Exercise training increases resting circulating cardiac troponin T independent of changes in left ventricular mass

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Conflict of Interest

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Exercise training increases serum cardiac troponin T independent of left ventricular mass

Abstract

The purpose of this study was to determine whether exercise training mediated cardiac troponin T (cTnT) and whether this was associated with increases in left ventricular mass (LVM). Fifty-four sedentary obese women were randomised to high-intensity interval training (HIIT, repeated 4-min cycling at 90% $\dot{V}O_{2max}$ interspersed with 3-min rest), work-equivalent continuous aerobic training (CAT, continuous cycling at 60% $\dot{V}O_{2max}$) or a control group (CON). Resting serum cTnT was assessed using a high-sensitivity assay before and after 12 weeks of training. LVM was determined from 2D echocardiography at the same timepoints. Both HIIT and CAT induced a similar elevation (median 3.07 to 3.76 $ng.l^{-1}$, p <0.05) in resting cTnT compared with pre-training and the CON (3.49 to 3.45 $ng.l^{-1}$, p >0.05). LVM index in HIIT increased (62.2 ±7.8 to 73.1 ±14.1 $g.m^{-2}$, p <0.05), but not in CAT (66.1±9.7 to 67.6±9.6 $g.m^{-2}$, p >0.05) and CON (67.9 ±9.5 to 70.2 ±9.1 $g.m^{-2}$, p >0.05). Training-induced changes in resting cTnT did not correlate with changes in LVM index (r = -0.025, p = 0.857). These findings suggest that twelve weeks of either HIIT or CAT increased resting cTnT, but the effects were independent of any changes in LVM in sedentary obese women.

Keywords: cardiac biomarker, high-intensity interval training, aerobic training, cardiovascular risk factor

Introduction

Cardiac troponin (cTn, cTnT and/or cTnI) is a highly specific marker for cardiac injury and serves as a central biomarker in diagnosing acute myocardial infarction [1]. New high-sensitivity assays for cTn can detect concentrations ten times lower than earlier assays, extending their potential utility to monitoring cardiovascular risk in asymptomatic populations [2]. Minimally elevated basal cTn, even at concentrations below the 99th percentile of a healthy reference population, is associated with an increased risk of adverse cardiac events in the general population, including young people [2]. In contrast, temporal reductions in cTn are associated with relative decreases in clinical events [3]. In addition, growing evidence suggests that cTn levels may decrease in response to lifestyle modifications, so cTn may serve as a useful, dynamic surrogate for monitoring cardiovascular risk [2, 4].

Regular exercise activity is an important component of lifestyle interventions and a proven strategy for cardioprotection [5]. Whether cTn could be used as a biomarker of the change in cardiovascular health risk due to exercise interventions is unclear [6]. Several cross-sectional reports have described lower values of resting cTn to be associated with higher levels of daily physical activity, in large sample sets such as the Dallas Heart Study [7] and the British Regional Heart Study [8]. Conversely, some short-term intervention studies have suggested that structured exercise training can result in increased resting cTn [9] or have no effect on resting cTn [10, 11]. It has been speculated that this apparent paradox may be due to a lack of accounting for increases in heart size (physiological cardiac hypertrophy) with training [9, 12]. Although this speculation is supported by community-based investigations, which suggest that higher resting cTn levels are associated with left ventricular hypertrophy [13, 14], no studies have directly examined the importance of physiological changes in cardiac size with training and their mediating effect on resting cTn levels. This information may be important to determine the true utility of measuring resting cTn when monitoring the beneficial effects of regular exercise on cardiovascular risk.

The purpose of this study was to determine left ventricular mass (LVM) and resting cTnT before and after high-intensity interval training (HIIT) and continuous aerobic training (CAT) in

sedentary obese females. The focus on sedentary obese females was due to the fact that the presentation of obesity, sedentary behaviour and low cardiorespiratory fitness represent important cardiovascular risk factors [15] that are associated with higher resting cTn [16, 17]. Furthermore, untrained females have a pronounced cardiac hypertrophic response to training when compared to males [18]. Finally, there is evidence that changes in LVM may be greater following HIIT when compared to CAT [19]. Therefore, we hypothesised that (1) among sedentary obese females, HIIT and CAT would result in an increase in resting cTnT compared to pre-training levels, (2) the increase in resting cTnT would be greater after HIIT than in CAT, and (3) the larger increase in cTnT after HIIT would be associated with a more pronounced increase in LVM.

