Title: Cardiac biomarker release after endurance exercise in male and female adults and adolescents with different pubertal status

Short title: Cardiac biomarker after exercise in adolescents and adults

Key words: NH2-terminal pro-brain natriuretic peptide, Tanner stage, high-sensitivity cardiac troponin T, sex, swimming.

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Abstract

Objectives To compare the responses of high-sensitivity cardiac troponin T (hs-cTnT) and NH_2-terminal pro-brain natriuretic peptide (NT-proBNP) after 60 min of swimming in male and female adults and adolescents with different pubertal status.

Study design Fifty adolescent swimmers (25 males and 25 females) and 16 adult swimmers (7 males and 9 females) participated in a 60-min maximal swimming test with serial assessment of hs-cTnT and NT-proBNP at rest, immediately post-exercise and at 1, 3, 6, 12, and 24 h post-exercise. Adolescents were classified according to pubertal status: Tanner stages 3 (n = 14), 4 (n = 22), and 5 (n = 14).

Results Exercise resulted in an increase in both biomarkers. hs-cTnT responses to exercise were similar in adolescents with different pubertal status and adults although there was substantial individual variability in peak hs-cTnT, with the upper reference limit (URL) exceeded in 62% of the participants. Post-exercise kinetics for hs-cTnT were largely consistent across all groups with a return to near baseline levels 24 h post-exercise. The males showed higher values of hs-cTnT at baseline and post-exercise. All groups had similar NT-proBNP responses to acute exercise and recovery. One swimmer exceeded the upper reference limit for NT-proBNP values.

Conclusions An exercise-associated increase in hs-cTnT and NT-proBNP occurred in response to a 60-min maximal swimming test that was independent of pubertal status/adolescent vs. adults. The present data also suggests that baseline and post-exercise hs-cTnT values are higher in male compared to female, with no sex differences in NT-proBNP values.

Abbreviations

cTnI	Cardiac troponin I
cTnT	Cardiac troponin T
HR	Heart rate
hs-cTnT	High-sensitivity cardiac troponin T
NT-proBNP	NH_2-terminal pro-brain natriuretic peptide
RPE	Ratings of perceived exertion
URL	Upper reference limit

Introduction

Cardiac biomarkers are established as part of standard evaluation for the diagnosis and prognosis of patients with myocardial infarction [cardiac troponin T (cTnT) and troponin I (cTnI)][1] and heart failure [NH_2-terminal pro-BNP (NT-proBNP)].[2] Given these important clinical roles it is somewhat surprising that both biomarkers are elevated after prolonged exercise, a physiological stimulus (e.g., Marathon[3,4]) as well as shorter bouts of physical activity lasting 30-60 min.[5,6] The clinical relevance of these phenomenon is a current topic of discussion[3,7] that is relevant for clinical investigations in athletes after exercise.[7,8]

Whilst most cardiac biomarker data is derived from adults there is a small but consistent dataset suggesting similar responses in adolescents completing prolonged exercise bouts.[9-13] Direct comparison of the release of cardiac biomarkers with exercise in adults and adolescents is limited to two studies.[10,14] In a well-controlled study,[10] adolescents demonstrated a peak high-sensitivity cTnT (hs-cTnT) that was 11 times higher than adults after a long-distance run and was still significantly elevated in adolescents at 24 h of recovery. In contrast, López-Laval et al[14] observed no differences in peak cTnI and post-exercise cTnI kinetics during 24 h of recovery after a basketball match. These contradictory findings may be associated with differences in the pubertal status of adolescents as well as other personal differences (e.g., size, fitness, sex), and/or differences in the exercise stimulus. The influence of pubertal status on the post-exercise release of biomarkers has only been assessed in a small sample of male adolescent runners.[10] The authors observed a trend toward higher release of hs-cTnT in adolescents of lower Tanner stage, suggesting a role for maturity in mediating hs-cTnT release with prolonged exercise.

