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REVIEW

Cardiac Biomarker Release After Exercise in Healthy Children and Adolescents: A Systematic Review and Meta-Analysis

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Purpose: The authors evaluated the impact of acute exercise and 24-hour recovery on serum concentration of cardiac troponins T and I (cTnT and cTnI) and N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP) in healthy children and adolescents. The authors also determined the proportion of participants exceeding the upper reference limits and acute myocardial infarction cutoff for each assay. ***Method:*** Web of Science, SPORTDiscus, MEDLINE, ScienceDirect, and Scopus databases were systematically searched up to November 2017. Studies were screened and quality-assessed; the data was systematically extracted and analyzed. ***Results:*** From 751 studies initially identified, 14 met the inclusion criteria for data extraction. All 3 biomarkers were increased significantly after exercise. A decrease from postexercise to 24 hours was noted in cTnT and cTnI, although this decrease was only statistically significant for cTnT. The upper reference limit was exceeded by 76% of participants for cTnT, a 51% for cTnI, and a 13% for NT-proBNP. Furthermore, the cutoff value for acute myocardial infarction was exceeded by 39% for cTnT and a 11% for cTnI. Postexercise peak values of cTnT were associated with duration and intensity ($Q_{(3)} = 28.3$, $P < .001$) while NT-proBNP peak values were associated with duration ($Q_{(2)} = 11.9$, $P = .003$). ***Conclusion:*** Exercise results in the appearance of elevated levels of cTnT, cTnI, and NT-proBNP in children and adolescents. Postexercise elevations of cTnT and NT-proBNP are associated with exercise duration and intensity.

Keywords: sport medicine, cTnT, cTnI, NT-proBNP

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Cardiac troponins T and I (cTnT and cTnI) are accepted indicators of myocyte necrosis and are considered sensitive markers of myocardial injury (MI) and acute myocardial infarction (AMI) (74). Serum cTnT and cTnI are elevated after irreversible heart muscle damage and levels peak during the subsequent days (1,59). The N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP) is a marker accepted to reflect myocardial stretch (73), which is currently used to detect heart failure and asymptomatic left ventricular dysfunction (14,52) with the magnitude and duration of release dependent on the severity of stretch and stress (3).

The lower detection limits of cTnT and cTnI assays have been greatly reduced in recent years (58) with new high-sensitivity assays available for both biomarkers. These assays can detect the 99th percentile with a coefficient of variation <10% and measure cTn concentrations in at least a 50% of a healthy population at rest (58). Although the higher sensitivity of these assays enables better rates of true positive detection (40), a decline in specificity has been reported such that cTn appearance might be related to etiologies other than AMI (1,16,40). This can include physical exercise as a known nonpathological cause of cTn increase (1).

Numerous investigations have described the serological release of cTnT, cTnI, and NT-proBNP after physical exercise and its kinetics (15,22,60). Contrary to an AMI-related release, cTn values normally peak within 2 to 5 (cTnT) and 3 to 6 (cTnI) hours of postexercise and then decrease returning to basal levels after 24 hours of recovery in most participants (15,25). The differences between cTnT and cTnI peaks might be related to differences in their molecular weights (11). NT-proBNP release normally peaks immediately after exercise and remains elevated during the subsequent 72 hours, and its clearance, which seems to take longer than cTn, has been related to a temporary reduction in kidney function subsequent to exercise (7,11). These observations have important clinical implications, since the elevation of these cardiac biomarkers for several hours after physical exercise might be misinterpreted in physically active patients, who are admitted to the emergency department for chest pain of origins other than acute coronary syndrome and heart failure.

