Sex Differences in Release of Cardiac Troponin T after Endurance Exercise

Zhaowei Kong[2], Jinlei Nie[1], Hua Lin[3], Keith George[4], Gang Zhao[5], Haifeng Zhang[6], Tomas K. Tong[7], Qingde Shi[2]

[1]School of Physical Education and Sports, Macao Polytechnic Institute, Macao, China; Tel: +853-8559 6832 (Nie) & +853-8559 6832 (Shi); E-mail: jnie@ipm.edu.mo (Nie) & qdshi@ipm.edu.mo (Shi)

[2]Faculty of Education, University of Macau, Macao, China; Tel: +853-88228730; E-Mail: zwkong@umac.mo

[3]College of Physical Education, Liaoning Normal University, Dalian, Liaoning 116029, China; Tel: +86-411-83627459; E-mail: wam3627459@163.com

[4]Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK; Tel: +44-151-9046228; E-mail: K.George@ljmu.ac.uk

[5]Department of Ultrasonography, The Third Hospital of Shijiazhuang, Shijiazhuang, Hebei 050011, China; Tel: +86-311-85990586; E-mail: ssygnk@126.com

[6]College of Physical Education, Hebei Normal University, Shijiazhuang, Hebei 050024, China; Tel: Tel: +86-311-80787718; E-mail: hbnuzhanghaifeng@sina.com

[7]Dr. Stephen Hui Research Centre for Physical Recreation and Wellness, Department of Physical Education, Hong Kong Baptist University, Hong Kong, China; Tel: +852-34117770; E-Mail: tongkk@hkbu.edu.hk

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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Abstract

CONTEXT: Post-exercise cardiac troponin release has been extensively described in athletic groups but little attention has been given to any role of sex in mediating this phenomenon. **OBJECTIVE:** We compared the release of cardiac troponin T (cTnT) after endurance running in training-experience, biological-age and maturity-matched young male and female runners. **MATERIALS AND METHODS:** Nineteen male (training history: 2.3±1.0 yr; mean age: 16.1±1.2 yr; Tanner stage: 3.7±0.6) and 19 female (training history: 2.2±1.0 yr; mean age: 15.9±1.4 yr; Tanner stage: 4.0±0.4) runners performed a 21 km run with "all-out" effort. Serum cTnT levels were assessed at pre-exercise (Pre-ex) and at 4 h post-exercise (Post-ex). **RESULTS:** At Pre-ex, cTnT concentrations were below the 99th percentile value (10 $ng.l^{-1}$) in 32/38 runners. Post-ex cTnT increased in all subjects but the response was substantially higher ($P<0.05$) in males [median (range): 210 (20–1360) $ng.l^{-1}$] than females [median (range): 80 (10–550) $ng.l^{-1}$]. At Post-ex, 95% (95% confidence interval: 75-99%) of males and 63% (95% confidence interval: 41-81%) of females ($P<0.05$) had cTnT concentrations above the cut-off for acute myocardial infarction. **CONCLUSIONS:** The present data suggest that post-exercise cTnT elevation occurs in all runners but is augmented in young male compared to female athletes.

Keywords: cardiac biomarker, adolescents, sex, endurance exercise

Running Head: Sex Differences in Post-exercise Cardiac Troponin T

Introduction

A growing body of evidence suggests that prolonged, strenuous exercise may result in the appearance of cardiac troponins (cTnT and cTnI) (Shave *et al.*, 2010) which are highly specific biomarkers of cardiomyocyte insult (Wu *et al.*, 1999). To date, however, there has been no consensus as to the performance impact or clinical relevance of such findings (Shave *et al.*, 2010). An important part of exploring this biomarker response to exercise is understanding factors that may be associated with the presence and amplitude of the elevation in cTn. The information may be useful for clinicians and the challenging interpretation of elevated cTn levels in athletes.

