Impact of high-intensity interval training and moderate-intensity continuous training on resting and post-exercise cardiac troponin T concentration

Jinlei Nie[1], Haifeng Zhang[2], Zhaowei Kong[3], Keith George[4], Jonathan P. Little[5], Tomas K. Tong[6], Feifei Li[2], Qingde Shi[1]

[1]School of Physical Education and Sports, Macao Polytechnic Institute, Macao

[2]College of Physical Education, Hebei Normal University, Hebei, China

[3]Faculty of Education, University of Macau, Macao

[4]Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK

[5]School of Health and Exercise Science, University of British Columbia, Kelowna, Canada

[6]Dr. Stephen Hui Research Centre for Physical Recreation and Wellness, Department of Physical Education, Hong Kong Baptist University, Hong Kong, China

Address for Correspondence:

Dr. Jinlei Nie

School of Physical Education and Sports, Macao Polytechnic Institute, Rua de Luis Gonzaga Gomes, Macao, China

Tel: +853-8559 6832

Fax: +853-2851 8538

E-mail: jnie@ipm.edu.mo

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What is the central question of this study?

Does exercise training impact resting and post-exercise cardiac troponin T (cTnT) concentration?

What is the main finding and its importance?

This randomized controlled intervention study demonstrated that 12 weeks of either high-intensity interval training or moderate-intensity continuous training largely abolished the exercise-induced elevation in cTnT when exercise was performed at the same absolute intensity. There was no impact of training on resting cTnT or post-exercise cTnT appearance when exercise was performed at the same relative intensity. These findings provide new information that may help clinicians with decision-making in relation to basal and post-exercise values of cTnT in individuals with different training status.

Abstract

We evaluated the influence of 12 weeks high-intensity interval training (HIIT, repeated 4-min cycling at 90% $\dot{V}O_{2max}$ interspersed with 3-min rest, 200-300KJ/session, 3–4 days/wk) and work-equivalent moderate-intensity continuous training (MICT, continuous cycling at 60% $\dot{V}O_{2max}$) on resting cardiac troponin T (cTnT) as well as exercise-induced cTnT appearance. Forty-eight sedentary obese young women were randomly assigned to HIIT, MICT, or a control group. $\dot{V}O_{2max}$ and body composition were measured before and after training. At baseline, cTnT was assessed using a high-sensitivity assay at rest and immediately, 2 h and 4 h after 45-min cycling at 60% $\dot{V}O_{2max}$. After a 12-wk training period, cTnT was assessed before and after 45-min cycling at the same relative and absolute intensities as before training. Training led to higher $\dot{V}O_{2max}$ and lower fat mass in both HIIT and MICT (all $P < 0.05$). Before training, cTnT was significantly elevated in all three groups (35 to 118%, all $P < 0.05$) with acute exercise. After training both resting and post-exercise cTnT levels (same relative intensity) were similar to pre-training values. In contrast, post-exercise cTnT (same absolute intensity, which represented a smaller exercise stimulus) was not elevated from rest in both HIIT and MICT groups. In conclusion, 12 weeks of either HIIT or MICT largely abolished the elevation of post-exercise cTnT concentration when exercise was performed at the same *absolute* intensity. There was, however, no impact of training on resting cTnT or post-exercise cTnT appearance for exercise performed at the same *relative* intensity.

Key words: High-intensity interval training; Moderate-intensity continuous training; Cardiac biomarker

Introduction

The elevation of cardiac troponin (cTn, cTnT and/or cTnI) in the bloodstream is a highly sensitive and specific marker for cardiac injury and serves as a key biomarker in the diagnosis of acute myocardial infarction (Wu *et al.*, 1999). With the introduction of high-sensitivity assays cTn concentrations are now detectable in apparently healthy subjects (Daniels, 2013). This has expanded the role of cTn from acute cardiac care to risk stratification and prognostic medicine in the general population (Daniels, 2013). Minimally elevated basal cTn, even at concentrations below the 99th percentile of a healthy reference population, are associated with an increased risk of adverse cardiac events in the general population including young people (Daniels, 2013) and have consequently emerged as intervention targets (Januzzi, 2016).

Low cardiorespiratory fitness (CRF) and obesity are known to be two strong and independent predictors for risk of cardiovascular disease, mortality and morbidity (Lavie *et al.*, 2014). As such, improving CRF and/or reducing adiposity may be an effective strategy to reduce overall cardiovascular risk and this could be associated with changes in cTn. Indeed, Florido *et al*. (Florido *et al.*, 2017) have recently reported in an epidemiological study that physical inactivity was associated with higher cTnT concentrations and that there was a significant interaction with obesity status such that obese individuals with low physical activity had the highest concentrations of basal cTnT. It is therefore of interest to examine how different exercise interventions, which can increase CRF and reduce adiposity, might impact basal (resting) cTn concentrations in obesity.

Observational studies have reported an inverse association between physical activity and resting cTn concentrations in aged populations (deFilippi *et al.*, 2012; Florido *et al.*, 2017). To date the limited evidence linking training status and resting cTn from randomized longitudinal training interventions is inconsistent. DeFilippi *et al.* (deFilippi *et al.*, 2016) reported that completion of a supervised physical activity program resulted in a small increase in resting cTnT in an elderly population, but two other studies showed that the training had no effect on resting cTnT (van der Linden *et al.*, 2014; van der Linden *et al.*, 2015). An insufficient training stimulus due to the light exercise load adopted in the elderly subjects and lack of CRF data in the three studies (van der Linden *et al.*, 2014; van der Linden *et al.*, 2015; deFilippi *et al.*, 2016) make it difficult to interpret the effect of exercise training interventions on basal cTn.

Recently, scientific literature is replete with observations of elevated cTn during and after acute exercise in apparently healthy populations (Gresslien & Agewall, 2016). Empirical evidence for underlying mechanisms in humans is absent but it has been suggested that exercise-induced changes in cTn may be related to cardiomyocyte membrane "injury" or subclinical myocardial ischemia during exercise (Shave *et al.*, 2010). Further, there is, to date, no consensus as to the clinical relevance of such findings (Gresslien & Agewall, 2016).