The 99th percentile of a normal reference population, considered the upper reference limit (URL), is designated as the decision level for the diagnosis of MI for both general and pediatrics populations (34,74). In this respect, the reported 99th percentiles for children are lower than in adults for cTn and NT-proBNP (17,26,50), and both are used for clinical diagnostic (24). The magnitude of cTn and NT-proBNP postexercise release, as well as the prevalence of data above clinical cutoffs, have been extensively studied in healthy adults. Only a limited number of studies addressing the cardiac biomarker response to exercise in children and adolescents are currently available. Moreover, these studies are heterogeneous in terms of exercise exposure and often occur with small sample sizes and thus a limited statistical power. As a result, the association of cTn and NT-proBNP with exercise is currently controversial (8,29,44,51,63,64,66,69) and might be confounded with either individual as well as exercise characteristics.

Based on studies with adult participants, other individual characteristics except age might influence cardiac biomarkers release. Sex differences in cTn and NT-proBNP are controversial (4,6,10,23,30,36,55,80). Previous exercise experience has been negatively associated with cTn release (10,21,46,76) while training load might be not associated with biomarker appearance (18,21,28,33,67,78). NT-proBNP is not associated with previous exercise experience either (62,67,75) while its association with training load remains controversial (18,28,43,61–64,67). Finally, fitness condition has not been associated with cTn or NT-proBNP data (67,70). Exercise characteristics have also been studied as to their influence on cardiac biomarker release (15,68). Exercise intensity was mentioned as a predictor for cTn release while exercise duration has been correlated with both cTn and NT-proBNP data (9,7,12,61,67,83). Exercise mode and type have not been fully evaluated, and any associations remain controversial (32,53,85).

Previous systematic reviews and meta-analyses related to cardiac biomarker release after exercise have been focused on adult participants (15,65,68,82). To the best our knowledge, no systematic review or meta-analysis has been published addressing the cardiac biomarkers response to exercise in children and adolescents. Considering that children and adolescents have a low cardiovascular risk (2), we selected this special group to get a "clean" background and preclude the potential effects of concealed cardiovascular diseases and get "pure" effect of exercise on cardiac biomarkers. Due to variations in sample size and the diversity of participant and exercise characteristics, a systematic review with a meta-analysis could contribute to the current knowledge by synthesizing available data into single, more powerful estimates of effect. Moreover, the secondary analysis might help to identify possible associations with individual and exercise characteristics that could explain a certain degree of heterogeneity between the current findings.

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (41), the main objective of this study was to systematically review studies whose participants were healthy children and adolescents who were exposed to physical exercise and whose resting and postexercise measures of cTnT, cTnI, and NT-proBNP were described. A secondary objective was to analyze the moderator effects of (1) age, (2) pubertal status, (3) sex, (4) previous training (y), (5) current training (in hours per week or kilometers per week), (6) exercise duration (in minutes), (7) exercise intensity (average HR), (8) maximum oxygen uptake (VO_2max), and (9) exercise mode on the pooled effects determined by the main objective.

Methods

Search Strategy

We searched Web of Science, SPORTDiscus, MEDLINE, ScienceDirect, and Scopus databases between July 1, 2017 and November 30, 2017. A 3-component additive search key (*#A AND #B AND #C*) was used with: #A, measurement; #B, intervention; and #C, population. All searches were restricted to title or abstract, and keywords were stated in English. The measurement was defined with the expression *"cardiac biomarker*" OR Troponin OR TnT OR TnI OR cTn* OR hs-cTn* OR "N-terminal prohormone of brain natriuretic peptide" OR "NT-proBNP" OR "NT-pro-BNP"*. Intervention was specified with: *exercise OR sport* OR "physical activity" OR running OR marathon OR soccer OR swim* OR athletes*. Finally, the population was stated with *"children OR adolescent* OR young"*.

Inclusion and Exclusion Criteria

We selected observational or experimental studies with a repeated measures design. Participants (or a subset of them) must be under the age of 18, not have a personal history or clinical evidences of cardiovascular disease, and have a normal 12-lead electrocardiogram and/or echocardiogram at rest (71). Interventions of interest were those which involved exposure to physical exercise, including sport events and laboratory tests. We searched primarily for studies that reported cTnT and/or cTnI and/or NT-proBNP concentrations before and after exercise. Inclusion criteria included the necessity to report some quantitative measure of location and variation (mean [SD], median with range, or median with interquartile range) of the biomarker's value for a minimum of one time point postintervention. Studies, where participants were exposed to specific pharmacological or nutritional interventions, were excluded and the remaining articles were included in our review.

