-ECG 1200, Norav, Yokneam, Israel) was recorded along with anthropometric measurements and data from a personal questionnaire, which included information on personal characteristics, training history and cardiac symptoms history.

Initially, subjects performed an incremental exercise test on a cycle ergometer (Ergoselect, Cosmed, Italy) to evaluate VO_{2MAX} and HR_{MAX}. Briefly, this test consisted of a stepwise protocol of 50-watt increments every minute with a constant cycling cadence of 60-65 rpm. The incremental test continued until exhaustion or until the cadence was not maintained. Ventilatory data were recorded continuously using an automated online metabolic cart (Quark PFT, Cosmed, Italy). HR was recorded continuously at 5-s intervals using a monitor (Polar Electro Oy, Kempele, Finland). The $VO2_{MAX}$ and HR_{MAX} were recorded as the highest 10-s average values of O2 uptake and HR, respectively, during the test. In the final two visits, subjects performed 1- and 6-h cycling exercise trials in a randomized order. In both exercise trials, subjects were instructed to perform the maximum possible intensity. The two trials occurred at the same time of day (09:00 am) and were separated by a period of at least 72 h, during which the subjects were instructed to abstain from all training activities. The cycling tests were performed on a cycle ergometer (Ergoselect, Cosmed, Italy) in an air-conditioned sports hall with the temperature and relative humidity set at 20 °C and 45%, respectively. 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 $\%HR_{MAX}$ determined from the prior incremental exercise test. The distance covered on each test was recorded every 10 min. Immediately after the test was completed, the participants provided their rating of perceived exertion (RPE).[15]

Venous blood samples were taken before exercise, immediately after exercise (0 h), and 1, 3, 6, 12, and 24 h after exercise to assess the serum hs-cTnT concentration. In the 6-h trial, hs-cTnT was also evaluated every hour during exercise. For each sample, 5 ml of venous blood were drawn from the antecubital vein using venous puncture with subjects in a sitting position. The blood was allowed to clot at room temperature. The clotted blood was then centrifuged at 2,000 g for 20 min. Serum was drawn and stored at -80 °C for later analyses of hs-cTnT. Levels of hs-cTnT were measured quantitatively with a new high-sensitivity enzyme immunoassay based on electrochemiluminescence technology using a Cobas E 601 analyzer (Roche Diagnostics, Penzberg, Germany). This assay has a range from 3 to 10 000 ngL^{-1} with a lower limit (blank) of 3 ngL^{-1}. The intra-assay coefficient of variation at a mean hs-cTnT level of 13.5 ngL^{-1} was 5.2%. Before the assays were performed, the analyzers were calibrated with standard calibrators according to the manufacturer recommended protocols. The upper reference limit (URL) for hs-cTnT, defined as the 99th percentile of healthy participants, was 14 ngL^{-1}.[16]

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY, USA). Cohort data are presented as the mean ± standard deviations unless otherwise stated. After Shapiro–Wilk analysis, the raw data for hs-cTnT were log-transformed to achieve a normal distribution prior to inferential statistical testing. The baseline data before each trial and the exercise data were compared using repeated-measures analysis of variance (ANOVA). To determine the impact of sampling time (pre-exercise, 0 h, 1 h, 3 h, 6 h, 12 h and 24 h after exercise) and test duration (1 h and 6 h) on hs-cTnT, we employed repeated-measures two-way ANOVA with post hoc Bonferroni correction when approriate. The delta score (baseline to peak postexercise values) was compared between exercise trials by repeated measures one-way ANOVA. This analysis was also performed by establishing the $\%HR_{MAX}$ obtained in both

exercise trials (1 and 6 h) as a covariate. The associations between the increase in hs-cTnT (peak postexercise value minus the baseline value) during the two exercise bouts and other relevant variables (e.g., baseline biomarker concentration, mean HR and $\%HR_{MAX}$) were assessed using bivariate Pearson's product-moment correlation coefficients. $p<0.05$ was considered to indicate statistical significance.