Methods

Participants

Briefly, local advertisements were used to recruit 325 volunteers who were willing to participate in the study. Each participant received a comprehensive physical examination by a qualified physician to exclude potential disease before inclusion in the study. Among them, 86 females met the inclusion criteria: (1) body mass index (BMI) ≥25 $kg.m^{-2}$, i.e. the obesity cut-off for Asian adults [20]; (2) aged between 18 and 25 years; (3) had not participated in regular physical activities in the past 6 months, based on International Physical Activity Questionnaire [21]; (4) no history of smoking, cardiovascular, orthopaedic, or hormonal diseases, hypertension, hyperlipidaemia, diabetes, and polycystic ovary syndrome; and (5) no current use of prescribed medication (including contraceptive pills). Of the 86 participants, 30 refused to enter the research for personal reasons. The remaining 56 participants were randomly assigned into three groups: high-intensity interval training (HIIT, n=19), continuous aerobic training (CAT, n=19) and control (CON, n=18). One participant in the HIIT group and 1 in the CON group discontinued the intervention. All participants provided written informed consent after receiving a thorough briefing. The experiment was approved by the regional ethics committee for the use of human and animal subjects in research. The study was performed in accordance with the ethical guidelines outlined in the Declaration of Helsinki and with the ethical standards of the International Journal of Sports Medicine [22].

Experimental design

After avoiding moderate or vigorous exercise for 48 h, participants attended the lab and underwent venous blood sampling, and echocardiographic and anthropometric assessments. On separate days, the CAT and HIIT groups were acclimated to pacing and exercise intensity in their respective training sessions on a cycle ergometer. In a final lab session, the maximal oxygen uptake ($\dot{V}O_{2max}$) of all participants was assessed. Five days after pre-intervention assessments, the HIIT and CAT groups commenced training. For the two groups, the training intervention contained 44 training sessions and lasted for 12 weeks. Two days after the last training session or the CON period, venous blood samples were collected again, followed by echocardiography, anthropometric and $\dot{V}O_{2max}$ measurements. All participants were required to abstain from moderate or strenuous exercise for 48 h before the post-training test. The timing for the post-exercise blood samples was based on: 1) previous studies have shown that the cTnT elevation response to exercise is transient and cTnT generally return to baseline within 48 hours post-exercise [23, 24]; and 2) this is the longest resting time between two training sessions when training is performed 4 days per week, the cTnT values obtained may be considering baseline (resting) values during structured training period.

All tests were conducted from 11:00 am in a lab with an air-conditioned controlled temperature of 20°C and 50% relative humidity. All participants maintained eating habits and other lifestyle habits throughout the experiment.

Exercise training

In each training session, participants in the HIIT group 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 work was achieved. Participants in the CAT group performed continuous cycling exercise (Monark, 839E, Sweden) at an intensity of 60% $\dot{V}O_{2max}$ until the targeted work was achieved. Both groups 1) adopted a pedal frequency of 60 rpm, and an identical 10 min of warm-up followed by 5 min of cool-down at 50–60% of maximal heart rate in each session, 2) completed a total work of 200 kJ in each session (excluding warm-up and cool-

down) per day for the first 4 weeks, 3 days each week, and 3) adopted an increased training frequency to 4 days per week, and the total work in each session of 300 kJ during weeks 5–12. All participants exercised with close supervision, and exercise heart rate and rating of perceived exertion (RPE, Borg scale 6–20) were monitored at every training session. Details of the exercise in a single session of HIIT and CAT are shown in Table 1. At the end of weeks 4 and 8, the measurement of the two groups' $\dot{V}O_{2max}$ was performed to re-adjust the workload corresponding to the pre-set intensity. Overall compliance with the exercise training was calculated as the ratio of the number of sessions completed following the targeted intensity and duration to that of the total sessions.

Protocols and measurements

Graded exercise test

The $\dot{V}O_{2max}$ was determined using a graded cycling exercise protocol that has been previously described [25]. On a cycle ergometer (Monark, 839E, Sweden) with a pedal frequency of 60 rpm, participants started exercising at 25 W. The power output grew by 20 W every 3 min before they experienced volitional exhaustion. A Cosmed breath-by-breath metabolic analyser (Quark-PFT-ergo; Cosmed, Rome, Italy) was used to measure oxygen consumption in the exercise test. The highest average value within 30 s was obtained as the $\dot{V}O_{2max}$. After the graded exercise test, a power output that elicited approximately 60% and 90% $\dot{V}O_{2max}$ in the CAT and HIIT groups, respectively, was selected from the linear relationship of steady-state oxygen consumption versus power output.