Data Extraction

Studies were inspected to gather the data for (where available): sample size, sex, maturational status, age, training status (years of previous experience, weekly hours of training, and weekly kilometers of training); VO_2max; performed exercise; exposure duration (in minutes); average heart rate (surrogate of intensity); and absolute concentration of cTnT, cTnI, or NT-proBNP before and after exercise. We also recorded the proportion of participants above the URL for each biomarker, and the rate of participants above the cutoff for AMI for cTnT and cTnI. Outcomes reported as median [range] were transformed to mean (SD) using Wan et al. (84) formulas. All concentrations were expressed in nanograms per liter (74), and concentrations of cTn reported as "under limits of detection of 10 ng/L" were represented as 5 ng/L (12,48).

Quality Assessment

We analyzed the methodological quality of studies that met all inclusion criteria to detect possible methodological discrepancies that might explain a degree of heterogeneity between studies. In this sense, studies' quality was assessed by 2 authors independently, filling the Quality Assessment Tool for before–after (Pre–Post) studies with no control group from the National Heart Lung and Blood Institute (42). This scale considers 12 binary items, which average scores of each article from 0 indicating high risk of bias to 1 indicating low risk of bias (QAT_i). Discrepancies between assessors were resolved by a third author.

Statistical Analysis

All analyses were performed in R (R Foundation for Statistical Computing, Vienna, Austria; 54) using Viechtbauer's "metafor" package v 1.9-9 (81). Random effects meta-analyses were conducted by biomarker (cTnT, cTnI, and NT-proBNP) using the following estimates: the baseline concentration, the peak concentration, the concentration at 24 hours, the absolute mean difference between baseline and peak concentrations, the absolute mean difference between baseline and concentration after 24-hours recovery, the absolute mean difference between peak concentrations and concentrations at 24-hour postexercise, the rate of participants whose peak concentration exceeded the assay URL, and the rate of participants exceeding the cutoff for AMI. Rates were log-transformed for statistical comparisons, and estimates were then back-transformed for ease of interpretation. Heterogeneity was measured with Cochrane's Q statistic and I^2 values (19). We assessed publication bias using Egger's regression test for funnel plot asymmetry (5,56). Subgroup analyses were conducted when heterogeneity was significant to assess the possible influence of exercise mode, age, intensity, and duration on the absolute mean difference between baseline and peak concentrations. In addition, when data was available, we investigated for the possible influence of Tanner stage, sex, VO_2max, years of previous training, weekly hours of training, and weekly kilometers of training, regardless of exercise mode, age, intensity, and duration. Outcome multiplicity from the same groups (12) was controlled introducing a study identified as a random effect (79,81). Measures are expressed as mean ± 95% confidence intervals (CI) unless otherwise stated, and we considered statistically significant differences when $P < .05$.

Results

The search process is outlined in Figure 1. Fourteen studies met the inclusion/exclusion criteria that included 21 groups covering a total sample of 336 participants (72 females) who had a mean age of 15.1 (2.3) years (12,13,20,27,30,38,39,46–49,75–77). Two studies provided complete data from more than 1 subgroup contributing with different estimates by sex (27,77) or Tanner stage (30), which were treated as different units for the analysis. One study provided 4 outcome measurements from the same group at different exposures (12), which were controlled for multiplicity within the models (79,81). Interventions were based on 5 different modalities: in 9 studies, participants ran [3 treadmill protocols [45–90 min] (13,47,75); 5 half marathons (12,27,46,48,76); and 1 full marathon (77)]; in 2 studies, basketball was employed (38,49); in 1 study, a soccer match was played (20); in 1 study, participants swam for 60 min (30); and 1 study included a set of table tennis exercises (39). Table 1 shows the number of groups available for each comparison (k) as well as their respective pooled effect sizes.