Although we (Tian *et al.*, 2012) (Nie *et al.*, 2011b) (Nie *et al.*, 2011a) (Fu *et al.*, 2009) and others (Eijsvogels *et al.*, 2015) (Mehta *et al.*, 2012) (Sahlen *et al.*, 2009) have demonstrated that subject characteristics (i.e. age and training experience), exercise characteristics (i.e. exercise duration and intensity) and environmental strain may relate to the exercise-induced increase in cTn, the magnitude of exercise-induced cTn release can only be partially explained by such parameters (Eijsvogels *et al.*, 2015). Further research into personal or exercise characteristics associated with exercise-related values of cTn is required.

The observation of a lower release of creatine kinase from skeletal muscle cells in women compared to men after strenuous exercise suggests that women may be more protected against skeletal muscle damage (Enns and Tiidus, 2010). Whether sex imbues any protective effect in the face of cardiomyocyte insult after exercise is not known. There is evidence that better haemodynamic preservation and reduced cellular injury is observed in female piglets after resuscitation from clinically relevant haemorrhage and circulatory arrest (Semenas *et al.*, 2010). In human clinical work, men had markedly higher serum cTnI than women after cardiac surgery suggesting a sex-based difference

in the cellular damage associated with ischemia-reperfusion (Schwarzenberger *et al.*, 2003).

To the best of our knowledge, only one study has reported cTn in male and female runners after prolonged exercise and they reported no sex-based differences (Traiperm *et al.*, 2012). This study did not match athletes for training experience and age that have been identified as important factors that influence exercise-induced cTn release (Nie *et al.*, 2011a) (Tian *et al.*, 2012) (Mehta *et al.*, 2012) (Sahlen *et al.*, 2009). Consequently this topic requires further controlled evaluation.

The aim of the present study was to determine sex-related differences in the cTnT response to exercise in young male and female athletes matched for training experience, biological age and sexual maturity. The study of younger athletes reduces any potential confounding effects of ageing and associated cardiac pathologies (Eggers *et al.*, 2008). We hypothesize that the magnitude of cTnT responses to prolonged exercise will be significantly higher in young male compared to female athletes.

Materials and Methods

Subjects

A total of 45 male and 29 female adolescent endurance runners, performing at a national level and training professionally in running clubs in China, were invited to participate in the experiment. Nineteen male and 19 female runners were selected having been matched for biological age, sexual maturity and training experience (all $P>0.05$). Maturational status was evaluated by self-assessment of the genitalia and pubic hair stage and a Tanner stage assigned (Tanner, 1981) using a previously validated procedure (Duke *et al.*, 1980). None of the subjects had any clinical evidence or personal history of cardiac disease or arterial hypertension as assessed by a cardiologist (Siddiqui and Patel, 2010). All procedures conformed to the Declaration of Helsinki and were

approved by the Local Ethics Committee. Written informed consent was obtained from all the subjects as well as parents or legal guardians in the case of adolescents.

Design, Procedures and Measurements

All the adolescents participated in a simulated half-marathon running race, performing the 21 km run at their own maximal sustainable pace with "all-out" effort on a standard 400 m track where the ambient temperature and relative humidity ranged from 5 to 10 °C and 30 to 50 %, respectively. All the trials were scheduled in the morning from 8:00 to 10:00 in order to fit in with the subjects' routine training schedules, and were carried out on three different days, with 10–14 subjects (same number of males and females) running together on each day. The performance times were recorded. Testing occurred during the "pre-season" training period. The training volume of the subjects was 60–70 km.week^{-1}, 6–21 km.day^{-1} for 6–7 days.week^{-1}. The subjects refrained from eating for at least 2 h and from participating in strenuous physical activity for at least 24 h before the 21 km run.