Results

Exercise test data

All cyclists completed the study. No subjects reported cardiac symptoms during or after exercise. The principal performance results are reported in Table 1. The mean exercise power, mean HR, and $\%HR_{MAX}$ were highest during the 1-h trial. No differences were observed in the RPE between trials.

****Insert Table 1 approximately here****

hs-cTnT release

No significant difference was observed in baseline hs-cTnT between the exercise trials ($p=0.651$). A significant main effect of sampling time was observed for hs-cTnT ($p=0.000$). In the 1-h trial, hs-cTnT was elevated at 0, 1, 3, 6, 12 and 24 h postexercise compared with that at baseline. In the 6-h trial, hs-cTnT was elevated at 0, 1, 3, 6, and 12-h postexercise compared with that at baseline (Table 2). Levels of hs-cTnT exceeded the URL in 83% and 42% of the participants in the 1- and 6-h trials, respectively (Figure 1).

****Insert Table 2 approximately here****

****Insert Figure 1 approximately here****

A main effect of exercise duration on the release of hs-cTnT in response to exercise (p=0.020) was observed. The hs-cTnT values at 1 and 3 h postexercise were significantly greater in the 1-h trial than in the 6-h trial. In support of this, the maximal increase in hs-cTnT (peak–baseline) was significantly greater in the 1-h trial than in the 6-h trial (p=0.023). This difference was not significant when controlling for $\%HR_{MAX}$ (p=0.182). In 75% of the subjects, the peak value of hs-cTnT was greater in the 1-h trial.

In the repeated-measures two-way ANOVA analysis, a significant interaction effect was observed between sampling time and exercise duration on postexercise hs-cTnT values (p=0.000). In the 1-h trial, the maximum postexercise hs-cTnT values were observed at 3 h in all subjects. In the 6-h trial, the maximum postexercise hs-cTnT values were observed at 0 h for 1 individual, 1 h for 1 individual, 3 h for 2 individuals, 6 h for 3 individuals, and 12 h for 1 individual. In this test, evidence of increased hs-cTnT during or after exercise in 4 subjects was not observed. At 24 h postexercise, one subject had hs-cTnT levels exceeding the URL. In the 1-h trial, the hs-cTnT values at 3 h postexercise were significantly greater than those observed during the remainder of the sampling time. No significant differences were observed in hs-cTnT values in the 6-h trial during the first 12 h postexercise, although these values were greater than those observed during exercise.

In the 1-h trial, the maximum postexercise hs-cTnT values correlated significantly with the baseline hs-cTnT values (r=0.698), hours of cycling training per week in the last month (r=0.583), mean HR (r=0.842), and $\%HR_{MAX}$ (r=0.906). In the 6-h trial, the maximum postexercise hs-cTnT values were correlated with the mean HR (r=0.740) and $\%HR_{MAX}$ (r=0.735). The basal hs-cTnT levels in the 1- and 6-h trials were correlated (r=0.782). Between the two trials, we did not observe a correlation in peak postexercise hs-cTnT values.

Discussion

To our knowledge, this is the first controlled repeated-measures study comparing the detailed kinetics of hs-cTnT between all-out short- and long-duration endurance trials. The main findings are as follows: 1) a single 1- or 6-h bout of all-out cycling resulted in a significant increase in hs-cTnT in amateur cyclists; 2) substantial individual variability was noted in peak hs-cTnT during recovery, with higher values in the 1-h trial than in the 6-h trial; 3) there were differences between both exercise trials in the kinetics of the increase in hs-cTnT during the 24 h postexercise period, with peak values occurring at 3 h in the 1-h trial and comparable values ocurring during the first 12 h in the 6-h trial; 4) in the 6-h trial, hs-cTnT values during exercise were lower than those observed postexercise.