Quality Assessment and Risk of Publication Bias

Studies had a mean quality score of .61 (.07). Prespecification of sample eligibility criteria, enrollment of all eligible participants and sample size calculation were rated as *high risks of bias* in all studies. Other concurrent items rated as high risk of bias were blinding of outcome assessors; controlling for confounding variables in the statistical analysis; reporting the main effect of time with P values; and validity and reliability of outcome measures in 12, 9, 3, and 1 cases, respectively. On the other hand, Egger's

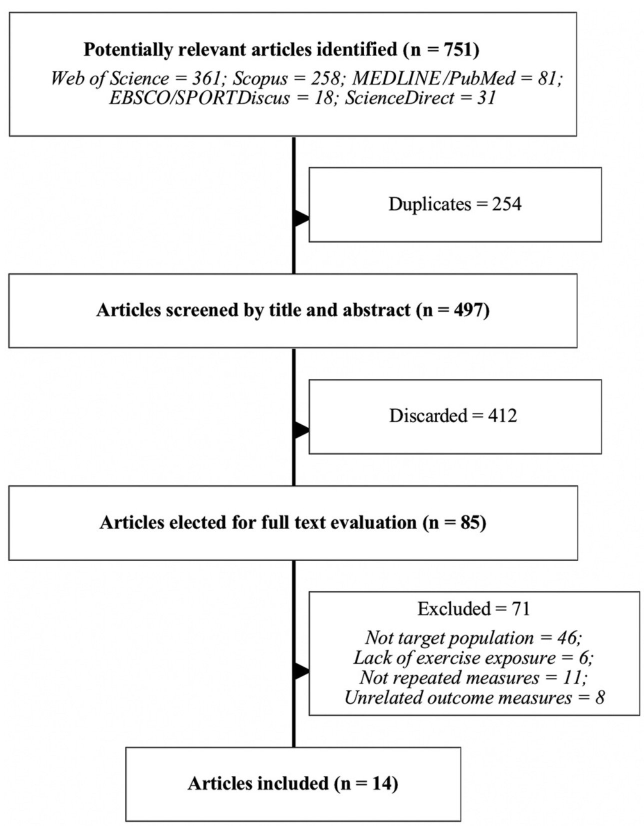

Figure 1 — Flowchart for study inclusion and exclusion stages.

Table 1 Estimated Pooled Effect Sizes (95% CI) by Biomarker

	k	Pooled effect size	*Z*	$P_{(Z)}$	*Q*	$P_{(Q)}$	I^2, %
Cardiac troponin T							
Mean baseline, ng/L	16	5 (4 to 6)	11.84	<.001	206.47	<.001	98.7
Mean peak, ng/L	14	144 (83 to 205)	4.65	<.001	105.78	<.001	96.5
Mean at 24 h, ng/L	9	11 (5 to 16)	3.86	<.001	146.52	<.001	98.2
Dif. peak–pre, ng/L	14	139 (79 to 198)	4.53	<.001	102.72	<.001	96.4
Dif. 24 h–peak, ng/L	7	−89 (–147 to –32)	−3.04	.002	33.85	<.001	93
Dif. 24 h–pre, ng/L	9	7 (1 to 12)	2.5	.01	87.22	<.001	96.3
MI threshold IR	18	0.76 (0.66 to 0.87)	−3.83	<.001	27.86	.047	13.5
AMI threshold IR	14	0.39 (0.26 to 0.6)	−4.38	<.001	39.1	<.001	75.4
Cardiac troponin I							
Mean baseline, ng/L	7	16 (10 to 22)	5.15	<.001	89.67	<.001	96.4
Mean peak, ng/L	5	248 (17 to 478)	2.1	.04	61.42	<.001	99
Mean at 24 h, ng/L	7	38 (19 to 56)	4.05	<.001	348.01	<.001	97.7
Dif. peak–pre, ng/L	5	228 (6 to 450)	2.01	.04	54.53	<.001	98.9
Dif. 24 h–peak, ng/L	5	−199 (–404 to 5)	−1.91	.06	42.56	<.001	98.2
Dif. 24 h–pre, ng/L	7	21 (8 to 33)	3.23	.001	100.97	<.001	93.2
MI threshold IR	7	0.51 (0.32 to 0.81)	−2.85	.004	16.74	.01	60.5
AMI threshold IR	4	0.11 (0.05 to 0.24)	−5.4	<.001	3.41	.33	24.4
NT-proBNP							
Mean baseline, ng/L	6	77 (14 to 140)	2.38	.02	217.98	<.001	99.5
Mean peak, ng/L	6	106 (17 to 195)	2.34	.02	288.19	<.001	99.5
Mean at 24 h, ng/L	4	83 (0[a] to 182)	1.63	.10	173.89	<.001	99.6
Dif. peak–pre, ng/L	6	20 (2 to 38)	2.20	.03	13.64	.02	79.2
Dif. 24 h–peak, ng/L	4	−2 (–11 to 7)	−0.48	.63	7.26	.06	0.1
Dif. 24 h–pre, ng/L	4	4 (–8 to 28)	1.55	.44	0.65	.88	0
MI threshold IR	6	0.13 (0.04 to 0.44)	−3.32	<.001	18.02	.003	74.1