The first blood sample was collected at rest (Pre-ex) prior to the 21-km running test. Immediately following this, the subjects performed the 21 km run, with a second blood sample (Post-ex) being taken 4 h after completion of the run. The timing for the post-exercise blood sample was in accordance with our previous work that demonstrated that serum cTnT concentrations peaked 4 h after competition of a 21 km run (Nie *et al.,* 2011c) and a laboratory-based 90 min run (Tian *et al.,* 2012) by employing multiple sampling points among similar adolescent runners of a similar fitness level. At both sampling times, 2 ml of venous blood was drawn from the antecubital vein with subjects in a sitting position. The blood was allowed to clot at room temperature and then centrifuged at 2,000 g for 20 min. The separated serum was stored at –20 °C for later analyses.

For analysis of serum cTnT, a third-generation assay was performed using an electrochemiluminescence technology employed by the Elecsys 2010 automated batch analyzer (Roche Diagnostics, Basel, Switzerland). The inter-assay coefficient of variation was 10% at 30 $ng.l^{-1}$ and 3% at 100 $ng.l^{-1}$. The intra-assay coefficient of variation was 8% at 30 $ng.l^{-1}$ and 2% at 100 $ng.l^{-1}$, with a detection limit of 10 $ng.l^{-1}$ (which coincides with the 99th percentile value) and an upper limit of 25000 $ng.l^{-1}$. Serum cTnT levels that were below the limit of detection (< 10 $ng.l^{-1}$) are reported as 5 $ng.l^{-1}$ (Fu *et al.*, 2009, Nie *et al.*, 2011c). The cut-off value for acute myocardial infarction (AMI) for serum cTnT is 50 $ng.l^{-1}$ (Collinson *et al.*, 2003). This value based on an international multicentre clinical evaluation of the third-generation cTnT assay through construction of receiver operating characteristic curves. (Collinson *et al.*, 2003).

At rest prior to the 21-km running test, the basic echocardiographic data was also collected using an ultrasound system (GE LOGIQ Book XP; GE Healthcare, San Jose, CA) according to the American Society of Echocardiography (ASE) guidelines (Lang *et al*., 2015). In brief, cardiac structure was evaluated from parasternal long-axis two-dimensional recordings, and left ventricular mass was calculated using the ASE formula and indexed according to body surface area. Left ventricular volume and ejection fraction (EF) (%) were evaluated with Simpson's biplane method.

In addition, follow-up was performed by a cardiologist for each runner at one day, 6 months and 13 months after the experiment to exclude the possibility of clinical signs or symptoms indicative of cardiac events during the follow-up period.

Statistical Analyses

The Kolmogorov–Smirnov test was used to evaluate the normality of the data. Group differences between males and females in physical and training characteristics, and

echocardiographic indices were analysed by independent *t*-tests. The non-parametric Wilcoxon signed-rank test was used to compare the cTnT data across the time points (Pre-ex and Post-ex) because of a skewed distribution. Concentrations of cTnT in males and females were compared using the Mann-Whitney U test. The percentage of subjects with cTnT exceeding the AMI cut-off criterion of 50 $ng.l^{-1}$ and the 99th percentile value of 10 $ng.l^{-1}$ at each assessment point were compared using Fisher's exact test. Correlations between post-exercise cTnT and cardiac echocardiographic variables were determined via a Pearson product–moment correlation analysis. Statistical significance was assumed at a level of $P<0.05$. Data analysis was performed using the statistical software package SPSS 11.5 (SPSS Inc., Chicago, Illinois, USA).

Results

The physical characteristics of the subjects and their training background are shown in Table 1. Although height and body weight was higher in males than females ($P<0.05$), training volume, biological age and Tanner stage were not different ($P>0.05$) between the two groups (Table 1).

All subjects completed the 21 km run and none of runners had any clinical signs or symptoms indicative of myocardial ischemia either during or after exercise. During the 21 km run, the mean running time in males (81.7 ± 6.5 min) was shorter than that in females (93.8 ± 8.7 min; $P<0.05$) (Table 1).