There is very limited information on the influence of sex on exercise-induced cardiac biomarker release.[11,15,16] Traipern et al[11] noted similar increases in male and female adolescent marathon runners but data were limited by assay precision, the number of sampling times post-

exercise, and the lack of control of the duration/intensity of exercise and pubertal status. In contrast, in a recent well-controlled study, although limited by assay precision and by the number of sampling times post-exercise, was observed after a half-marathon that cTnT elevation occur in all runners but is augmented in young male compared to female athletes.[15] Specifically, no studies in adolescents have evaluated the influence of sex on NT-proBNP values.

Consequently, faced with limited and contradictory information, we employed multiple sampling points during 24 h of recovery from a 60-min swimming time trial to examine the influence of high-intensity aerobic exercise on hs-cTnT and NT-proBNP appearance in male and female adults and adolescents with different pubertal status. Our hypothesis was that the release of hs-cTnT with exercise would be greater in males than in females, higher in adolescents than in adults and with the highest values in adolescents with lower maturity status. We hypothesize any influence of sex or adolescent-adult and pubertal status on the release of NT-proBNP with exercise.

Methods

Participants

Sixty-six highly trained swimmers were recruited from a large water polo club in Mexico through an open invitation to all of its members. Volunteers included adolescent (25 males and 25 females, age range = 12–18 years) and adult (7 males and 9 females, age range = 22–46 years) swimmers (Table I). None of the subjects had any clinical evidence or personal history of cardiac disease or arterial hypertension, and all had a normal 12-lead electrocardiogram at rest. All swimmers provided written informed consent (and parental consent for adolescents). The study followed the ethical guidelines of the Declaration of Helsinki and was approved by

the Research Ethics Committee of the Universidad Autónoma de Nuevo León [Autonomous University of Nuevo Leon].

Research design and methods

All participants visited the laboratory and swimming pool on two occasions. During the first laboratory visit, subjects underwent anthropometric assessment. Body height was measured to the nearest 0.1 cm (SECA 225, SECA, Hamburg, Germany). Body mass was determined to the nearest 0.05 kg (SECA 861, SECA, Hamburg, Germany). The percentage of total body fat was calculated according to Faulkner.[17] A questionnaire obtained training and medical history. Pubertal status was assessed directly by two experienced pediatricians according to the standardized Tanner stages based on external primary and secondary sex characteristics.[18] The adolescents were categorized in the middle of puberty, Tanner stage 3 (4 males and 10 females), or late puberty, Tanner stage 4 (11 males and 11 females) and 5 (10 males and 4 females). Finally, maximal heart rate (HR) was recorded using a specific protocol commonly used in training of swimmers consisting of the execution of 6 repetitions of 25 m swimming at maximum intensity with 10 s of rest in between repetitions.

In the second visit, the swimmers completed a self-paced 5-min warm-up (<60% of %HRmax) followed by a 60-min "all-out" swimming test. All participants were fully habituated to the 60 min all-out swimming test protocol and were asked to abstain from strenuous exercise for 48 h before the exercise test. During the exercise test, swimmers made a continuous effort without periods of rest time in order to complete the maximum possible distance at self-paced velocity. The swimming test took place at 08:00 am in a 50-m indoor pool (water temperature 26°C, air temperature 29°C, relative humidity 75%). Pairs of subjects competed side-by-side to provide motivation and competition, and strong verbal encouragement was provided during the test. Subjects were constantly aware of the time and distance covered. Water intake was allowed *ad*

libitum. HR was recorded continuously during the tests via a Polar HR monitor (Polar Team 2, Kempele, Finland). The distance covered was recorded every 10 min. The 6-20 Ratings of Perceived Exertion (RPE)[19] were recorded immediately after the test was completed. Repeated venous blood samples were taken before, immediately after (5 min), and at 1, 3, 6, 12, and 24 h after exercise to assess serum hs-cTnT and NT-proBNP levels.