Our results support the findings of previous studies showing that hs-cTnT is released after short- and long-duration exercise bouts.[11,17] Short-duration exercise can be very intense, but the energy expenditure and total external work are small compared to that of long-duration exercise, suggesting that despite different cardiac workloads, maximal-effort exercise bouts induce the release of hs-cTnT. Consistent with the findings of other studies,[17,18] the present study showed that compared with baseline values, hs-cTnT was elevated in all subjects after the 1-h trial and in the majority of subjects after the 6-h trial; however, in the present study, a larger percentage of participants exceeded the URL. Despite this difference, our findings confirmed a marked individual variability in hs-cTnT release in response to exercise.[17,19] In both exercise trials, this variability could be explained in part by differences in the $\%HR_{MAX}$ between the subjects, suggesting that the release of hs-cTnT during exercise is greater in subjects who are usually capable of maintaining higher $\%HR_{MAX}$ values for specific durations of effort. In this context, our results also showed that differences in the $\%HR_{MAX}$ between both exercise trials significantly influenced hs-cTnT release. Previous studies also demonstrated that working at a greater relative exercise intensity was associated with greater cTn release.[20,21]

Interestingly, although the subjects were instructed to perform the maximum possible intensity, the increase in hs-cTnT was greater in the 1-h trial than in the 6-h trial. This finding suggested that the magnitude of cTn release is more significantly associated with absolute exercise intensity than with extended duration.

Our current findings seem to be in agreement with a report showing that cTnI concentrations measured after high-intensity cycling (1 h at 80%−90% of the lactate threshold) were significantly greater than those measured after moderate-intensity cycling for a longer duration (4 h at 60%−70% of the lactate threshold).[9] In our laboratory, trials with a fixed duration (45, 80 and 180 min) and intensity (85%−95% of the individual anaerobic threshold) were used to demonstrate that higher-intensity longer-duration exercise induces an increase in cTnI levels.[10] However, the relationship between cTn release and exercise duration remains controversial, with inconsistent results among different meta-analyses.[2,22,23,24] Among other factors, combining data from multiple race distances may have yielded different results because of the interaction between exercise duration and intensity. In support of this, a meta-analysis showed that completing a marathon induces greater cTn release than completing a half-marathon or ultramarathon.[22] In a mechanistic study, we proposed that there may be an exercise-intensity threshold at which cTn release becomes more marked,[25] and this has been supported in field-based studies.[20,26] Taken together, these findings suggest that the relationship between the intensity-duration domain of exercise and cTn release is potentially parabolic. Thus, because of the duration of exercise, in the 6-h trial, the relative intensity of the cyclists was not high enough to induce a greater increase in hs-cTnT. These points require further study.

While there is evidence of heterogeneity in the magnitude of hs-cTnT release in response to exercise, in the 1-h trial, the overall kinectics of hs-cTnT throughout the 24-h recovery period were consistent across all subjects. The data reflect a rapid increase in hs-cTnT in the early hours of recovery, with all subjects reaching a peak at 3 h, followed by an almost complete recovery to baseline levels at 24 h. These findings coincide with the hs-cTnT kinetics reported in previous

studies involving short-duration high-intensity exercise.[11,19] This is the first study to establish comprehensive data on hs-cTnT kinetics within the first 24 h of completing a 6-hour exercise bout. Our results demonstrate that, unlike those of the 1-h trial, the overall kinetics of hs-cTnT release in response to the 6-h trial exhibit a degree of individual heterogeneity. Whether this difference can be associated with between-subject differences in pacing strategy requires future research. Interestingly, in the 6-h trial, no significant differences were observed in hs-cTnT values across the first 12 h postexercise. This finding is somewhat consistent with the findings of a few previous studies showing that a marathon and a cycling race (approximately 4 h) induced comparable hs-cTnT values during the first 3-4 h of recovery and that most subjects obtained the peak value within the first hour after the race.[13,27,28] This finding suggested that the hs-cTnT peak occurs earlier during long-duration exercise than during short-duration exercise. Therefore, the duration of exercise seems to be the most important comparative factor, allowing more time for cTn levels to increase before postexercise measurements are taken.