Data for cTnT in male and female runners before and after the 21 km run are presented in Table 2 and Figure 1. At Pre-ex, cTnT levels in most subjects (32/38) were below the 99th percentile value (10 $ng.l^{-1}$) and data were not different between two groups. cTnT increased Post-ex in all subjects but the median cTnT data were significantly higher in male compared to female athletes ($P<0.05$) (Figure 1). In

addition, 95% (95% confidence interval: 75-99%) of males and 63% (95% confidence interval: 41-81%) of females ($P<0.05$) presented with cTnT data above the cut off for AMI (50 $ng.l^{-1}$).

****Table 1, Table 2 and Figure 1 near here****

Basic echocardiographic data are presented in Table 3. Male athletes presented with higher left ventricular internal diameter at end diastole, left ventricular posterior free wall at end diastole, end-diastolic left ventricular volume and left ventricular mass ($P<0.05$). There were, however, no significant correlations ($P>0.05$) between post-exercise cTnT levels and cardiac morphologies.

****Table 3 near here****

Further, all runners continued their routine training and long-distance run races for more than one year after the experiment, and none had any clinical signs or symptoms indicative of cardiac events during the follow-up period.

Discussion

This is the first study to demonstrate that the magnitude of the cTnT responses to endurance exercise was significantly higher in young male compared to female athletes. Of note was the fact that all subjects had an elevated Post-ex cTnT compared to the Pre-ex assessment.

Sex-differences in cTnT appearance with prolonged exercise

The reduced cTnT at 4 h Post-ex in young female athletes compared to biological-age, sexual maturity and training experience-matched young male athletes is a new finding

that contradicts the only previous study of cTn response to exercise in male and female runners who reported no sex-differences (Traiperm *et al.*, 2012). It is entirely possible that the divergent results are influenced, at least in part, by the lack of control over training experience and age in the Traiperm study that have been reported in a range of studies (Nie *et al.*, 2011a) (Tian *et al.*, 2012) (Mehta *et al.*, 2012) (Sahlen *et al.*, 2009). The apparent role that sex had in mediating the peak response, as well as the percentage of subjects with values exceeding the AMI cut-off for cTnT, support the concept that there may be sex-related differences in cardio-protection during stress and clinical scenarios (Schwarzenberger *et al.*, 2003).

It is worth noting that we used the third-generation cTnT assay, but not the latest fourth-generation high-sensitivity assay. Using the high-sensitivity cTnT assay, Sribhen et al. reported that male adolescents have a higher resting cTnT concentration than female adolescents (Sribhen *et al.*, 2010). Our current Pre-ex data did not confirm this finding. The fact that resting cTnT in most subjects (32/38) was below the detection limit of the assay suggests that the relatively low-sensitivity assay used in our study might, at least in part, explain the discrepancy. This is a limitation in the present study and warrants further investigation. Nonetheless, corresponding with our research goal, the prominent response of post-exercise cTnT and the statistically significant sex differences observed in the current study indicate that the use of the high-sensitivity assay may not substantially alter the key results.

The mechanism(s) responsible for the lower levels of cTnT observed in young female athletes after endurance exercise cannot be directly determined from the current observational, cross-sectional design. Some researchers have speculated a role for sex hormones to explain the sex-differences in resting cTnT concentration (Sribhen *et al.*, 2010). Though we did not determine the sex hormone levels it is entirely likely that due to the subjects biological age and sexual maturity that there are substantial differences

in estrogen level between males and females (Mendelsohn and Karas 1999). In fact, it has long been known that the estrogen may exert protective effects on the myocardium (Mendelsohn and Karas 1999). Estrogen is thought to have a high antioxidant capacity and as such may have the ability to scavenge free radicals and stimulate the expression and activities of certain antioxidant enzymes, thereby limiting the oxidative damage of cardiomyocytes exposed to conditions of stress or injury (Mendelsohn and Karas 1999). Interestingly, our laboratory's recent animal study showed a temporal association between elevations of serum cTnT and myocardial oxidative stress after prolonged exercise (Nie *et al.*, 2010). Alternatively it has been speculated that sex-differences in resting cTnT were as a consequence of the heart mass of men being larger than women, although no empirical study has specifically addressed this (Sribhen *et al.*, 2010). In the present study, male runners had greater cardiac diameters, thicknesses and mass than the female runners. This is in line with previous investigation about gender differences in heart growth, in which showed similar between-sex physiological left ventricular differences in this age (de Simone et al., 1995). No significant correlations were observed between post-exercise cTnT levels and these cardiac echocardiographic variables in the current study. Our findings do not support a role for heart mass in cTn release with exercise.