An important part of exploring the cTn response to exercise is understanding the association between training status and the amplitude of cTn concentrations. This information may be useful for clinicians when interpreting an exercise-associated cTn elevation in individuals with different training status. Based on cross-sectional studies the impact of training status on post-exercise cTn appearance is equivocal. We (Nie *et al.*, 2011a) and others (Gresslien & Agewall, 2016) have reported that individuals with less training experience had a greater cTn appearance consequent to acute exercise. In contrast, some studies show no association between training status and exercise-induced cTn appearance (Middleton *et al.*, 2006; Jassal *et al.*, 2009). These discrepancies may be largely based on the limitations associated with cross-sectional studies and the lack of control in field-based competitive studies. To the best of our knowledge, Legaz-Arrese *et al.* (Legaz-Arrese *et al.*, 2015) is the only study to employ a randomized controlled intervention trial to investigate the effects of training on the appearance of cTnT following acute exercise. These authors noted that endurance training resulted in higher post-exercise values of cTnT. However, the use of an “all-out” running “time trial” before and after training confounded the interpretation as the training intervention improved participants’ fitness.

High-intensity interval training (HIIT) is increasingly popular as an exercise training intervention and meta-analyses have suggested HIIT to be more effective at improving CRF and reducing adiposity compared to moderate-intensity continuous training (MICT) (Weston *et al.*, 2014). Currently, the effects of HIIT on resting and post-exercise cTn appearance have not been investigated.

Consequently, we employed a randomized controlled trial design to investigate the effects of 12-wk HIIT and MICT in young obese female participants, compared with a control (CON) intervention. We evaluated potential changes in resting cTnT and the cTnT response to acute 45-min cycling trials performed at the same relative and absolute exercise intensity as that

completed in a single trial pre-training. Our hypotheses were as follows: 1) training would reduce resting cTnT; 2) training would not alter the cTnT response to exercise at the same relative intensity, but reduce the elevation of post-exercise cTnT at the same absolute exercise intensity, and 3) changes in resting and post-exercise cTnT would be similar with HIIT and MICT.

Materials and Methods

Ethical Approval

All procedures conformed to the latest revision of Declaration of Helsinki, except for registration in a database and were approved by the ethics committee at Macao Polytechnic Institute (protocol no. RP/ESEFD-01/2012). After receiving a thorough briefing, the participants gave their written informed consent to participate.

Participants

Seventy volunteers were publicly recruited through local advertisements to participate in the study. In total, 52 females were eligible according to the following inclusion criteria: 1) age range of 18–25 years; 2) body fat percentage ≥ 35%, which is the obesity cut-off for women (Deurenberg *et al.*, 1998); 3) body weight remained constant (±2 kg) during the past three months; 4) no regular physical activities or exercise training; 5) no history of smoking and 6) no history of hormonal, orthopaedic, or cardiovascular diseases, diabetes, hyperlipidaemia, hypertension and polycystic ovary syndrome, and no current use of prescribed medication (including contraceptive pill). Four eligible participants declined to enter the study for personal reasons; the remaining 48 participants were randomly assigned to one of three groups: HIIT (n=17), MICT (n=15), and CON (n=16). One participant in the HIIT group (discontinued intervention), one participant in the MICT group (discontinued intervention), and three participants in the CON group (did not complete the exercise test) were not included in the final analysis. At the completion of the study, 16 participants from the HIIT group, 14 participants from the MICT group, and 13 participants from the CON group were included in the intervention analysis.

Experimental design and procedures

147 The experimental design is illustrated in Figure 1. Briefly, on the first and second visits to
148 the laboratory, two exercise sessions of 20- and 30-min duration were performed to accustom the
149 participants to cycling and pacing exercise intensity on a cycle ergometer. At least three days
150 later, anthropometric measurements including body composition analysis, as well as the
151 assessment of $\dot{V}O_{2max}$ were completed. On a separate day and after having refrained from
152 strenuous exercise for 48 h, subsequent to a general warm-up, all participants performed an acute
153 45-min exercise bout at an intensity of 60% $\dot{V}O_{2max}$ (PRE60) on a cycle ergometer (Monark,
154 839E, Sweden). This exercise bout represented a typical physical activity session recommended
155 by public health guidelines (e.g. a bout of exercise that, if performed 3-4 days per week, would
156 allow one to accumulate 150 $min.wk^{-1}$ at moderate intensity) (Haskell *et al.*, 2007). Heart rate
157 (HR) was recorded continuously via a Polar HR monitor (Polar Electro Oy, Kempele, Finland).
158 Immediately afterward, the participants rated the test for perceived exertion (RPE, Borg scale 6–
159 20). Venous blood samples were drawn before exercise (Pre-exe), immediately after (0HR) as
160 well as 2 h (2HR) and 4 h (4HR) after the PRE60 to assess serum cTnT. The timing for the post-
161 exercise blood samples were in accordance with our previous work that demonstrated that blood
162 cTnT concentrations peaked within 4 h after exercise in a laboratory-based study (Tian *et al.*,
163 2012).

164

165 Insert Figure 1 here

166

167 After pre-intervention assessments, the HIIT group commenced training with prescribed
168 work of 300 kJ in most training sessions; the MICT group was prescribed exercise during each
169 training session that was matched for total work (details below). The CON group received no
170 training. All participants were asked to maintain their daily activity outside of the study and
171 avoid altering their eating habits during the experimental period.

172 After a 12-wk training intervention (two days after last training session) or control period,
173 anthropometric and $\dot{V}O_{2max}$ measurements were repeated. Two tests were performed in a random
174 sequence in the HIIT and MICT groups: (1) a 45-min cycling trial at the same absolute intensity
175 as in the PRE60 (POST60ABS) and, (2) a 45-min cycling trial at the same relative intensity

corresponding to 60% new $\dot{V}O_{2max}$ obtained following training (POST60REL). In the CON group, only the POST60REL was performed as we expected little change in CRF. All measurements of HR, RPE, and serial cTnT were determined in the same manner as pre-training tests. All exercise tests started at 11:00 and were performed in an air-conditioned laboratory (20°C and 50% relative humidity).