Body composition measurement

After voiding, barefoot height was determined using a stadiometer and body mass and composition were assessed using multi-frequency bioelectrical impedance with eight electrodes (InBody 720, Biospace Co., Seoul, Korea) [26].

Blood sampling procedures

Venipuncture was performed to collect 5 ml of venous blood with participants seated. Blood was allowed to clot at room temperature and then centrifuged at 3500 g for 20 min. Serum was extracted and stored at -80°C for the later analysis of cTnT. cTnT was measured with a high-sensitivity immunoassay based on electrochemiluminescence technology using a Cobas e601 analyser (Roche Diagnostics GmbH, Mannheim, Germany). This assay has a lower detection limit of 3 $ng.l^{-1}$ with an upper limit of 10 000 $ng.l^{-1}$. Serum cTnT concentrations that were below the limit of detection are reported as 1.5 $ng.L^{-1}$ [27]. The coefficient of variation at a mean cTnT concentration of 3.82 $ng.l^{-1}$ is 10 %. Defined as the 99^{th} percentile of healthy participants, the upper reference limit (URL) for cTnT was 14 $ng.l^{-1}$ [28].

Echocardiography

The participants underwent 2D transthoracic echocardiography in the left lateral decubitus position using an ultrasound system (Vivid-Q, GE Healthcare, Milwaukee, Wisconsin, USA) according to the American Society of Echocardiography guidelines [29]. Left ventricular internal dimension (LVID), inter-ventricular septal thickness (IVS) and left ventricular posterior wall thickness (LVPW) were measured at end-diastole, and LVM was calculated using a necropsy validated formula [30]:

$$LVM = 0.8 \times (1.04 \times [(LVID + IVS + LVPW)^3 - (LVID)^3]) + 0.6 \text{ g}$$

LVM was corrected for body surface area, and left ventricular hypertrophy was defined as LVM index > 100 $g.m^{-2}$ for women [31]. Prior study has demonstrated that the reliability of 2D echocardiographic measurements of LVM was high and the intraclass correlation coefficient, an estimator of variability between replicate measurements, was 0.90 or higher for absolute LVM and indexed values [32]. All echocardiography was performed by an experienced sonographer blinded to the group allocations. Pre-training assessments were performed in random order by allocating a randomly generated number (Excel, Microsoft Co, Redmond, WA, USA) to each participant and then generating a list ordered according to the value of the associated random number. For post-training, the assessments were done in the order of completion of the last training session.

Statistical analysis

Data normality was measured by the Kolmogorov-Smirnov test. Given the skewed distribution of cTnT, cTnT data across the time points (pre-training and post-training) were compared through a non-parametric Wilcoxon signed ranks test. Additionally, cTnT in the HIIT, CAT, and CON groups were compared using the Kruskal-Wallis test, and the Mann-Whitney U test was completed for pairwise comparisons where appropriate. Fisher's exact test was used to compare the proportions of participants whose cTnT exceeded the detection limit of 3 $ng.l^{-1}$ (cTnT positive rate) at each assessment point.

A two-way ANOVA with repeated measures on anthropometry, body composition, fitness and LVM was used to examine the changes across the three groups (HIIT, CAT, and CON) and training (pre- and post-training). In the case of the significant main effect, post-hoc analyses based on *Newman-Keuls* were performed. Correlations between delta change (pre- to post-training) in cTnT and other variables (body composition, fitness and LVM) were determined via Pearson's product-moment bivariate correlation analysis. Statistical significance was assumed at a level of $p < 0.05$. Data are mean ± SD unless otherwise indicated. The statistical software package SPSS 26.0 (IBM Corp., Armonk, NY, USA) was applied for data analysis.

Results

Overall compliance with the exercise intervention was 97% in the HIIT group and 96% in the CAT group. Pre- and post-training participant characteristics are presented in Table 2. No between-group differences in subject characteristics existed before training. Both HIIT and CAT resulted in a similar decrease in BMI, body fat mass, and body fat percentage, 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 (29.1 ±3.4 to 28.0 ±3.2 $ml.kg^{-1}.min^{-1}$, p <0.05), but BMI, body fat mass, and body fat percentage were unchanged (all $p > 0.05$).