Blood sampling and analysis

Blood samples were drawn from the antecubital vein using venous puncture. The blood was allowed to clot at room temperature and then centrifuged. Serum was drawn off and stored at -80°C for later analysis. hs-cTnT was measured via electrochemiluminescence technology using a Cobas 6000 analyzer (Roche Diagnostics, Tokyo, Japan). This assay has a range from 3 to 10,000 ng/L with a lower detection limit of 3 ng/L. The coefficient of variation at a mean hs-cTnT level of 13.5 ng/L was 5.2%, and the upper reference limit (URL) for hs-cTnT, defined as the 99th percentile of healthy participants, was 14 ng/L.[20] NT-proBNP was analyzed with an Elecsys proBNP electrochemiluminescent immunoassay on a Cobas 6000 analyzer (Roche Diagnostics, Tokyo, Japan) with an analytical range of 5–35,000 ng/L and intra- and inter-assay imprecisions of 0.7–1.6% and 5.3–6.6%, respectively.[21] The URL for NT-proBNP was considered to be 125 ng/L.[22]

Statistical analysis

Statistical analyses were performed using the IBM Statistical Package for the Social Sciences (IBM SPSS Statistics, version 21.0 for Windows). Cohort data are presented as means ± SD unless otherwise stated. Kolmogorov-Smirnov tests were used to check for normal distribution, and data for hs-cTnT and NT-proBNP were log-transformed before statistical testing. Three-way ANOVA were conducted with one within-subject factor (TIME: pre-exercise and at 5 min

and 1, 3, 6, 12, and 24 h post-exercise) and two between-subject factors (GROUP: Tanner Stage 3, 4, 5 and adult; and SEX: male and female). To support this analysis, we performed two-way ANOVAs on peak post-exercise hs-cTnT and peak NT-proBNP levels. Finally, we calculated change scores for both biomarkers from pre-exercise to peak post-exercise. The association between the exercise increase in both biomarkers and other relevant variables (e.g., baseline biomarker concentration, mean HR, and maximal exercise HR) were assessed using bivariate Pearson's product-moment correlation coefficients. Differences were considered significant if $P \leq .05$.

Results

The adolescents lighter than the adults ($P = .043$) with similar heights and percentage fat values. Adolescents had a higher weekly training volume ($P = .010$) but fewer years of training ($P = .001$). Performance and exercise intensity (%HRmax and RPE) during the 60-min all-out test were similar between adolescents and adult swimmers (Table I). Both sexes had similar age and training characteristics, but the females were shorter and lighter with a higher percentage fat than the males ($P < .05$). Overall swim performance was lower in the females but exercise intensity was similar between sexes (%HRmax: Female: 85 ± 8 vs. Male: 85 ± 8, $P = .919$).

hs-cTnT release

A significant main effect of sampling TIME was observed for hs-cTnT, which was elevated at 5 min, 1, 3, 6, and 12 h post-exercise compared with baseline ($P = .000$; Table II). The hs-cTnT was above the URL in 62% of the participants. The maximum post-exercise hs-cTnT values were observed at 1 h in 2 individuals, 3 h in 56 individuals, 6 h in 2 individuals, and 12 h in 1 individual. There was no evidence of increased hs-cTnT after exercise in 5 subjects: 2 females with Tanner stage 3, 1 female with Tanner stage 4, 1 male with Tanner stage 5, and 1 female

adult. The variability (CV) of the hs-cTnT values was lowest at baseline (40%) and highest in the peak post-exercise values (145%). There was no main effect of GROUP on the hs-cTnT response to exercise (P = .578). The maximal increase in hs-cTnT (peak – baseline) was not significantly different between the groups: Tanner stage 3 [median (range): 8.9 (0–159.7) ng/L]; Tanner stage 4 [median (range): 16.5 (0–332) ng/L]; Tanner stage 5 [median (range): 19.6 (0–156.7) ng/L]; adults: [median (range): 8.0 (0–117.0) ng/L]; P = .449. There was a significant main effect of SEX with males demonstrating higher values of hs-cTnT (P = .000). In addition, a significant interaction was evident between sampling TIME and SEX (P = .000). This SEX difference in the kinetics of hs-cTnT is a consequence of the females having a delayed peak post-exercise (males: 5 min post-effort; females: 1 h post-effort) and a return to baseline (males: 24 h post-effort; females: 12 h post-effort). There was no significant interaction between sampling TIME and GROUP (P = .307), SEX and GROUP (P = .209) or TIME and GROUP and SEX (P = .135). The increase in hs-cTnT was significantly associated with the %HRmax (r = .339, P = .005). The 5 subjects without an increase in hs-cTnT after exercise worked at a lower %HRmax (77 ± 3 vs. 85 ± 8, P = .019).