Exercise training

In each training session, the HIIT group participants repeated 4-min exercise bouts on a cycle ergometer (Monark, 839E, Sweden) at an intensity of 90% $\dot{V}O_{2max}$, followed by a 3-min passive recovery until the targeted 300 kJ of work was achieved. By contrast, the MICT group participants performed continuous cycling exercise at an intensity of 60% $\dot{V}O_{2max}$ until the targeted 300 kJ of work was achieved. The pedal frequency was maintained at 60 rpm during each training session in both groups. In each training session, both groups completed an identical 10-min warm-up and 5-min cool down at 50–60% of HR_{max}. For the first four weeks, the participants in the two training groups completed 200 kJ of work (excluding warm-up and cool-down) for one session per day, three days per wk. During the fifth through twelfth weeks, the training frequency was increased to four days per wk, and the total work done in each session was increased to 300 kJ in both groups. All participants exercised with close supervision, and exercise HR and RPE (Borg scale 6–20) were monitored at every training session. Details of the exercise in a single session of HIIT and MICT are shown in Table 1. At the end of the fourth and eighth weeks, the $\dot{V}O_{2max}$ of all participants was determined to readjust the workload corresponding to the pre-set intensity. The training adherence of the participants was calculated as the percentage of the actual number of training sessions completed in compliance with the targeted intensity and duration, relative to the total number of training sessions prescribed.

Insert Table 1 here

Protocol and measurements

Graded exercise test. $\dot{V}O_{2max}$ was determined using a graded cycling exercise protocol that has been described previously (Zhang *et al.*, 2017). The participants began at 50 W with a pedal frequency of 60 rpm; power output was increased by 30 W every 3 min until volitional exhaustion. Oxygen consumption during the exercise test was measured using a Cosmed breath-

by-breath metabolic analyzer (Quark-PFT-ergo, Cosmed, Rome, Italy). $\dot{V}O_{2max}$ was calculated as the highest 30-s average value. Following the graded exercise test, a power output that elicited approximately 60% and 90% $\dot{V}O_{2max}$ in the MICT and HIIT groups, respectively, was selected from the linear relationship of steady-state $\dot{V}O_2$ versus power output.

Body composition measurement. The participants were instructed to refrain from exercise and alcohol consumption for 24 h. Before each test participants underwent a 12-hour overnight food and fluid fast. After voiding, barefoot height was determined using a stadiometer and body mass and composition (fat mass, percent fat and lean body mass) were assessed using multi-frequency bioelectrical impedance with eight tactile electrodes (InBody 720, Biospace Co., Seoul, Korea) (Kyle *et al.*, 2004).

Blood sampling procedures. For each sample, 5 mL of venous blood was drawn from the antecubital vein by venipuncture with the subjects in a seated position. To separate serum, the blood was allowed to clot at room temperature and then centrifuged at 3500g for 20 min. The serum was drawn off and stored at -80 °C for later analyses of cTnT. cTnT was measured quantitatively with a new high-sensitivity 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 $ng.l^{-1}$ with a lower limit of detection of 3 $ng.l^{-1}$. Serum cTnT concentrations that were below the limit of detection are reported as 1.5 $ng.l^{-1}$ (Tian *et al.*, 2012; Kong *et al.*, 2017). The coefficient of variation at a mean cTnT concentration of 13.5 $ng.l^{-1}$ is 5.2%. The upper reference limit (URL) for cTnT, defined as the 99^{th} percentile of healthy participants, was 14 $ng.l^{-1}$ (Giannitsis *et al.*, 2010).

Statistical analysis

The Kolmogorov–Smirnov test was used to evaluate the normality of the data. Non-parametric Friedman's test was used to compare the cTnT across the time points (Pre-exe, 0HR, 2HR, and 4HR) and three intensities because of the skewed distribution of the cTnT data. Wilcoxon signed ranks tests were completed for pairwise comparisons where appropriate. Moreover, cTnT in the HIIT, MICT, and CON groups were compared using the Kruskal–Wallis test, and the Mann–Whitney U test was completed for pairwise comparisons where appropriate. The percentages of subjects with cTnT exceeding the limit of detection of 3 $ng.l^{-1}$ and the URL of 14 $ng.l^{-1}$ at each assessment point were compared using Fisher’s exact test.

A 3 × 2 mixed ANOVA with repeated measures on time was used to examine the changes in $\dot{V}O_{2max}$ as well as body size and compositions across the three groups (HIIT, MICT, and CON) from pre-training to post-training. In addition, a 3 × 3 two-way ANOVA with repeated measures was used to examine the differences in HR_{mean}, HR_{max}, RPE, and $Power_{exe}$ across the three groups (HIIT, MICT, and CON) and three intensities (60% $\dot{V}O_{2max}$ at pre-training, 60% new $\dot{V}O_{2max}$ at post-training, and same absolute intensity as in the pre-training at post-training). *Post-hoc* analyses using Newman–Keuls were performed for cases in which the main effect was significant. Spearman's rank correlation analysis was used to determine the correlation among (1) post-exercise peak cTnT and pre-exercise resting cTnT; (2) pre-training and post-training resting cTnT; (3) pre-training and post-training post-exercise peak cTnT. Statistical significance was assumed at a level of $P < 0.05$. Data analysis was performed using the statistical software package SPSS 20.0 (IBM Corp., Armonk, NY, USA).

Results

Among the participants (n=43) who completed the study, compliance with the exercise intervention was 96% ±3% and 95% ±1% in the HIIT and MICT groups, respectively. No adverse events were reported during testing or training in either group.

