Review

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High-sensitivity cardiac troponins in pediatric population

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Abstract: Apparently healthy children often complain of chest pain, especially after physical exercise. Cardiac biomarker levels are often measured, but the clinical relevance of these assays in children is still debated, even when a cardiac disease is present. Coronary artery disease is exceedingly rare in children, but elevated circulating levels of cardiac troponin I (cTnI) and T (cTnT) in an acute setting may help detect heart failure due to an unknown cardiac disorder, or worsening heart failure, particularly in combination with other biomarkers such as B-type natriuretic peptides. However, the interpretation of biomarkers is often challenging, especially when institutions transition from conventional cTn assays to high-sensitivity (hs-cTn) methods, as well demonstrated in the emergency setting for adult patients. From a clinical perspective, the lack of established reference values in the pediatric age is the main problem limiting the use of hs-cTn methods for the diagnosis and managements of cardiac diseases in infants, children and adolescents. This review aims to discuss the possibility to use hs-cTnI and hs-cTnT to detect cardiac disease and to explore age-related differences in biomarker levels in the pediatric age. We start from some analytical and pathophysiological considerations related to hs-cTn assays. Then, after a systematic literature search, we discuss the current evidence and possible limitations of hs-cTn assay as indicators of cardiac disease in the most frequently cardiac disease in pediatric setting.

Keywords: cardiac troponins; high-sensitivity methods; myocardial injury; NT-proBNP; pediatric cardiology; reference intervals.

Introduction

Since 2000, worldwide guidelines have recommended cardiac troponins (cTn) be regarded as the biomarkers of choice for the diagnosis of acute coronary syndrome (ACS) in adults [1–3]. In 2018, the Fourth Universal Definition of Myocardial Infarction (MI) [2] defined myocardial injury as elevated cTnI or cTnT concentrations with at least one value above the 99th percentile of the distribution of biomarker values in a reference population of apparently healthy individuals (99th percentile Upper Reference Level, URL) [2]. Myocardial injury in a setting compatible with cardiac ischemia identifies a MI, but myocardial injury can occur without infarction in several cardiac and systemic pathologies [2, 3]. The most important consequence of the application of this statement to current clinical practice is that cTnI or cTnT are measured using high-sensitivity methods (hs-cTnI and hs-cTnT) in all adult individuals with chest pain [1–3]. Furthermore, over the last 10 years, several clinical studies (including some meta-analyses) have demonstrated that pathophysiological and clinical relevance of hs-cTnI and hs-cTnT measurement can predict incident heart failure and major cardiovascular events in adult individuals from the general population [4–6].

Apparently healthy children often complain of chest pain, especially after physical exercise. Cardiac biomarker levels are often measurable, but the clinical relevance of these assays in children is still debated [7], even when a cardiac disease is known. Coronary artery disease is exceedingly rare in children, but elevated hs-cTnI or hs-cTnT in an acute setting may help detect heart failure due to an unknown cardiac disorder [7–9], or worsening heart failure, particularly in combination with other biomarkers such as B-type natriuretic peptides [7–11]. However, the interpretation of hs-cTn assays is often challenging, especially when institutions transition from conventional cTn assays to hs-cTn methods, as demonstrated in the emergency setting for adult patients [1, 3]. From a clinical perspective, the lack of established reference values in the pediatric age is the main problem limiting the use of hs-cTn methods in infants, children and adolescents [1, 7].

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This review aims to discuss the possibility of measuring hs-cTnI and hs-cTnT to detect cardiac disease in the pediatric age and to explore age-related differences in biomarker levels. We start from some analytical and pathophysiological considerations related to hs-cTn assays, then we discuss current evidence on hs-cTn as indicators of cardiac disease in the pediatric setting.

Analytical and pathophysiological considerations on cardiac troponins as biomarkers

Analytical properties

The 2018 Expert Opinion from AACC and IFCC [18] recommends that hs-cTn methods satisfy two fundamental criteria. First, these laboratory tests should measure the 99th percentile URL with an imprecision (expressed as coefficient of variation) $\leq 10\%$. Second, these assays should be able to detect the biomarker concentration at or above the limit of detection (LoD) in 50% of healthy individuals. The estimation of 99th percentile URL strongly depends not only on demographic and physiological variables of the reference population, but also on the analytical performances of laboratory methods, and the mathematical algorithm to calculate the 99th percentile value [1, 13, 16–18]. Identification of the URL is a very difficult task usually undertaken in the setting of multicenter studies [1, 3, 7, 18].

Only the most recent hs-cTnI and hs-cTnT methods fully satisfy these analytical specifications [18]. Their analytical sensitivity ranges from 1 to 3 ng/L, allowing to measure the URL with a mean imprecision of about 5% (i.e., half of the level required by guidelines) (Figure 1) [1, 5, 6, 16, 17]. The few studies using hs-cTnI and hs-cTnT methods in apparently healthy infants and children have demonstrated that biomarker values are generally higher if compared to those observed in apparently healthy subjects aged >18 years [19–27]. In detail, hs-cTnI and hs-cTnT are higher in healthy neonates and infants compared to children and adolescents, while boys have usually higher values than girls [19–38] (Table 1). Therefore, the sensitivity of commercially available hs-cTnI and hs-cTnT methods seems more than adequate to accurately measure circulating levels of biomarkers in the pediatric age. This is very important because it is not clear whether some of the cTnI methods [28–37], cited in a 2016 systematic review [38], actually meet the quality specifications for hs-cTn assays [18]. For this reason, only the circulating levels of biomarker measured with hs-

cTnI and hs-cTnT methods in healthy neonates, children and adolescents are reported in Table 1.