Participants in the HIIT group increased their LVM and LVM index (both p <0.05), but CAT and CON interventions did not affect the LVM and LVM index (both p >0.05) (Table 2). Compared with baseline testing and the CON group, a significant increase (p <0.05) in resting cTnT was

observed after HIIT and CAT with no between-modality differences (p >0.05) in the change in resting cTnT levels (Table 2 & Figure 1). CAT increased the percentage of subjects with cTnT exceeding the limit of detection (positive rate, p <0.05), but HIIT and CON interventions did not affect the positive rate (Table 2). When all participants were combined, the change in pre-training to post-training cTnT was not associated with a change in absolute LVM (r = -0.034, p = 0.810) or LVM index (r = -0.025, p = 0.857, Figure 2). In addition, changes in resting cTnT also did not correlate with changes in BMI (r = -0.208, p = 0.130), body fat percentage (r =-0.230, p =0.094) and $\dot{V}O_{2max}$ (r = 0.174, p =0.209).

Discussion

The main findings of this study are that (1) 12 weeks of equal-work HIIT and CAT resulted in a significant increase in resting cTnT compared with baseline testing and the CON group, (2) there were no between-modality differences in the change in resting cTn levels, and (3) the change in resting cTnT with training could not be explained by a significant association with alterations in LVM.

Traditional Training Adaptations

In agreement with previous meta-analyses [33-35], the current randomised controlled trial revealed that exercise training led to relatively modest improvements in traditional cardiovascular risk factors, such as body weight (-3.6 kg), BMI (-1.4 $kg.m^{-2}$), body fat percent (-1.6%), fat mass (-2.5 kg) and VO_{2max} (+4.9 $ml.kg^{-1}.min^{-1}$). Moreover, these improvements in HIIT and CAT were equivalent and consistent with previous studies [33, 36] that matched for total mechanical work. In addition, the present study demonstrated that HIIT, but not CAT, resulted in a significant increase in LVM. The present data support the findings of Kemi et al. [37], suggesting that the higher intensity of exercise yielded substantially larger effects on physiological hypertrophy. We speculate that the exercise volume of CAT, at a lower intensity, might be too low to exert significant positive effects on LVM [38].

Despite the remarkable consistency in observational studies of the association between higher physical activity and lower resting cTn levels [7, 8], the limited data from intervention studies, including the current study, do not seem to support increased fitness as a direct cause of the lower resting cTn levels. In an elderly population, 12- or 24-wk resistance-type exercise training [10, 11] did not change resting cTn levels. Moreover, Legaz-Arrese et al. [9] observed that a 14-wk endurance running program resulted in increased resting cTnT in non-obese middle-aged individuals. The current study supplements and extends these existing works in relation to the participant cohort and exercise modalities employed (variable vs. constant intensity). Like typical studies to capture the resting cTnT level and avoid bias due to acute exercise effects [9, 39], our participants were sampled 48 hours after the last training session. In young obese females, compared with baseline testing and a CON group, a significant increase in resting cTnT was observed after equal-work HIIT and CAT with no between-modality differences in the change resting cTnT levels. The current results lend further support that short-term exercise training does not result in decreased resting cTn levels.

Considering minimally elevated basal cTn is associated with an increased risk of adverse cardiac events in the general population [2, 40], our findings of elevated resting cTnT are noteworthy. An important purpose of the present study was to determine whether physiological cardiac hypertrophy, as a confounder mediated by exercise training, could influence resting cTnT levels. In the current randomised controlled study, HIIT simultaneously increased the LVM and resting cTnT levels, whereas CAT only increased the resting cTnT values. Thus, these findings suggest that, in contrast to our hypothesis, an LVM increase does not directly mediate resting cTnT concentrations in all participants. This was supported by correlational analysis between post-training changes in cTnT and LVM (Figure 2). This observation differs from the results of previous community-based cross-sectional studies, where resting cTnT was positively associated with left ventricular hypertrophy [13, 14]. It is noteworthy, however, that the subjects in these cross-sectional studies were middle to older age populations, who had a higher prevalence of pathological cardiac hypertrophy and other related occult cardiac disorders than young people

[41]. Thus, the divergence of our results from those of cross-sectional studies might reflect that cardiac physiological hypertrophy has different biochemical consequences than pathological hypertrophy when combined with participant-to-participant differences in habitual physical activity.