Impact of exercise training on participant characteristics and exercise data

Pre- and post-training participant characteristics are presented in Table 2. Both HIIT and MICT led to a similar decrease in body mass, BMI, body fat mass, and percent fat, and a similar increase in $\dot{V}O_{2max}$ (all $P < 0.05$). After the CON period $\dot{V}O_{2max}$ was marginally but significantly reduced (29.6 ±3.7 to 28.1 ±3.5 $ml.kg^{-1}.min^{-1}$, $P < 0.05$). As expected, training led to a significant increase in power output ($Power_{exe}$) in the POST60REL (Table 3). Nevertheless, the exercise data, including HR_{mean}, $\%HR_{max}$, and RPE, in the POST60REL were similar to those in the PRE60 in all subjects, but these variables in the POST60ABS were significantly ($P < 0.05$) lower than those in the PRE60 and POST60REL (Table 3).

Insert Table 2 and Table 3 here

Effect of exercise training on resting and post-exercise cTnT

cTnT data for all groups at rest and after 45-min cycling (PRE60, POST60REL, and POST60ABS) are presented in Table 4 and as individual data points in pre-exercise and peak post-exercise in Figure 2. The HIIT and MICT interventions had no effect on resting cTnT concentrations or the number of participants presenting with a cTnT exceeding the limit of detection of 3 $ng.l^{-1}$ or the URL of 14 $ng.l^{-1}$. cTnT increased ($P < 0.05$) after the PRE60 and POST60REL in the three groups, with substantial variability in individual post-exercise data. After POST60ABS post-exercise cTnT concentrations and positive rates were no different to rest in both the HIIT and MICT groups ($P > 0.05$).

Insert Table 4 and Figure 2 here

The post-exercise concentrations of cTnT in the CON group after the 12-wk control period elapsed were higher than those in the two training groups, as well as those in the CON group at pre-intervention (all $P < 0.05$). Accordingly, the POST60REL also led to a significant ($P < 0.05$) increase in number of participants presenting with an cTnT exceeding the URL (0 to 46% [6 of 13]) in the CON group. When all subjects were combined, peak post-exercise cTnT after the PRE60 and POST60REL were not associated with pre-exercise cTnT (r=0.110 and 0.044, both $P > 0.05$). Nevertheless, the pre-exercise resting concentrations were strongly correlated among the three bouts of 45-min exercises (i.e. PRE60 vs. POST60REL, r=0.563; PRE60 vs. POST60ABS, r=0.810; POST60REL vs. POST60ABS, r=0.903, all $P < 0.05$). Further, the between pre- and post-training correlation for peak cTnT of post-exercise at the same relative intensity (i.e. PRE60 vs. POST60REL) was also significant (r=0.331, $P < 0.05$).

Discussion

The main findings of this study are that in young females with obesity 1) a single 45-min bout of cycling at 60% $\dot{V}O_{2max}$ resulted in a significant increase in cTnT with substantial variability in individual post-exercise data, 2) 12 weeks of HIIT or MICT program substantially improved CRF and reduced body fat mass, 3) training did not alter resting cTnT or the cTnT response to exercise at the same relative intensity, but 4) training largely abolished the elevation of post-exercise cTnT at the same absolute exercise intensity, which represented a smaller exercise stimulus.

Effect of exercise training on resting cTnT

In the current study, the prevalence of resting cTnT over the assay detection limit of >3 ng.l^{-1} was 77% (33 of 43). In a multi-ethnic population-based study, using the same high-sensitivity assays, the prevalence of resting cTnT above the limit of detection (3 ng.l^{-1}) was 25% (de Lemos *et al.*, 2010). This between-study difference is presumably due to the larger proportion of obese individuals in our population as obesity may be associated with higher resting cTn concentrations in the general population (Daniels, 2013). We observed no evidence for an effect of 12 weeks of HIIT or MICT on the positive rate and concentration of cTnT under resting conditions in the previously sedentary individuals, despite the favorable effects on CRF and body composition. In two recent randomized longitudinal resistance training studies in frail participants aged older than 65 years (van der Linden *et al.*, 2014; van der Linden *et al.*, 2015), there was no effect on resting cTnT despite favourable training effects on strength. Our current work extends this to HIIT and MICT in young individuals. In contrast, Legaz-Arrese *et al.* (Legaz-Arrese *et al.*, 2015) reported that a controlled endurance training intervention resulted in higher resting values of cTnT in young healthy participants. The reason for these discrepancies is not clear. Whether uncontrolled potential confounders, such as diurnal rhythm (Klinkenberg *et al.*, 2014) and mental stress (Eggers *et al.*, 2013) may have influenced resting cTnT concentrations requires further investigation.

hs-TnT concentrations after acute exercise

When all groups were combined, we observed that most of our participants (88%, 38 of 43) demonstrated an increase in cTnT after exercise at 60% $\dot{V}O_{2max}$, but only 12% (5 of 43) of them exceeded the URL (14 ng.l^{-1}). The prevalence (12%) is lower than that (83%) from a meta-analysis (Sedaghat-Hamedani *et al.*, 2015) that used the same high-sensitivity assays. Given that a higher cardiac load likely results in a larger cTnT elevation (Fu *et al.*, 2009), the findings are not surprising, as the total myocardial work undertaken in the present study was low when compared to previous studies that employed endurance tasks over many hours, days, and even weeks (Gresslien & Agewall, 2016). In addition, Ranjbar *et al.* (Ranjbar *et al.*, 2017) employed a similar moderate-intensity aerobic exercise (40 min duration) in sedentary non-obese males and reported similar cTnT elevation data to the current study. In combination, this suggests that the exercise-induced elevation of cTnT may occur even after a typical bout of physical activity

recommended by public health guidelines (Haskell *et al.*, 2007) and that cTnT elevations are not exclusive to an ultra-endurance effort.