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; Dif., difference; IR, incidence rates; MI, myocardial injury; NT-proBNP, N-terminal fragment of the prohormone brain natriuretic peptide. Note: Estimated effects for IR were back transformed for easier interpretation.
[a]Mathematically negative and truncated to 0 avoiding values outside the parameter space.

regression test was significant for all 3 biomarkers cTnT, cTnI, and NT-proBNP ($P < .001$), suggesting that current literature was still unrepresentative of the population of completed studies.

Cardiac Troponin T

Participants had an overall cTnT concentration at baseline of 5 ng/L (4–6 ng/L). This concentration was increased ($P < .001$) after 2 to 5 hours, reaching a peak of 144 ng/L (83–205 ng/L). Finally, 24 hours after exercise, cTnT was reduced ($P < .002$) with a pooled concentration of 11 ng/L (5–16 ng/L), which was slightly higher than at baseline ($P = .01$) (Figure 1). All 3 pooled concentrations, as well as their differences, were heterogeneous between studies ($P < .001$ in all comparisons). Overall, 76% (66%–87%, $P < .001$) of participants had a cTnT peak above the assays URL, and a 39% (26%–60%, $P < .001$) exceeded the cutoff for AMI. Again, both rates, for MI and for AMI, were heterogeneous between studies ($P = .047$ and $P < .001$, respectively).

In the subgroups analyses, cTnT was measured in 4 exercise modes, namely half marathon, treadmill running, table tennis, and swimming. Exercise mode, available in $k = 14$ units with a total of n = 193 participants, had a main effect on cTnT increase to peak ($Q_{(3)} = 9.98$, $P = .02$). Post hoc analysis revealed that after a half marathon and treadmill run cTnT increases were higher than after intermittent table tennis and swimming ($P < .001$ and $P = .004$, respectively). Multiple regression with exercise mode as a random effect ($k = 11$, n = 138), revealed that age had a negative association ($P < .001$) while intensity and duration were positively associated ($P < .001$ and $P = .003$, respectively) with cTnT increase ($Q_{(3)} = 28.3$, $P < .001$). Moreover, participants' VO_2max correlated negatively with cTnT increase ($k = 7$, n = 60, $P = .04$). We did not find associations between cTnT increase and sex ($k = 11$, n = 138, $P = .3$), Tanner stage ($k = 4$, n = 63, $P = .504$); years of previous training ($P = .16$); or weekly kilometers of training ($k = 10$, n =110, $P = .32$).