Implications

Identifying favourable lifestyle variables associated with temporal reductions in cTn is increasingly relevant, as this assay tracks well with clinical cardiovascular risk during the subclinical period [2, 4]. Thus, the most immediate clinical implication of our results relates to the use of exercise to reduce cardiovascular risk in at-risk populations, a strategy that has been perpetuated in the literature as accepted wisdom [42]. Our results suggest that measurements of cTnT under training conditions might not be reliable surrogates for the health benefits of exercise when structured training is performed on a regular basis (3 or more days per week). This renders it challenging to advocate the use of cTnT as a novel biomarker for screening purposes in clinical practice in the exercise-setting, although the exact mechanism and pathophysiological significance of elevated post-training cTnT levels remains unclear. This information may assist with clinical interpretations and judgments when conducting cardiovascular risk stratification of individuals presenting with raised baseline cTnT during the exercise training period; for example, short-term exercise training-induced elevations in resting cTnT do not necessarily reflect increased cardiovascular risk.

Another novel finding in the present study is that considerable inter-individual variation exists in the change in resting cTnT in response to training (Figure 1), regardless of highly controlled experimental conditions and homogeneity of participants. The marked inter-subject variability in the training-associated cTnT level might further complicate the use of cTnT for assessing the change in cardiovascular risk due to exercise interventions. The current study focused on a single factor (LVM) only, thereby being unable to assess multiple parameters which may relate to post-training cTnT levels. Thus, ongoing and additional studies are required to determine what personal or training-related factors mediate this heterogeneity of cTnT adaptation.

The strengths of the present study include the randomised controlled design with two diverse exercise interventions and the employment of a CON group, the well-controlled and highly defined training regimens and a highly sensitive cTnT assay. However, several limitations should be considered, and future studies are warranted. First, we only measured cTnT on two occasions within the study. Although HIIT led to the substantial increase in LVM (by 17%, $p < 0.05$), the post-training LVM was less than the clinical cut-off value (100 $g.m^{-2}$ for females) for left ventricular hypertrophy in all but one subject. Thus, we cannot exclude the possibility that 12-wk training might be too short to reveal a true correlation between resting cTnT and LVM. In addition, training significantly improved traditional cardiovascular risk factors, but the correlation between changes in cTnT and improvements in these factors was non-significant, suggesting that small sample sizes may also be a limitation. Therefore, further studies using longer training interventions in larger sample sizes are necessary. Second, we studied young, sedentary obese females, so our results may not be generalisable to other populations such as patients with cardiovascular diseases. Third, training-induced changes of right ventricular mass were not addressed in this study. In comparison to the left ventricle, the right ventricle suffers a disproportionately higher afterload during intense exercise [43] and therefore should not be neglected in any future studies in this area. Finally, we did not measure the plasma volume. Such measurements could have extended our understanding of the cTnT change due to training and should be undertaken in future studies.

Conclusion

In the current study of sedentary, obese, young females, both HIIT and CAT increased resting cTnT independent of any changes in LVM. The findings seem to suggest that short-term, structured exercise training may interfere with the utility of cTnT for monitoring the beneficial impacts of regular exercise on cardiovascular risk.

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Figure 1. Resting cardiac troponin T (cTnT, ng.l^{-1}) before (Pre-training) and after (Post-training) 12-week high-intensity interval training (HIIT, n=18), continuous aerobic training (CAT, n=19), and control condition (CON, n=17).

Note: Individual data points are presented by circles with values for the same participant connected by lines for each condition. Logarithmic scale is plotted due to spread of data. The double-arrow line is the median of cTnT values. ○, single subject; ^{n}●, n subjects