The observation that cTnT elevation after acute exercise is quite variable among individuals (see Figure 2) is important to note and this supports data from our laboratory (Nie *et al.*, 2011b; Nie *et al.*, 2011c; Tian *et al.*, 2012) as well as others' (Legaz-Arrese *et al.*, 2015). The factors that influence the between-subject variability could not be explained in our data by exercise mode, duration, intensity, time of day, environment, or pre-exercise basal cTnT concentrations (Gresslien & Agewall, 2016). Despite the high between-subject variability, we observed within-subject consistency in peak cTnT concentrations post-exercise at the same relative intensity over a 12-wk HIIT or MICT. This confirms and extends the work of Legaz-Arrese *et al.* (Legaz-Arrese *et al.*, 2015), in which peak post-exercise concentrations of cTnT correlated between two bouts of exercise at self-selected "all-out" intensity before and after 14-wk of MICT. These findings support the notion that the post-exercise cTnT do not increase randomly but maybe accentuated in certain "susceptible" individuals (Tian *et al.*, 2014). Future studies should determine the causes of the high between-subject variability in quantitative exercise-induced cTn elevation.

The underlying mechanism(s) contributing to exercise-induced cTnT elevation remains unclear, as no direct mechanistic evidence is available in humans. Nevertheless, our recent animal studies (Nie *et al.*, 2010; Nie *et al.*, 2016) support the notion that an increase in the production of reactive oxygen species could lead to a reversible membrane "insult" and hence transient leakage of cytoplasmic cTn from cardiomyocytes. Moreover, using a remote ischemic preconditioning model in healthy individuals, Cocking *et al.* (Cocking *et al.*, 2017) recently provided the first indirect human evidence of the role of myocardial ischemia in exercise-induced cTnT elevation, though other potential mechanisms cannot be rule out.

Effect of exercise training on hs-TnT concentrations after acute exercise

We used two different modes of matched-work exercise training, HIIT and MICT, and saw similar effects including improved CRF and reduced body fat mass. The findings are similar to our previous study (Zhang *et al.*, 2015), which used similar HIIT and MICT protocols. The key finding from the current trial was that post-training exercise performed at the same absolute intensity as imposed before training had no effect on cTnT concentrations. Conversely when

post-training acute exercise was performed at the same relative intensity as pre-training similar cTnT appearance kinetics were observed. On first sight, these findings may be controversial, since Legaz-Arrese *et al.* (Legaz-Arrese *et al.*, 2015) noted that an endurance training intervention resulted in higher post-exercise values of cTnT. Of note Legaz-Arrese et al. (Legaz-Arrese *et al.*, 2015) employed an all-out time trial as the acute exercise bout before and after training, and thus a higher relative and absolute exercise intensity of the post-training bout would be expected due to improved fitness and performance; the higher post-exercise values of cTnT after training might be due to the higher exercise intensity. In other words, perhaps the training-induced differences observed in post-exercise values of cTnT would disappear when the intensity is controlled at the same relative level. Intensity has been identified by our group (Fu *et al.*, 2009) and other groups (Legaz-Arrese *et al.*, 2011), as an essential factor in eliciting cTnT elevations following exercise. Our current study adds to the literature in this area of research by distinguishing the roles of absolute and relative intensity. Specifically, our current findings suggest that increased cTnT with exercise is associated with relative exercise intensity but not with absolute intensity.

Training abolished the elevation of post-exercise cTnT at the same absolute intensity. This finding implies that training increased the absolute intensity threshold for the post-exercise cTnT elevations. The reduced myocardial work at the same absolute intensity resulting from the improved CRF, as reflected by lower mean heart rates (before vs. after training: ~146 vs. ~128 beats.min^{-1}), is likely to at least partially explain these findings.

It was somewhat surprising to see higher post-exercise concentrations of cTnT in the CON group after a 12-wk control period elapsed. The fact that the same period was associated with a significant reduction in $\dot{V}O_{2max}$ may be partially responsible. In future studies, it would be important to determine whether more intense and/or a longer training intervention may reduce post-exercise cTn responses at the same relative intensity. In addition, further research should be conducted to assess the clinical significance of a change in the absolute intensity threshold for post-exercise cTnT increases. It may be postulated that a threshold for cTn response to acute exercise may be a better marker for prognostic or risk stratification purposes.

Implications

In the current study, almost all participants presented with an increase in cTnT following exercise at 60% $\dot{V}O_{2max}$ that suggests that an exercise-induced cTnT elevation is largely obligatory and thus physiological. This argument is supported by our recent animal study, which demonstrated that the elevation of cTnT post-exercise was not associated with any electron microscopy-based histological evidence of irreversible cardiomyocyte injury, suggesting a cytosolic release of the biomarker rather than a breakdown of bound contractile proteins (Nie *et al.*, 2016). In addition, none of the participants in the present study had any clinical symptoms indicative of myocardial ischemia during the experiment. This provides further support for a physiological, as opposed to pathological, mechanism responsible for the post-exercise elevation of cTnT.

Based on our current data, when diagnosing AMI and/or undertaking risk stratification, clinicians should be aware that, regardless of a subject's training status, an elevated cTnT is not limited to long-term strenuous exercise. These findings also provide new information that may help clinicians with decision-making in relation to basal and post-exercise values of cTnT in individuals with different training status, e.g. the appearance of large cTnT increase (above URL of 14 $ng.l^{-1}$) in HIIT or MICT training-experienced participants with a recent history of endurance exercise at low relative intensity should raise a potential red flag for further clinical investigation.

Limitations

There are a few limitations that should be considered. The data in the current study pertain only to young, female participants with obesity and as such generalizability of the data is limited. The recruitment of young females is predicated on the relative lack of use of female participants in prior research and the availability of data for analyses of cTnT from a broader study on cardiovascular health in this sample. Further, although we attempted to control for global menstrual cycle health (no oral contraceptive users and no one with menstrual dysfunction) in the female participants we could not constrain testing to specific phases of the menstrual cycle both pre- and post-training. This could have some influence upon resting and post-exercise cTnT concentrations and a specific menstrual cycle phase study would be useful. In addition, we selected previously sedentary subjects in order to get a "clean" training background and preclude the effects of prior training experience. For this reason, our work was limited to assessing the

response of the appearance of cTnT after an exercise of relatively low load that would be achievable in participants (45 min at 60% $\dot{V}O_{2max}$). Thus, though we used high-volume training programs, which may not reflect typical interventions in obese individuals, our results, and their clinical impact, cannot be directly extrapolated to the effects of different acute and chronic exercise exposures. Finally, the current investigation had relatively small samples sizes which may have restricted our ability to detect some group differences in cTnT data. Considering ongoing debate about relative effectiveness of the HIIT and MICT paradigms (Holloway & Spriet, 2015; Wisloff *et al.*, 2015), future research studies with larger sample sizes are required.