Cardiac Troponins I

The pooled baseline concentration for cTnI was 16 ng/L (10–22 ng/L). After 3 to 6 hours of exercise exposure, participants increased this concentration ($P = .04$) up to a peak of 248 ng/L (17–478 ng/L). After 24-hour recovery, this reduced to 38 ng/L (19–56 ng/L) which was not statistically different from the estimated peak concentration ($P = .06$) (Figure 2). However, all 3 pooled concentrations, as well as their differences, were heterogeneous between studies ($P < .001$ in all comparisons). The proportion of participants with cTnI above the URL was 51% (32%–81%) and the rate exceeding the cutoff for AMI was 11% (5%–24%). The rate for

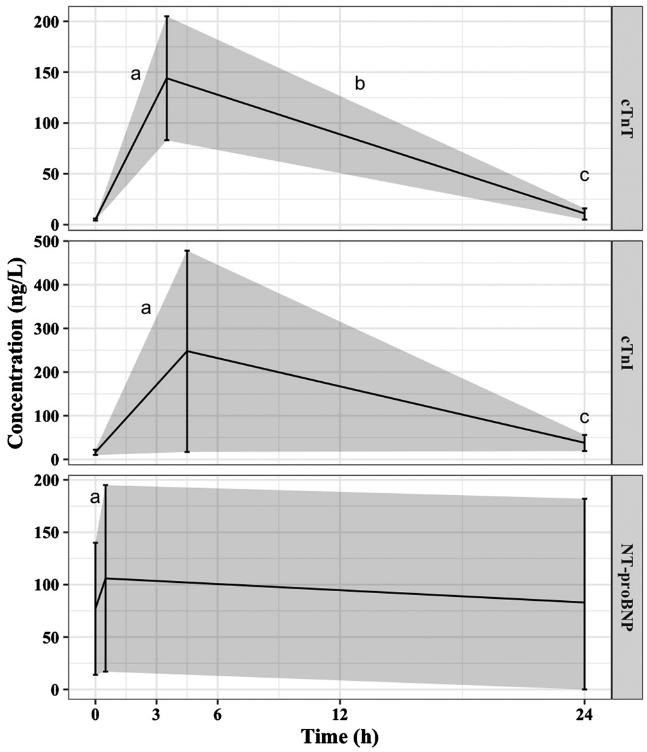

Figure 2 — Estimated kinetics by biomarker before, at peak value, and 24 hours after exercise, with their 95% confidence interval, respectively. cTnT indicates cardiac troponin T; cTnI, cardiac troponin I; NT-proBNP, N-terminal fragment of the prohormone brain natriuretic peptide. Note: a = significant increase; b = significant decrease; and c = higher than at baseline.

MI was heterogeneous ($P = .01$) while the rate for AMI was not ($P = .33$) between individual studies.

In the subgroup analysis, cTnI was measured in 4 exercise modes, namely half marathon, basketball, table tennis, and soccer. The cTnI increase to peak did not differ between exercise modes ($k = 5$, n = 83, $Q_{(4)} = 4.75$, $P = .31$); multiple comparisons ($k = 4$, n = 61) at different ages ($P = .33$); intensities ($P = .59$); or durations ($P = .31$). In addition, we did not find differences due to years of training ($k = 3$, n = 33, $P = .37$) or participants' VO_2max ($k = 3$, n = 33, $P = .54$). Tanner stage and weekly training load data were not available to be modeled.

N-Terminal Prohormone Brain Natriuretic Peptide

The pooled baseline concentration for NT-proBNP corresponded to 77 ng/L (14–140 ng/L). This concentration was increased immediately after exercise ($P = .03$) achieving a peak of 106 ng/L (17–195 ng/L). Finally, 24 hours after exercise, NT-proBNP concentration did not differ from its peak ($P = .63$) or baseline ($P = .44$) with an estimate of 83 ng/L (0–182 ng/L) (Figure 2). All 3 concentrations were heterogeneous ($P < .001$). The rate of participants with NT-proBNP concentration above the URL was 13% (4%–44%, $P < .001$), and studies were heterogeneous ($P = .003$).