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

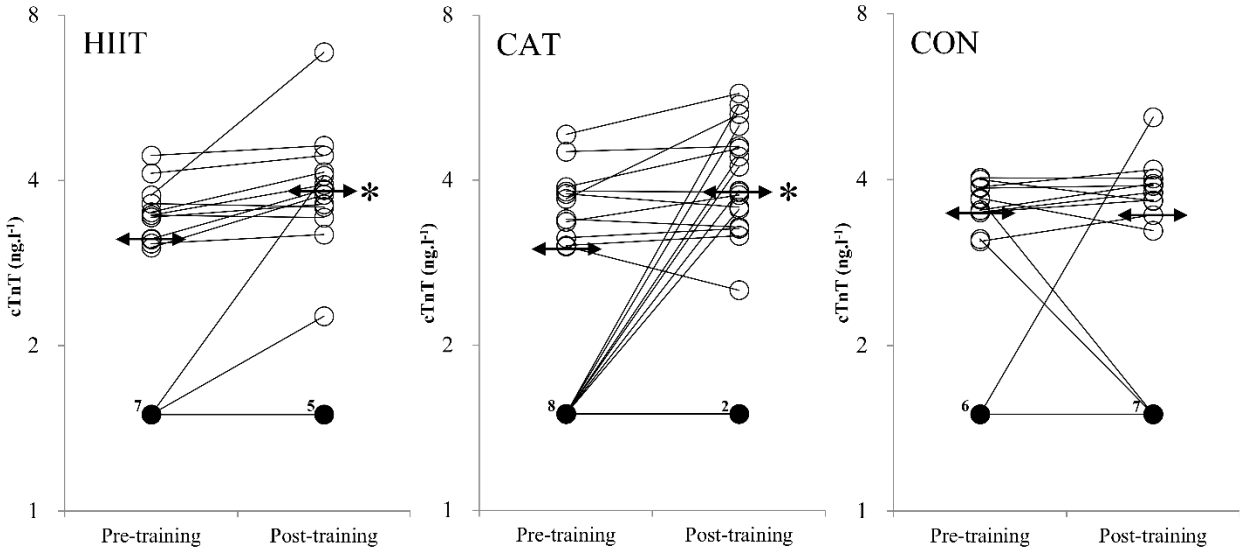

Figure 2. Delta changes (pre- to post-training) in cardiac troponin T (cTnT) and left ventricular (LV) mass index (n=54).