Conclusion

In conclusion, a 12-wk HIIT or MICT program in previously sedentary young females with obesity largely abolished the post-exercise elevation of cTnT at the same absolute intensity but had no effects on resting concentrations or the post-exercise cTnT appearance at the same relative intensity. Clinicians should be aware that an elevated cTn can be observed even after a typical bout of endurance-oriented exercise, and training that improves CRF may increase the absolute intensity threshold for the post-exercise cTnT elevation.

Additional information

Conflict of Interest

The authors declare no conflicts of interest.

Author contributions

J.N., H.Z. and K.G. conceived and designed the study; J.N., H.Z., Z.K., K.G., J.L., T.T., F.L. and Q.S. performed experiments and analysed data; and J.N., H.Z., Z.K., K.G. and J.L. drafted the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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587 **Table 1**. Work, power, exercise time, heart rate (HR) and rating of perceived exertion (RPE) of training sessions
588 every four weeks during the 12-wk high-intensity interval training (HIIT) and moderate-intensity continuous training
589 (MICT) intervention. (Data are mean ±SD)

	HIIT（n=16）			MICT (n=14)		
	week 1-4	week 4-8	week 8-12	week 1-4	week 4-8	week 8-12
Work (KJ)	200	300	300	200	300	300
Power (Watt)	114±15	133 ±16	148 ±17	65 ±7	68 ±11	81 ±6
Exercise time (min)	30 ±4	37 ±5	34 ±4	51 ±5	74 ±10	63 ±6
HR (beats.min^{-1})	168 ±13	169±20	164 ±6	141±9	133 ±8	136 ±7
RPE	15 ±1	15 ±2	16 ±1	11 ±1	12 ±1	11 ±2

590 **Table 2**. Pre- and post-training participant characteristics in high-intensity interval training (HIIT), moderate-intensity continuous
591 training (MICT) and control (CON) groups. (Data are mean ±SD)

	HIIT (n=16)		**MICT** (n=14)		**CON** (n=13)	
	Pre-training	Post-training	Pre-training	Post-training	Pre-training	Post-training
Age (yr)	21.0±1.1	-	20.9±1.6	-	20.8±1.1	-
Height (cm)	161.6±6.5	-	159.4±4.7	-	159.6±7.9	-
Weight (kg)	68.9±12.1	65.0±10.2*	68.3±9.5	64.1±7.9*	64.6±6.7	64.2±7.0
Body mass index ($kg.m^{-2}$)	26.3±3.6	24.8±2.9*	26.9±3.0	25.2±2.4*	26.8±4.0	26.7±3.9
Body fat (%)	38.2±2.4	36.3±2.5*	38.7±3.3	37.0±2.5*	40.5±2.1	40.5±2.8
Fat mass (Kg)	26.5±6.1	23.8±5.0*	26.5±5.2	23.8±3.7*	28.9±9.1	28.8±8.6
HR_{max} ($beats.min^{-1}$)	181±13	180±13	177±12	178±12	185±6	187±11
VO_{2max} ($ml.kg^{-1}.min^{-1}$)	30.2±4.4	34.3±4.6*	27.9±3.6	31.7±3.7*	29.6±3.7	28.1±3.6*
VO_{2max} ($ml.kg_{FFM}^{-1}.min^{-1}$)	48.8±6.4	53.9±6.3*	45.5±5.4	50.4±5.7*	50.0±5.0	47.7±5.2*

592 * Significantly different from corresponding Pre-training value, $P<0.05$

593 **Table 3.** Pre- and post-training acute exercise data for a 45-min cycling bout in high-intensity interval training
594 (HIIT), moderate-intensity continuous training (MICT) and control (CON) groups. (Data are mean±SD).

	HR_{mean} (beat.min^{-1})	$\%HR_{max}$	RPE	$Power_{exe}$ (W)
HIIT (n=16)				
PRE60	151±17*	84±7*	17±1*	84±14
POST60REL	148±15*	83±7*	17±1*	116±21*
POST60ABS	129±11	72±6	14±3	84±14
MICT (n=14)				
PRE60	146±19*	82±9*	17±1*	85±15
POST60REL	144±14*	81±7*	15±2*	105±18*
POST60ABS	127±12	72±7	14±2	85±15
CON (n=13)				
PRE60	153±16	83±9	16±2	89±13
POST60REL	154±16	83±7	17±2	88±14

PRE60: pre-intervention exercise at intensity of 60% $\dot{V}O_{2max}$;
POST60REL: post-intervention exercise at the same relative intensity corresponding to 60% new $\dot{V}O_{2max}$
POST60ABS: post-intervention exercise at the same absolute intensity as in PRE60
HR_{mean}, mean heart rate during exercise; $\%HR_{max}$, percentage of individual maximal heart rate during exercise; RPE, rating of perceived exertion at end of exercise; $Power_{exe}$, power output during exercise
* Significantly different from corresponding POST60ABS value, $P<0.05$

595

596 **Table 4.** Pre- and post-training serum high-sensitivity cardiac troponin T (hs-cTnT, ng.l^{-1}) before (Pre-exe),
597 immediately (0HR), 2 (2HR) and 4 (4HR) h after a 45-min cycling bout in high-intensity interval training (HIIT),
598 moderate-intensity continuous training (MICT) and control(CON) groups.