Exercise-induced cTnT release

We observed that all athletes demonstrated an increase in cTnT, while 79% of our subjects exceeded the AMI clinical cut-off value. This is at odds with previous work employing a simple pre-/post-exercise design (Shave *et al.*, 2007) but confirms an elegant study using multiple time measurements (Middleton *et al.*, 2008). It is worth noting that the total myocardial work undertaken was low in the present study (21 km

run, ~1.5 h duration) when compared to previous studies that have employed endurance tasks over many hours, days and even weeks (Shave *et al.*, 2007). Given that a higher cardiac load likely results in a larger cTnT release (Fu *et al.*, 2009), the magnitude of the release of cTnT in the current study was pronounced. The prominent response in cTnT release may be partly attributed to the appropriate time point of post-exercise cTnT measurement based on our previous work (Nie *et al.*, 2011a) (Tian *et al.*, 2012) In addition, the prominent cTnT response in the current study may also be related to the unique participant group: adolescent runners. Our recent lab-based study showed that the magnitude of exercise-induced release of cTnT may be more pronounced in the immature hearts of adolescents (Tian *et al.*, 2012).

Implications

The fact that all subjects in the current study had elevated cTnT post-exercise suggests that this is likely a normal, physiological response. Further, all runners continued their routine training and long-distance run races for >1 year after the experiment, and none had any clinical symptoms indicative of cardiac events over this period.

It has been suggested that the use of the general population as a "reference" might not be appropriate for athletes being evaluated for medical conditions using biomarkers such as cTn (Kratz *et al.*, 2002). This has prompted some to suggest that cTn values might be stratified according to the physical activity of the subjects to improve the clinical usefulness of the biomarker (Lippi and Banfi, 2010). Our work extends this to sex-related differences. Our findings highlight the importance of interpreting the post-exercise cTn levels in a sex-specific manner. Recent reports suggest that women's involvement in endurance training and competitive events is increasing (Hoffman *et al.*, 2010), so the relationship between cTn release and sports in both genders will require further scrutiny.

Limitations and future research

Several limitations should be considered. The first important limitation is that the women were evaluated regardless of their menstrual cycle phase, which could influence blood estrogen concentration and, consequently, post-exercise cTnT release. Further, we also did not determine blood estrogen levels. Nevertheless, studies in reproductive endocrinology have shown that even in the low-estrogen menstrual phase (i.e. mid-follicular phase), the blood estrogenic concentration in women is substantially higher than that in men (Mendelsohn and Karas 1999). This does promote the idea that experimentally examining women at different points in their menstrual cycle, in future studies, may be insightful. In addition, all subjects in the present study were familiar with the 21 km run with "all-out" effort, which was always used in their routine training. Therefore, we are confident that males and females were at very close in terms of effort for the 21 km run. Due to the lack of VO_{2max} and in-exercise cardiorespiratory data it is not known whether males and females presented with equivalent HR or BP during the exercise test.

Conclusion

Endurance running for 21 km with "all-out" effort led to significantly higher levels of cTnT in young males than in training-experience, biological age and sexual-maturity-matched young female runners. Further, we observed that all athletes demonstrated an increase in cTnT, with 79% presenting with an elevated cTnT level above the AMI clinical cut-off value.

Declaration of interest

The authors report no declarations of interest.

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Table 1. Basline parameters among subjects (mean±SD).