In this study, we focused on hs-cTnT release during exercise. Previously, in an interesting study that was limited by assay precision, Middleton *et al*.[14] attempted to describe cTnT kinetics during and after a laboratory treadmill-based marathon. Although the data showed that cTnT increased during marathon running, cTnT then returned to baseline before the end of activity. Additionally, participants demonstrated a biphasic release pattern, with peak values returning 12–24 h postrace. Our data do not support a biphasic release of cTnT during exercise. In contrast, in our study, the mean hs-cTnT concentration tended to increase during the 6-h trial. In field-based studies, the information is limited to two reports that determined troponin levels at two intermediate points in an ultramarathon. Researchers have observed a progressive increase in cTnT with running distance.[29,30] A progressive increase in hs-cTnT during the initial hours of prolonged exercise seems reasonable if we consider that after short-duration high-intensity exercise (e.g., 1 h), the hs-cTnT peak was observed at 3 h postexercise in this study and in

others.[11,19] However, additional research is needed to understand changes in cTn levels during exercise.

Importantly, despite the differences in kinetics between both exercise trials, compared with baseline values, hs-cTnT was elevated in all subjects after the 1 h-trial and in the majority of subjects after the 6-h trial. The relatively low levels of hs-cTnT, the short time to peak, and the return to near-baseline levels within 24 h that were demonstrated in this and other studies[13,31] are somewhat different from the hs-cTnT kinetics observed in patients with AMI.[3] An increase in hs-cTnT was shown to occur in the absence of clinical signs and symptoms. Furthermore, greater values of hs-cTnT seem to be associated with individuals who are capable of maintaining effort at a higher $\%HR_{MAX}$. Although an elevated value of hs-cTnT reflects a myocardial "injury," it does not elucidate the cause of release: the increase in hs-cTn may indeed be a consequence of a preload-induced mechanical stretch or of other "physiological" stressors acting on otherwise normal hearts. Various pathophysiological mechanisms have been suggested for the release of cTn from the myocardium, including normal turnover of myocardial cells, apoptosis, cellular release of cTn degradation products, increased cellular wall permeability, the formation and release of membranous blebs, and myocyte necrosis.[1,32] Unfortunately, to date, the exact mechanism is unknown.[1,32] The clinical importance of our findings, therefore, is likely related to whether the athlete has elevated cTn levels after training or competition. Clearly, appropriate follow-up of any elevated cTn result is important, but prior exercise must also be recognized as a key component.

As a limitation, we studied only a relatively small sample of adult male cyclists; thus, the generalizability of the data is limited. Likewise, our findings and their clinical impact cannot be directly extrapolated to the effects of different exercise tests. The evaluation of other cardiac biomarkers, such as cTnI, could be of interest in future studies. We do not use imaging methods after the increase beyond URL of hs-cTnT. This has been done in previous studies but no

evidence of link between raised cTn with exercise and any imaging index of cardiac structure and function.[1]

In conclusion, our results with young male participants showed that a 1-h cycling trial induced greater hs-cTnT release than a 6-h cycling trial. Our data also suggest that the kinetics of exercise-induced changes in hs-cTnT levels are likely dependent on both exercise intensity and duration. This approach is valuable for assessing hs-cTnT in a clinical environment when the subject has recently performed a bout of exercise.

Practical Implications

- Clinicians should know that in young male participants, hs-cTnT release is common after high-intensity short-duration exercise (1 h) and after very prolonged exercise (6 h), with higher values expected in short duration exercises in which the athlete can perform a greater relative intensity.
- Clinicians should also consider that in very prolonged exercise typically characterized by low relative intensity, hs-cTnT values in young male participants are usually relatively stable during the first hours of recovery, and particularly high values are not expected during exercise. In contrast, in short-duration high-intensity exercise, a rapid increase in hs-cTnT should be expected in the early hours of recovery, with peak values typically ocurring at 3 h.
- These findings also have important implications when repeated blood sampling is not possible and for the future design of studies evaluating the influence of exercise intensity and duration on the exercise-induced cTn response.

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Table 1. Performance characteristics by exercise trial.

	Mean exercise power (w)	Mean HR (beats.min^{-1})	%HR_{MAX}	RPE
1-h trial	200±39* (156-291)	165±12* (139-180)	91±6* (79-98)	17±2 (14-20)
6-h trial	149±23 (119-190)	140±11 (120-155)	77±7 (65-87)	18±2 (13-20)

RPE, ratings of perceived exertion.

Data are expressed as the means ± SDs (ranges).

*Significantly different from the 6-h trial.