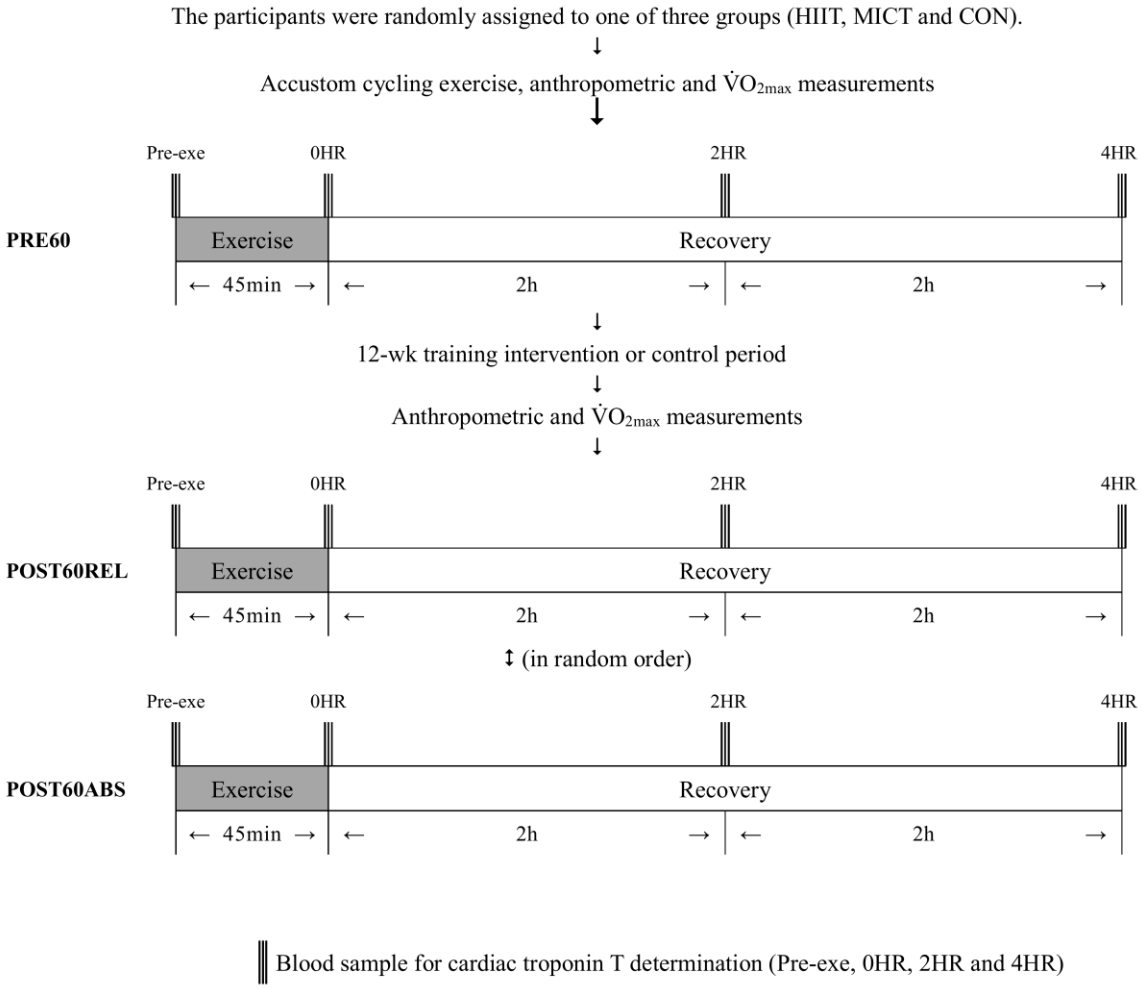
	Pre-exe	0HR	2HR	4HR
Median (Range)				
HIIT (n=16)				
PRE60	3.28 (1.50-4.44)	3.26 (1.50-4.62)	4.69 (1.50-19.36)*†	5.96 (1.50-25.11)*†
POST60REL	3.72 (1.50-6.73)	3.73 (1.50-5.79)	5.35 (1.50-24.82)*†	5.99 (1.50-44.96)*†
POST60ABS	3.72 (1.50-6.96)	3.71 (1.50-4.66)	3.35 (1.50-4.20)*	3.34 (1.50-4.35)*
MICT (n=14)				
PRE60	3.38 (1.50-4.85)	3.63 (1.50-5.08)	4.26 (1.50-11.60)*†	4.48 (1.50-13.36)*†
POST60REL	3.56 (1.50-5.68)	3.59 (1.50-5.17)	4.63 (3.20-25.61)*†	4.59 (3.06-41.88)*†
POST60ABS	3.48 (1.50-5.84)	3.76 (1.50-5.58)	3.50 (1.50-5.35)	3.63 (1.50-6.63)
CON (n=13)				
PRE60	3.52 (1.50-4.03)	3.54 (1.50-4.82)	7.42 (3.65-14.85)*	5.24 (3.59-22.00)*‡
POST60REL	3.67 (1.50-5.19)	3.70 (1.50-4.44)	12.46 (3.93-38.44)*	12.85 (3.36-45.42)*§
Positive Rate 1 / 2 (%)				
HIIT (n=16)				
PRE60	68.8 / 0	68.8 / 0	93.8 / 6.3	93.8 / 12.5
POST60REL	81.3 / 0	81.3 / 0	87.5 / 18.8	87.5 / 18.8
POST60ABS	75.0 / 0	81.3 / 0	62.5 /0	68.8 / 0
MICT (n=14)				
PRE60	78.6 / 0	71.4 / 0	92.9 / 0	92.9 / 0
POST60REL	85.7 / 0	85.7 / 0	100 / 7.1	100 / 7.1
POST60ABS	78.6 / 0	85.7 / 0	85.7 / 0	78.6 / 0
CON (n=13)				
PRE60	84.6 / 0	76.9 / 0	100 / 7.7	100 / 23.1
POST60REL	76.9 / 0	92.3 / 0	100 / 30.8	100 / 46.2*