	All (n=38)	Males (n=19)	Females (n=19)
Age (yr)	16.0±1.3	16.1 ± 1.2	15.9 ± 1.4
Height (cm)	171.9±6.4	175.0 ± 6.1	168.8 ± 5.2*
Weight (kg)	57.3±8.3	61.6 ± 8.2	52.9 ± 5.9*
BMI ($kg.m^{-2}$)	19.3±2.0	20.1 ± 2.0	18.6 ± 1.7*
Tanner stage	3.8±0.5	3.7 ± 0.6	4.0 ± 0.4
Training years (yr)	2.2±1.0	2.3 ± 1.0	2.2 ± 1.0
Training volume ($km.wk^{-1}$)	65.1±29.6	68.9 ± 26.3	61.2 ± 23.0
21 km run time (min)	87.8±9.8	81.7 ± 6.5	93.8 ± 8.7*

* Significantly different from corresponding males value, $P<0.05$

Table 2. Serum cardiac troponin T (cTnT) in male (n=19) and female (n=19) young runners before (Pre-ex) and after (Post-ex) a 21 km run.

	Pre-ex	**Post-ex**
All subjects (n=38)		
Median (Range) ($ng.l^{-1}$)	5 (5-20)	115 (10-1360)*
95% confidence interval ($ng.l^{-1}$)	5-8	155-382
Positive Rate 1 (95% confidence interval) (%)	10.5 (4.2-24.1)	97.4 (86.5-99.5)
Positive Rate 2 (95% confidence interval) (%)	0 (0-9.2)	79.0 (63.7-89.9)*
Males (n=19)		
Median (Range) ($ng.l^{-1}$)	5 (5-20)	210 (20-1360)*
95% confidence interval ($ng.l^{-1}$)	5-9	174-594
Positive Rate 1 (95% confidence interval) (%)	10.5 (2.9-31.4)	100.0 (83.2-100.0)
Positive Rate 2 (95% confidence interval) (%)	0 (0-16.8)	94.7 (75.4-99.1)*
Females (n=19)		
Median (Range) ($ng.l^{-1}$)	5 (5-20)	80 (10-550)* †
95% confidence interval ($ng.l^{-1}$)	4-9	74-233
Positive Rate 1 (95% confidence interval) (%)	10.5 (2.9-31.4)	94.7 (75.4-99.1)
Positive Rate 2 (95% confidence interval) (%)	0 (0-16.8)	63.2 (41.0-80.9)* †

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

† Significantly different from corresponding males value, $P<0.05$

Positive Rate 1: Percentage of subjects with cTnT exceeding the 99th percentile value of 10 $ng.l^{-1}$

Positive Rate 2: Percentage of subjects with cTnT exceeding the acute myocardial infarction cut-off of 50 $ng.l^{-1}$

Table 3. Basic echocardiographic data in male (n=19) and female (n=19) young runners are shown (mean ±SD)

	All subjects (n=38)	**Males** (n=19)	**Females** (n=19)
IVSd (mm)	9.6±1.6	10.1±1.9	9.0±1.1
LVIDd (mm)	48.0±4.4	51.3±2.2	44.8±3.5*
LVPWd (mm)	10.1±1.7	10.8±1.7	9.4±1.4*
LVEDV (ml)	110.5±24.0	128.5±14.3	92.5±17.2*
LV mass (g)	170.8±51.9	204±48	138±30*
LV mass index ($g.BSA^{-1}$)	102.6±26.0	117±25	87.7±17.5*
EF (%)	60.5±5.7	60.5±3.3	60.6±7.5

IVSd, interventricular septal end diastolic dimension; LVIDd, left ventricular internal diameter at end diastole; LVPWd, left ventricular posterior free wall at end diastole; LVEDV, end-diastolic left ventricular volume; LV mass, left ventricular mass; EF, ejection fraction; BSA, body surface area
* Significantly different from corresponding males value, $P<0.05$