NT-proBNP release

There was a significant main effect of sampling TIME for NT-proBNP as it increased from pre-exercise to 5 min and 1, 3, 6, 12, and 24 h post-exercise (P = .000; Table III). Only 1 participant exceeded the URL of NT-proBNP. Variable kinetics of NT-proBNP were evident among subjects during recovery, with the peak post-exercise values observed at 0 h (17 individuals), 1 h (4 individuals), 3 h (2 individuals), 6 h (4 individuals), 12 h (14 individuals), and 24 h (24 individuals). One subject had no increase in NT-proBNP after exercise. There was no significant main effect of GROUP on the NT-proBNP levels (P = .733). In support of the latter point, there was no difference between GROUPS with respect to the maximum increase

of NT-proBNP: Tanner stage 3 [median (range): 15.4 (3.6–38.9) ng/L]; Tanner stage 4 [median (range): 18.7 (0–52) ng/L]; Tanner stage 5 [median (range): 12.6 (4.8–54.9) ng/L]; adults: [median (range): 19.5 (2.8–49.2) ng/L]; P = .449). There was no main effect of SEX on NT-proBNP (P = .119). There were no significant interactions between TIME and GROUP (P = .709), TIME and SEX (P = .445), SEX and GROUP (P = .439) as well as TIME and GROUP and SEX (P = .982). The peak post-exercise level of NT-proBNP was strongly associated with pre-exercise concentration in males (r = .742, P = .000) and females (r = .868, P = .000). There was no correlation between the increases in NT-proBNP and hs-cTnT (r = .136, P = .277).

Discussion

This is the first controlled study comparing detailed post-exercise kinetics of cardiac biomarkers in adolescents of both sexes classified according to their pubertal status. Furthermore, this study compares the response of cardiac biomarkers to exercise between adolescents and adults. Our results provide confirmatory and novel data on the following points; 1) a single 60-min bout of all-out swimming resulted in significant increases in hs-cTnT and NT-proBNP in both adolescent and adult swimmers; 2) substantial individual variability was noted in peak hs-cTnT during recovery, with the URL exceeded in 62% of the swimmers, although the kinetics of hs-cTnT increase and recovery during the 24 h post-exercise period was more consistent; 3) there was less individual variability in peak NT-proBNP, with one subject above the URL, but the kinetics during recovery were inconsistent; 4) the baseline and post-exercise levels of both biomarkers were independent of pubertal status and were comparable between the adolescent and adult swimmers, and 5) males had higher baseline and post-exercise hs-cTnT values, but there were no sex differences in NT-proBNP values.

hs-cTnT and NT-proBNP release post-exercise

This study confirms that the exercise-induced release of cTn and NT-proBNP is not exclusive to an ultra-endurance effort in adult athletes.[5,6,23,24] There is some evidence to suggest that cTn release during prolonged exercise is positively associated with exercise intensity.[25,26] Thus, the high intensity shown by our swimmers could explain the release of hs-cTnT. The percentage of participants exceeding the URL (62%) of hs-cTnT was comparable to the only previous study with male adult swimmers who performed the same exercise test (64%).[23] These results confirmed findings of marked individual variability in the release of hs-cTnT with exercise.[6,10] This variability could partly be explained by differences in the %HRmax between the subjects and could be linked to recent findings that suggest that the release of hs-cTnT with exercise is higher in subjects with more training or with better "athletic" status[5,6] who are usually capable of maintaining higher %HRmax values for specific durations of effort. This seems the most probable explanation for the absence in some subjects of hs-cTnT increase after exercise. The %HRmax does not explain all of the variability in the hs-cTnT and high %HRmax values were observed in subjects with negligible release of hs-cTnT and this suggests that some other, currently unknown, factor/process may make participants more or less likely to release cTn in response to exercise. There was much more consistency in the overall "pattern" or "kinetics" of hs-cTnT throughout the 24-h recovery period. Our data reflect a rapid rise in hs-cTnT in the early hours of recovery, with most of the subjects reaching a peak at 3 h, with close to complete recovery to baseline at 24 h. These observations were consistent between individuals and largely agreed with the few studies reporting detailed hs-cTnT kinetics over 24 h.[6,10,23]