PRE60: pre-intervention exercise at intensity of 60% $\dot{V}O_{2max}$;
POST60REL: post-intervention exercise at the same relative intensity corresponding to 60% new $\dot{V}O_{2max}$;
POST60ABS: post-intervention exercise at the same absolute intensity as in PRE60;
Positive Rate 1, percentage of subjects with hs-cTnT exceeding the limit of detection of 3 ng.l^{-1};
Positive Rate 2, percentages of subjects with hs-cTnT exceeding the upper reference limit of 14 ng.l^{-1}
* Significantly different from corresponding Pre-exe value, $P<0.05$
† Significantly different from corresponding POST60ABS value, $P<0.05$
‡Significantly different from corresponding POST60REL value, $P<0.05$
§Significantly different from corresponding HIIT and MICT value, $P<0.05$

599

Captions to Figure

Figure 1. Study schematic



PRE60: pre-intervention exercise at intensity of 60% $\dot{V}O_{2max}$

POST60REL: post-intervention exercise at the same relative intensity corresponded to 60% new $\dot{V}O_{2max}$

POST60ABS: post-intervention exercise at the same absolute intensity as in **PRE60**; only was performed in HIIT and MICT groups

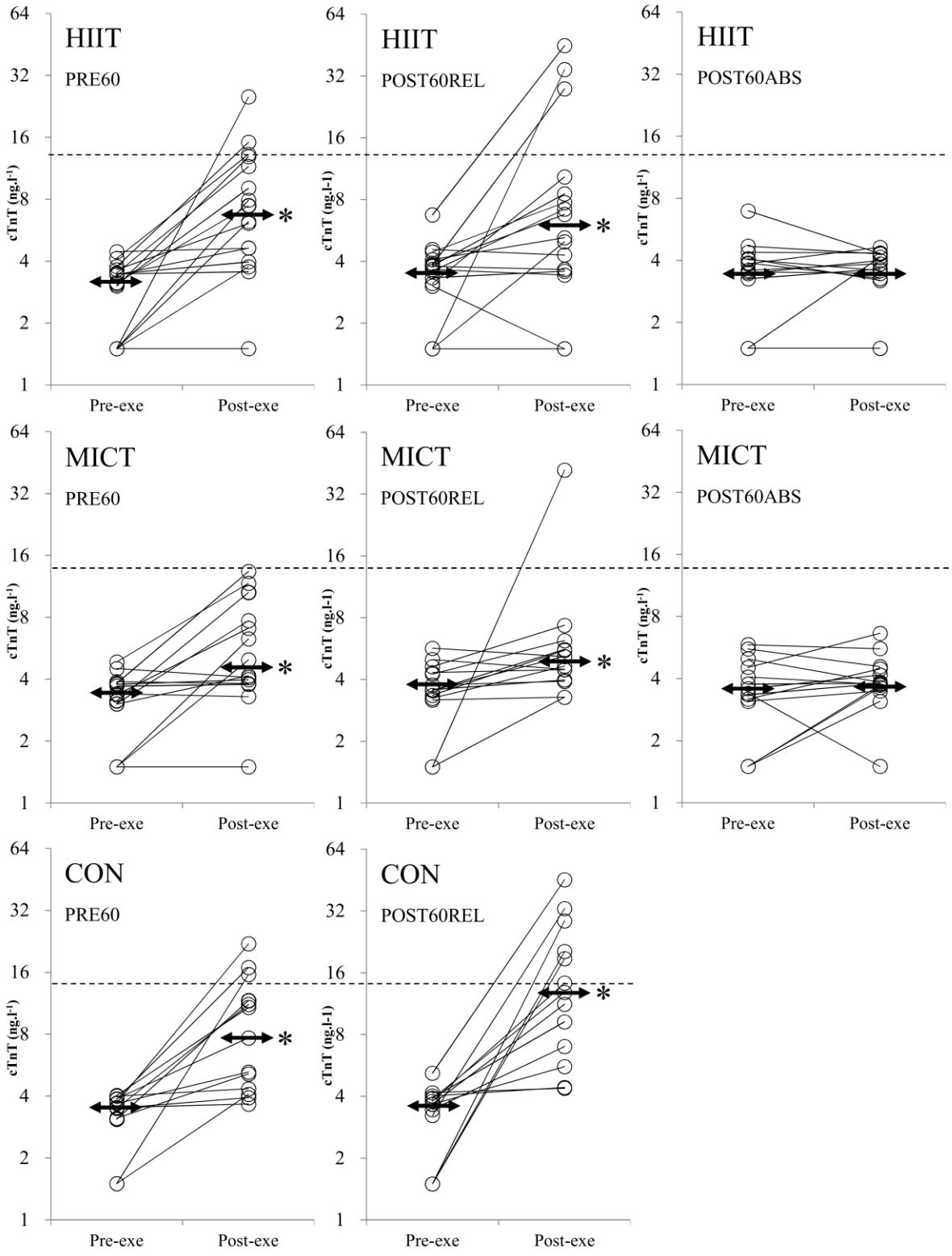
606 **Figure 2**. Pre-exercise (Pre-exe) and peak post-exercise (Post-exe) cardiac troponin T (cTnT,
607 $ng.l^{-1}$) after 45-min cycling in high-intensity interval training (HIIT), moderate-intensity
608 continuous training (MICT) and control (CON) groups assessed before (PRE60) and after
609 (POST60REL and POST60ABS) the 12-wk intervention. Individual data points are presented by
610 circles with values for the same participant connected by lines for each condition.

611 Note: **PRE60**: pre-intervention exercise at intensity of 60% $\dot{V}O_{2max}$; **POST60REL**: post-
612 intervention exercise at the same relative intensity corresponding to 60% new $\dot{V}O_{2max}$;
613 **POST60ABS**: post-intervention exercise at the same absolute intensity as in PRE60

614 Logarithmic scale is plotted due to spread of data. The horizontal dotted line is the 99th
615 percentile value. The double-arrow line is the median of cTnT values at each exercise

616 * Significantly different from corresponding Pre-exe value, $P<0.05$

617


HIIT
PRE60
HIIT
POST60REL
HIIT
POST60ABS
MICT
PRE60
MICT
POST60REL
MICT
POST60ABS
CON
PRE60
CON
POST60REL
cTnT (ng.l-1)
64
32
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Pre-exe
Post-exe
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