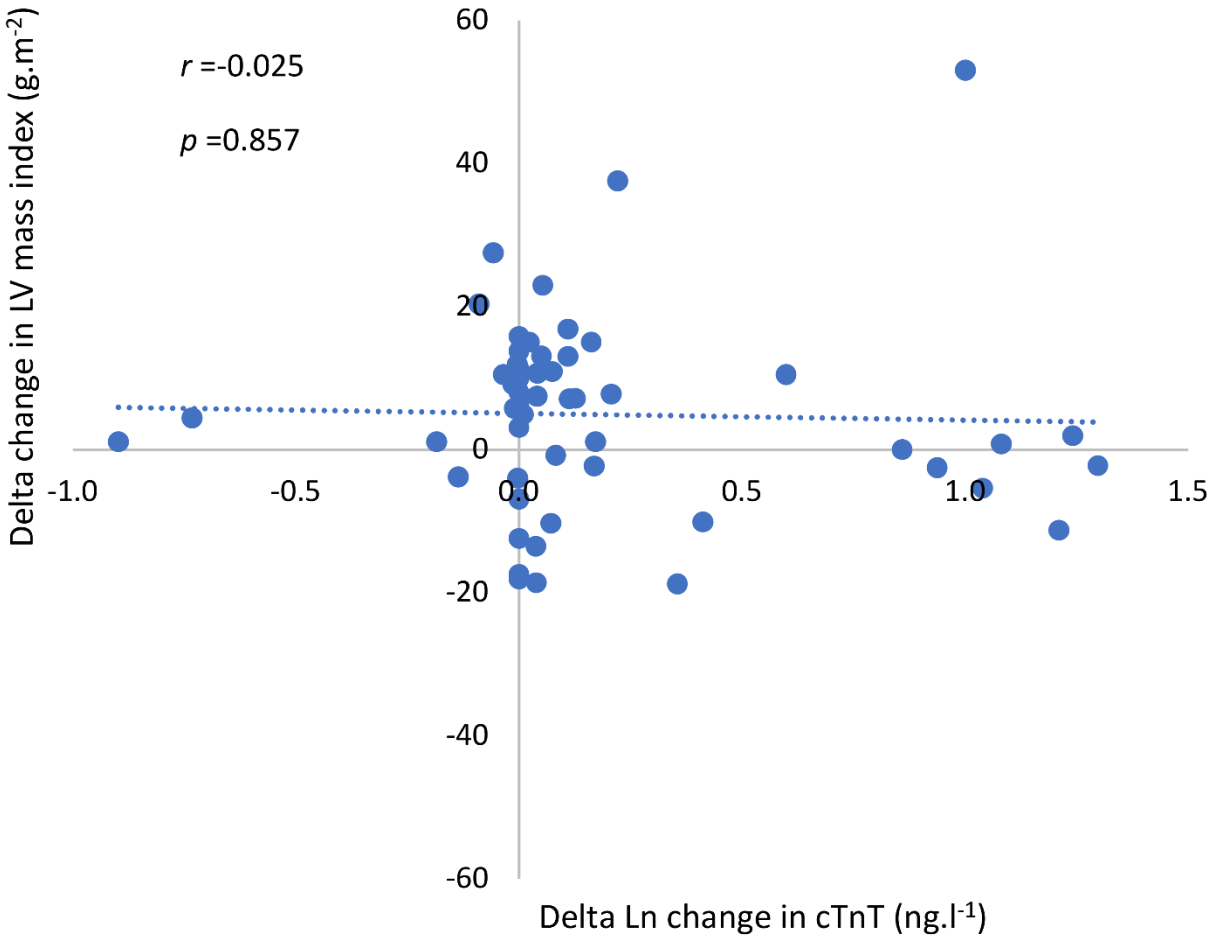

Table 1. Characteristics of the training programs

	HIIT (n=18)			CAT (n=19)		
	week 1-4	week 5-8	week 9-12	week 1-4	week 5-8	week 9-12
Work (kJ)	200	300	300	200	300	300
Power (Watt)	112±13	134 ±15	149 ±18	66 ±8	71 ±10	82 ±7
Exercise time (min)	30 ±5	36 ±5	35 ±5	52 ±6	73 ±11	64 ±5
HR (beats.min^{-1})	167 ±14	169±19	165 ±7	141 ±10	134 ±9	135 ±6
RPE	15 ±2	15 ±2	16 ±1	11 ±2	12 ±1	11 ±1

HIIT, high-intensity interval training; CAT, continuous aerobic training; HR, heart rate; RPE, rating of perceived exertion

Table 2. Subject characteristics and exercise data pre- and post-training

	HIIT (n=18)		**CAT** (n=19)		**CON** (n=17)	
	Pre-training	Post-training	Pre-training	Post-training	Pre-training	Post-training
Anthropometric data						
Age (yr)	20.9±1.2	-	20.8±1.5	-	21.1±1.4	-
Height (cm)	160.7±6.9	-	159.5±5.2	-	160.1±7.1	-
Body weight (kg)	68.9±11.5	65.2±9.7*	70.1±9.2	66.5±8.3*	70.4±14.5	70.5±14.1
BMI ($kg.m^{-2}$)	26.6±3.8	25.2±3.3*	27.5±2.9	26.1±2.6*	27.1±3.9	27.1±3.8
Body composition						
Body fat (%)	37.9±2.7	36.0±2.8*	37.8±3.2	36.4±2.4*	39.3±4.5	39.5±4.5
Fat mass (kg)	26.3±5.9	23.7±4.9*	26.6±4.6	24.2±3.4*	28.0±8.5	28.0±8.0
FFM (kg)	42.6±5.9	41.6±5.3*	43.5±5.8	42.3±5.6*	42.5±7.1	42.5±7.4
Cardiorespiratory fitness						
$\dot{V}O_{2max}$ ($ml.kg^{-1}.min^{-1}$)	30.0±4.2	34.3±4.3*	27.8±3.2	31.3±3.4*	29.1±3.4	28.0±3.2*
$\dot{V}O_{2max}$ ($ml.kg_{FFM}^{-1}.min^{-1}$)	48.4±6.2	53.6±6.0*	44.7±5.0	49.4±5.3*	48.1±5.8	46.3±5.4*
Cardiac morphology						
LV mass (g)	107.2±16.5	123.7±32.0*	113.6±16.3	114.8±20.4	118.6±23.9	122.4±22.6
LV mass index ($g.m^{-2}$)	62.2±7.8	73.1±14.1*	66.1±9.7	67.6±9.6	67.9±9.5	70.2±9.1
Cardiac troponin T ($ng.l^{-1}$)						
Median	3.10	3.60*	3.04	3.81*	3.49	3.45
Range	1.50-4.44	1.50-6.85	1.50-4.85	1.50-5.76	1.50-4.03	1.50-5.19
Positive rate (%)	61.1	72.2	57.9	89.5*	64.7	58.8

HIIT, high-intensity interval training; CAT, continuous aerobic training; FFM, fat-free mass; LV, left ventricular; Positive rate, percentage of subjects with cTnT exceeding the limit of detection.

* Significantly different from corresponding Pre-training value, p <0.05