In the subgroup analysis, NT-proBNP was present in 4 different exercise modes, namely half marathon, treadmill running, swimming, and soccer. Exercise mode had a main effect on the NT-proBNP postexercise increase ($k = 6$, n = 101, $Q_{(4)} = 25.06$, $P < .001$). Post hoc comparisons revealed that the higher NT-proBNP increases were related with soccer (estimated increase of 83 ng/L, 95% CI, 34–131 ng/L; $P < .05$) followed by half marathon (estimated increase of 59 ng/L, 95% CI, 12–105 ng/L; $P = .01$) and finally followed by swimming (estimated increase of 11 ng/L, 95% CI, 3–18 ng/L; $P = .01$), with no differences in the mode of treadmill running ($P = .93$). Moreover, in a multiple regression with exercise mode as a random effect ($k = 4$, n = 62), duration had a positive association with the estimate ($P < .001$) while age ($P = .34$) and intensity ($P = .37$) were not associated with NT-proBNP ($Q_{(2)} = 11.9$, $P = .003$). Finally, we did not find differences in NT-proBNP for sex ($k = 4$, n = 62, $P = .3$); Tanner stage ($k = 3$, n = 50, $P = .601$); and years of previous training ($k = 4$, n = 62, $P = .499$). VO_2max and weekly training load data were not available to be modeled.

Discussion

The main purpose of this systematic review and meta-analysis was to estimate how exercise modulated the blood concentration of cTnT, cTnI, and NT-proBNP in children and adolescents. Overall, this review found: (1) all 3 biomarkers were significantly elevated after exercise; (2) a decrease from peak values after 24-hour recovery was only significant for cTnT; (3) the rate of participants exceeding the biomarkers' URL were 76% for cTnT, 51% for cTnI, and 13% for NT-proBNP; (4) the rate of participants exceeding the cutoff value for AMI were 39% for cTnT and 11% for cTnI; (5) individual variability was observed between studies; and (6) exercise duration influenced both cTnT and NT-proBNP while intensity influenced only cTnT. Despite these findings, the quality assessment of studies together with the analysis for publication bias revealed that current studies have a fair degree of quality with limited bias.

Cardiac Troponins T and I

Our results indicate that cTn release in children and adolescents is inherent to physical exercise. Data reflect a fast increase of cTnT during the early hours of recovery, with close to complete recovery to baseline at 24 hours. Similar results were appreciable for cTnI, although statistical power was limited and lead to only marginally significant differences between peak and 24-hour values. Such observations suggest that cTn kinetics in children and adolescents during a 24-hour recovery are comparable with the observed in adults (15,25). Our results coincide with previous research observing the highest cTnT and cTnI concentrations about 2 to 3 and 3 to 5 hours postexercise, respectively (15,25). Based upon the previous text, when repeated blood sampling is not possible, single samples taken within such interval might detect concentrations close to the kinetics peak.

The current data suggest that, as in the case of adults (32,33), there is a marked individual variability regarding the exercise-induced release of cTn, with a high proportion of participants with values exceeding the URL for MI and AMI. As evidenced in controlled studies with adolescents (12) and adults (67), cTnT variability could be partially explained by exercise intensity and duration, what likely reflects an impact of exercise volume on cardiac work. We also observed a higher cTnT release in the younger participants, and this could explain that the proportion of participants exceeding the URL in our study is higher than the reported by a recent meta-analysis without age restrictions (65). This would suggest a role for maturity mediating the postexercise cTn release. However, direct comparisons of the release of cTn after exercise in adults and adolescents have disclosed contradictory findings (30,38,75). Moreover, with the scarce data currently available, we did not find any association between cTnT release and pubertal status. At all events, associations with pubertal status require further investigation. Running seems to induce higher cTnT releases than other modes as it was noticed in a previous meta-analysis based on adult participants (68); nevertheless, such an assertion is complex to verify through direct comparisons. Although we observed lower cTnT releases in participants with greater VO_2max, we could not corroborate whether the cTnT increase is mediated by current training or training history. It was not evident whether there were any sex differences in the cTn release. This coincides with previous studies in adults which reported a limited influence of sex and training history on the release of cTn (4,27,30,32,33,38,77). The scarce number of studies did not allow to explain the between-subjects variability regarding the release of cTnI.