Our results extend to swimming previous findings that NT-proBNP was elevated following short-duration (30–60 min), high-intensity exercise in rowers and runners, but with few subjects with values higher than the URL.[5,6] The release of NT-proBNP is largely associated with exercise duration and volume, with little influence exerted by exercise intensity.[25,27] A shorter, 60-min swim could explain why only one subject exceeded the URL of NT-proBNP

in the present study. Our study confirms that the variability in pre-exercise values is the key factor of the individual variability in the response of NT-proBNP to exercise.[5,6,10] Our results also confirm that the overall kinetics of NT-proBNP appearance exhibit some heterogeneity, with incomplete recovery to baseline at 24 h post-exercise.[5,6,10] The elevation in NT-proBNP at 24 h could reflect a temporary reduction in kidney function and changes in cardiac function,[10] but this possibility requires further study.

Pubertal and adult status impact on hs-cTnT and NT-proBNP release

Several studies have suggested that the cTn release after endurance exercise might be greater among adolescent athletes compared with adults, possibly due to the immature cardiac muscle of the adolescent.[10,12,13,28,29] The results of this study do not support this hypothesis and agree with a previous work in which no differences in cTnI release were observed in a male sample after a basketball match between adolescents and adults.[14] Conversely, in the only other study controlled according to the adolescent-adult condition, the assessment revealed that adolescents runners had a higher mean post-exercise value of hs-cTnT, with a greater number of subjects exceeding the peak URL and more time to recovery.[10] One possible explanation for these contradictory findings may be associated with differences in the pubertal status of the adolescents between the studies. Adolescents were Tanner stages 3–5 in the current study, 4–5 in basketball players,[14] and 2–3 in runners[10] suggesting than only early Tanner stage may exert an influence upon hs-cTnT. In fact, in runners it was observed that adolescents at Tanner stage 2 had higher peak hs-cTnT than those of Tanner stage 3, although the difference was not statistically significant.[10] Ongoing work should determine the causes of the high between-subject variability. Instead, our results agree with the study evaluating the runners[10] and suggest that adolescent-adult and pubertal status do not influence NT-proBNP release with exercise.

This is coherent because we observed no differences between groups in baseline NT-proBNP, which strongly explain post-exercise NT-proBNP values.

The impact of sex on hs-cTnT and NT-proBNP release

Our results suggest that there are higher post-exercise hs-cTnT values in males than females and that this may be partially explained by higher baseline values in males. Our results reflect that the sex difference in hs-cTnT release is not a consequence of differences in exercise intensity. These results partially agree with those recently observed in male and female adolescent runners.[15] The authors reported that the response of cTnT after endurance exercise was substantially higher in males than females, but at pre-exercise cTnT data were not different between two groups. In this study, exercise intensity was not controlled, and therefore we cannot rule out this factor as a contaminator variable. The authors also acknowledged the impact of assay choice upon their data. Using the hs-cTnT assay, higher baseline values in males than in females have been previously reported in adults[30] and adolescents.[31] Others researchers have speculated a role for sex hormones to explain the sex-differences in resting hs-cTnT concentration[15,31] where as we have speculated a role for sex differences in heart size.[5,6,32,33] This is an area that requires further research and insight to fully explain the mechanism(s) at play behind sex-based differences in the hs-cTnT response to exercise. Our results also confirmed that sex has limited influence on the release of NT-proBNP with exercise.[16] Again, these results may be due to that there are no sex differences in baseline NT-proBNP.