Table 2. Levels of hs-cTnT before, during and after the exercise trials.

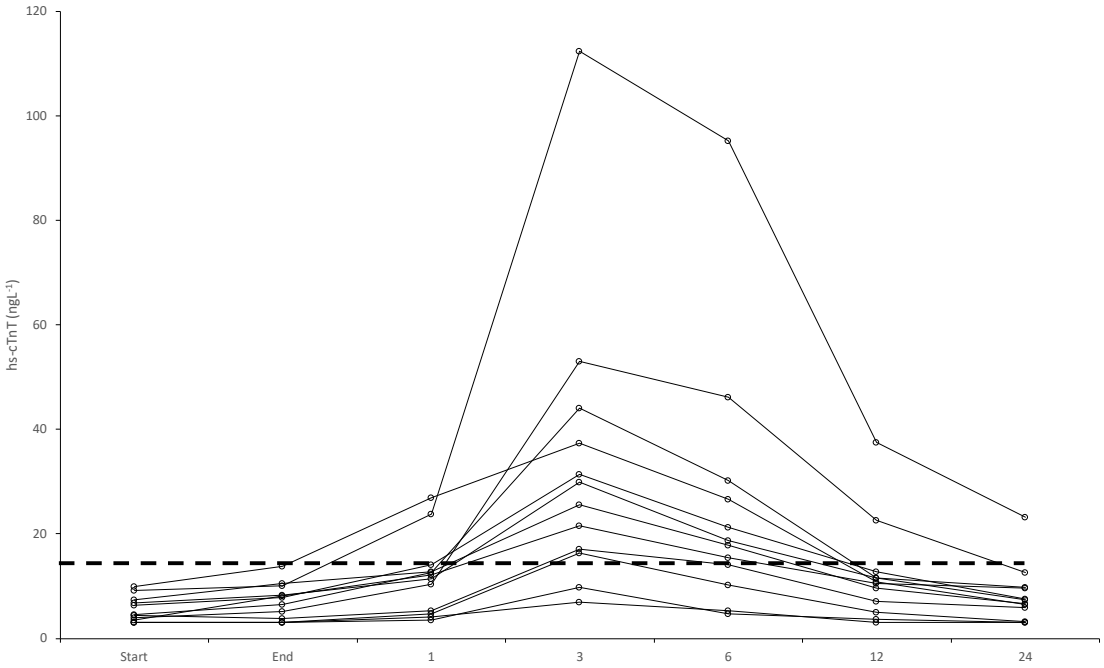
	1-h trial	6-h trial	ANOVA *p* Values
Pre-exercise	4.5 (3.2-7.2) [0]	4.2 (3.0-8.2) [0]	
During exercise			
1 h	-	4.2 (3.0-8.1) [0]	
2 h	-	4.5 (3.8-8.2) [0]	
3 h	-	5.4 (3.8-8.8) [0]	
4 h	-	4.8 (4.1-9.8) [8]	Time 0.000
5 h	-	6.2 (4.2-11.6) [17]	Trial 0.020
Post-exercise			Time x trial 0.000
0 h	7.2 (3.3-9.7) [0]	6.3 (4.9-13.7) [25]	
1 h	11.8 (4.8-13.8) [25]	7.2 (5.4-16.5) [25]	
3 h	27.7 (16.5-42.4) [83]	9.6 (5.8-17.6) [25]	
6 h	18.3 (11.2-29.3) [75]	8.7 (5.9-16.1) [33]	
12 h	10.7 (5.5-12.5) [17]	7.6 (4.7-13.1) [17]	
24 h	7.0 (3.9-9.7) [8]	4.6 (3.2-7.0) [0]	

Data are presented as medians (25th and 75th percentiles). Values in brackets are the percentages of subjects with hs-cTnT exceeding the upper reference limit.

Figures

Figure 1. Individual data points for hs-cTnT (ngL^{-1}) release during (min) and after (h, postexercise) completion of 1- *(a)* and 6-h *(b)* cycling trials. The horizontal dotted line is the URL (99th percentile) at 14 ngL^{-1}.

(a)



(b)