N-Terminal Prohormone Brain Natriuretic Peptide

An increase in NT-proBNP immediately after exercise was confirmed without a significant reduction within the 24-hour recovery period that supports past research with adults (31,37). NT-proBNP may have a longer clearance period that cTn possibly extended to 72 hours (7,11). In this regard, it has been suggested that BNP may play an important role in homeostasis during the transition of the circulation from children to maturity as a marker of myocardial growth (72). This might reflect an early myocardial adaptation to the intense training stimulus in children and adolescents. In either case, these possibilities require further study.

We noted that NT-proBNP changes with exercise were lower than the observed in cTn. Therefore, the proportion of participants exceeding the URL of NT-proBNP was lower than the reported in studies with adults (11,60). These differences might be associated with age. However, neither our analysis nor previous studies comparing directly adolescents with adults found NT-proBNP differences for age and pubertal status (30,75). It is therefore plausible to think that these differences might be related to exercises with less duration in studies conducted with adolescents compared with their equivalents with adults. Our results confirm indeed that in adolescents the release of NT-proBNP is largely associated with exercise duration, as it was reported previously in studies with adults (66,67). Given the close relationship between preexercise and postexercise values (31,33), baseline differences between studies might explain part of the differences we observed across NT-proBNP peak values depending on the exercise mode. Our results also confirmed that as in adults (4,30,31,33,66,67) exercise intensity, training, fitness, and sex have limited influence on the release of NT-proBNP with exercise.

Clinical Implications

A cardiac biomarker release was observed in most of the participants in all included studies, despite a certain degree of between-study variability. Importantly, this analysis shows that in children and adolescents, the factors mediating cardiac biomarkers after exercise as well as their kinetics, are comparable with the observed in previous studies in adults and differ from the observed after MI and AMI (73,74). It has been suggested that this reflects a reversible cellular process triggered by a normal physiological response to exercise (7,45,57,62). Likewise, the increase of cTn might reflect an increased rate and force of cardiac contraction during exercise that causes transient membrane damage and enables cytosolic cTn to pass into circulation (69). On the other hand, a release of NT-proBNP from the ventricular cardiomyocytes might reflect a volume overload and cardiac wall stretch during exercise (11). Furthermore, some authors suggested that the use of the general population values as a reference might not be appropriate for adult athletes being evaluated for medical conditions using blood indices of cardiac biomarkers. This has prompted the reflection that cardiac biomarkers values might be stratified according to the physical activity of the adult subjects for improving the clinical usefulness of the biomarker (35). In this sense, our analysis extends this to children and adolescents and suggests that when evaluating cTnT, cTnI, and NT-proBNP in emergency settings, detailed information regarding any recent exercise should be obtained (38).

Limitations

The main limitation of this systematic review and meta-analysis derives from the incomplete data provided by a range of heterogeneous studies. Moderator analyses were performed with reduced numbers that decreased statistical power. This lack of statistical power might explain some nonsignificant results such as the inconclusive decrease in cTnI within a 24-hour postexercise recovery. We did not incorporate assay precision to our meta-analysis which could have explained certain degree of the study-to-study heterogeneity (68). Finally, we found differences between studies regarding when peak concentrations were taken or noted. More research should be conducted with children and adolescents analyzing such covariate parameters.

Conclusion

Cardiac biomarkers in children and adolescents are significantly increased from rest to postexercise with the URL exceeded by a 76% of participants for cTnT, a 51% for cTnI, and a 13% for NT-proBNP, and the cutoff value for AMI is exceeded by 39% for cTnT and an 11% for cTnI. Finally, we confirmed that the cTnT release is mainly associated with exercise duration and intensity, while the NT-proBNP release remains influenced only by exercise duration.

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