Physiological and clinical implications

The clinical implications of exercise-associated changes in biomarkers still requires further study. Importantly, elevated hs-cTnT has been demonstrated in most subjects after short-term

exercise, which is known to have beneficial effects.[34] The relatively low levels of hs-cTnT and the short time to peak with resolution within 24 h demonstrated in this and other studies[6,10,23] are somewhat different from those observed for hs-cTnT in cases of acute myocardial infarction.[1] The hs-cTnT increase occurred in the absence of clinical signs and symptoms. Furthermore, the greater values of hs-cTnT seem to be associated with subjects who, likely due to better training/genetic condition, are capable of maintaining an effort at a higher %HRmax. Altogether, these observations suggest that the post-exercise hs-cTnT level may reflect a physiological, rather than pathological, response to the exercise stimulus that may indicate transient cytosolic leakage propagated by membrane damage. From a clinical perspective, there seems to be no strong rationale for full clinical cardiovascular examination in subjects with elevated post-exercise hs-cTnT in the absence of other clinical signs and symptoms. For medical decision-making, clinicians should know that the release of hs-cTnT with exercise is evident in the majority of subjects and is equivalently present in adolescents and adults after an intense effort of 60 min, with higher values expected in males than in females. Clinicians should also know that after short-duration exercise, NT-proBNP release is expected, likely in response to volume overload and myocyte stretch,[10] at a magnitude typically lower than the URL.

Strengths and limitations

The strengths of the present study include the controlled exercise regimen, matched male and female adult and adolescent swimmers, control of pubertal status, serial blood sampling, assay precision, and measurement of both hs-cTnT and NT-proBNP levels. Several limitations should be considered: (1) Although the release of cardiac biomarkers was higher than previously established regarding biological and analytical variability, the inclusion of a non-exercise control group would have allowed a better insight into this issue, (2) training volume

of adolescents was higher than adults, even though the differences were small and both groups were highly trained, (3) differences in the %HRmax achieved in the exercise test among adolescent groups, whereas not significant, may have had a minor influence on the results, (4) the results cannot be extrapolated to the effects of much more demanding exercise tests, (5) or lower Tanner stage males and females, (6) we note the inherent limitation of cross-sectional studies. Future studies should address testing subjects sequentially through adolescence and (7) control of the menstrual cycle may also be of interest in future studies.

In conclusion, 60 min of high-intensity swimming results in equivalent elevations and kinetics across a 24-h recovery period of both hs-cTnT and NT-proBNP in adolescents at Tanner stages 3, 4, and 5 of puberty and in adults. Our results suggest that higher post-exercise hs-cTnT values are present in males compared with females because of differences in their respective baseline values. Despite the high variability in post-exercise peak values, the kinetics of hs-cTnT appearance suggests that the exercise-induced release is a physiological process with no known clinical consequences.

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Table I. Subject characteristics and exercise data

	Adolescents			Adults (n = 7 males and 9 females)
	Tanner stage 3 (n = 4 males and 10 females)	**Tanner stage 4 (n = 11 males and 11 females)**	**Tanner stage 5 (n = 10 males and 4 females)**	
Subject characteristics				
Age	14.8 ± 1.8†‡	15.1 ± 1.3†‡	16.4 ± 1.6‡	31.1 ± 7.9
Height, m	1.59 ± 5.9*†	1.65 ± 7.6	1.71 ± 7.6‡	1.64 ± 7.0
Weight, kg	51.9 ± 7.6*†‡	62.8 ± 12.9†	69.4 ± 12.0	67.5 ± 10.8
Body fat, %	17.5 ± 5.2	18.8 ± 7.3	17.4 ± 6.6	18.4 ± 6.3
Maximum HR, bpm	194 ± 8‡	194 ± 8‡	194 ± 7‡	185 ± 7
Training history, years	2.3 ± 1.6†‡	2.7 ± 2.0‡	4.8 ± 3.6	7.1 ± 6.4
Training volume, h/wk	18.0 ± 0.0‡	18.0 ± 0.0‡	18.0 ± 0.0‡	14.5 ± 9.5
60-min performance				
Velocity, km/h	3.3 ± 0.4	3.4 ± 0.4	3.5 ± 0.3	3.3 ± 0.4
Mean HR, bpm	163 ± 13	165 ± 16‡	171 ± 11‡	152 ± 16
%HRmax	84 ± 7	85 ± 8	88 ± 6‡	82 ± 9
RPE	18 ± 1	18 ± 1	18 ± 1	18 ± 1

Values are presented as means ± SD.
*Significantly different from Tanner stage 4.
†Significantly different from Tanner stage 5.
‡Significantly different from adults.

Table II. hs-cTnT (ng/L) before and after 60 min of high-intensity swimming exercise

	Adolescents			Adults (n = 7 men and 9 women)	ANOVA *P*-values	
	Tanner stage 3 (n = 4 boys and 10 girls)	**Tanner stage 4 (n = 11 boys and 11 girls)**	**Tanner stage 5 (n = 10 boys and 4 girls)**			
Pre-exercise	3.0 (3.0–8.6) [0]	3.0 (3.0–7.5) [0]	3.0 (3.0–5.3) [0]	3.0 (3.0–10.0) [0]	Time	.000
5 min	3.5 (3.0–9.6) [0]	4.3 (3.0–36.7) [14]	8.7 (3.0–32.5) [29]	3.0 (3.0–15.0) [13]	Group	.578
1 h	8.1 (3.0–40.4) [36]	13.1 (3.0–145.5) [41]	14.2 (3.0–70.0) [50]	6.0 (3.0–31.0) [31]	Sex	.000
3 h	11.9 (3.0–168.3) [43]	21.0 (3.0–335.0) [77]	22.7 (3.0–135.6) [71]	12.5 (3.0–102.0) [50]	Time x Group	.307
6 h	7.9 (3.0–95.9) [36]	13.9 (3.0–170.9) [50]	16.3 (3.0–162.0) [64]	7.1 (3.0–120.0) [31]	Time x Sex	.000
12 h	4.3 (3.0–40.0) [21]	6.2 (3.0–62.5) [18]	7.0 (3.0–143.9) [29]	3.5 (3.0–36.0) [13]	Group x Sex	.209
24 h	3.0 (3.0–18.5) [7]	3.0 (3.0–26.7) [5]	4.3 (3.0–86.4) [14]	3.0 (3.0–14.0) [6]	Time x Group x Sex	.135

Data are presented as medians (ranges). Values in brackets are the percentages of subjects with hs-cTnT exceeding the upper reference limit.

Table III. NT-proBNP (ng/L) before and after 60 min of high-intensity swimming exercise

	Adolescents			Adults (n = 7 men and 9 women)	ANOVA *P*-values	
	Tanner stage 3 (n = 4 boys and 10 girls)	**Tanner stage 4 (n = 11 boys and 11 girls)**	**Tanner stage 5 (n = 10 boys and 4 girls)**			
Pre-exercise	18.4 (5.0–52.7) [0]	19.4 (5.0–94.4) [0]	12.4 (5.0–37.0) [0]	15.6 (5.0–43.0) [0]	Time	.000
5 min	25.8 (5.3–82.4) [0]	32.8 (5.0–133.5) [5]	24.7 (5.0–53.8) [0]	25.1 (5.0–50.3) [0]	Group	.733
1 h	26.2 (5.6–73.3) [0]	28.1 (5.0–121.2) [0]	24.5 (5.0–56.0) [0]	25.9 (5.8–53.6) [0]	Sex	.119
3 h	26.8 (6.5–70.3) [0]	26.4 (5.0–113.9) [0]	23.8 (5.0–49.8) [0]	28.0 (5.6–60.3) [0]	Time x Group	.709
6 h	26.3 (6.3–68.1) [0]	24.7 (5.0–95.7) [0]	24.8 (5.0–46.9) [0]	28.4 (9.0–57.3) [0]	Time x Sex	.445
12 h	28.7 (5.3–76.4) [0]	25.3 (5.0–108.0) [0]	30.0 (9.4–53.4) [0]	26.9 (9.8–64.9) [0]	Group x Sex	.439
24 h	34.4 (6.3–66.6) [0]	30.4 (5.0–144.3) [5]	20.3 (17.0–63.8) [0]	18.3 (7.5–82.5) [0]	Time x Group x Sex	.982

Data are presented as medians (ranges). Values in brackets are the percentages of subjects with NT-proBNP exceeding the upper reference limit.