The two most important limitations of studies on references intervals of hs-cTnI and hs-cTnT, particularly in neonates, infants and children, are the volume of blood usually collected (about 0.5–1.0 mL) and the number of subjects needed to accurately measured the distribution values of biomarkers. Indeed, almost 300 apparently healthy individuals are needed for each age (i.e., neonates, infants or children) and sex group (boys or girls) to calculate the URL with a 99% confidence interval [18, 39]. Unfortunately, even larger studies do not satisfy the criteria of at least 300 cases for different age and sex groups [23, 27] (Table 1).

Studies in adult subjects reported large systematic differences among hs-cTnI values measured through different methods, including URL and reference values [1, 16, 40–42]. There are concerns about the possibility to reliably harmonize results of hs-cTnI methods [1, 16, 40–42]. As an example, the sensitivity and URL values measured in the same population using standardized analytical protocols and statistical procedures are reported in Table 2. At present, data regarding only one hs-cTnI method are available in the pediatric age [20, 21, 23], but these systematic differences should be taken into account in future studies.

hs-cTn levels during the pediatric age

The studies on hs-cTnI and hs-cTnT levels across the pediatric age [19–26] confirm the trend previously reported with the less sensitive methods [27–36]. In particular, hs-cTnI and hs-cTnT show a similar trend with the highest values in the first month of life, followed by a rapid fall during the first six months, and then a slower decline during childhood, finally reaching a plateau during adolescence [19–26]. Minor sex-specific differences have been observed in healthy adolescents, with higher concentrations in boys [19–26, 43], in agreement with results from adult cohorts including healthy subjects aged >18 years [16, 19, 22, 40, 43]. These considerations underscore the importance of interpreting hs-cTnI and hs-cTnT concentrations according to age and sex [43]. Differences between the clinical utility of hs-cTnI and hs-cTnT are not well understood, especially in pediatric age, and there is a lack of harmonization in hs-cTnI methods that poses clinical challenges and complicates the comparison and interpretation of study findings, particularly in the pediatric age where literature is more limited [41–43].

Circulating hs-cTn in healthy adult subjects might be considered a reliable index of cardiomyocyte renewal

Figure 1: Mean imprecision profile calculated considering some hs-cTnI and hs-cTnT methods.

The mean imprecision profile (expressed as CV %) among three hs-cTnI methods (i.e. Architect, Access and ADVIA Centaur XPT) and the ECLIA hs-cTnT method was estimated using a standardized protocol, as previously reported in detail [1, 5]. In particular, for the calculation of the mean imprecision profile, 11 plasma pools collected from normal healthy subjects and patients with cardiac disease were repeatedly measured (more than 30 folds in different working days using at least two lots of reagents and standards) with the hs-cTnI and hs-cTnT methods. These plasma pools actually cover the concentration biomarker range from the LoD (about 1–3 ng/L) to the 99th percentile URL values (from 13 to 50 ng/L) of the hs-cTn methods (Table 2). Four different graphical symbols were used to represent the mean biomarker values measured with the four hs-cTn methods. The curvilinear relationship was then calculated between the CV values (Y axis) and the respective hs-cTn concentrations using the mean values obtained from the plasma pools measured with the four hs-cTn methods [1, 5]. Finally, the best fitting (reciprocal equation) among the 44 mean values of the 11 plasma samples measured with the four hs-cTn methods was calculated using the JMP 15.2.1 statistical program (SAS Institute Inc.) and reported in the Figure, also including the correlation coefficient R.

[1, 42, 44–58]. The changing rates of cardiomyocyte renewal during the pediatric age might account for different hs-cTn levels in neonates, infants and children [22, 25, 43–45, 59, 60]. Other possible reasons of this heterogeneity are the expression of fetal cardiac troponin in the skeletal muscle, transient hypoxia at birth and/or cardiac leakage [20, 42]. Sex-specific differences in healthy adolescents are commonly explained by the greater cardiac mass in males [16, 43–48].

hs-cTn increase after physical exercise

Increased hs-cTnI and hs-cTnT have been described in preadolescent and adolescent healthy athletes after intense physical exercise [61–66]. In particular, hs-cTn

usually increases during a prolonged exercise or within a few hours after exercise end, resolving within 24–48 h [61]. Nie et al. [64] examined the effect of two 45 min constant-load treadmill runs separated by 255 min of recovery in 12 trained adolescent runners (aged 14.5 ± 1.5 years). cTnT was undetectable before exercise, but was elevated post-exercise in 67% of runners, and then decreased progressively thereafter [64]. Peretti et al. [66] evaluated hs-cTnT and natriuretic peptides in 21 healthy male athletes (aged 9.2 ± 1.7 years) after an intensive cycling training until muscular exhaustion (mean duration 16 min). The majority of preadolescent athletes (62%) had an elevation of cardiac biomarkers: specifically, six children had increased hs-cTnT, and three had an elevation of NT-proBNP as well [66]. hs-cTnT elevation had no relationship with heart rate, age

Table 1: Circulating levels measured with hs-cTnI and hs-cTnT methods in healthy neonates, children and adolescents according to the literature data.

Reference	Laboratory method	Pediatric population studied Age range; number of subjects	Biomarker values, ng/L
Caselli et al. [21]	hs-cTnI architect	Newborns: <1 month; n=36 Infants: 1–12 months; n=57 Toddlers: 1–10 years; n=65 Adolescents: 10–18 years; n=221	Median: 21.5; IQR: 31.2 Median: 11.5; IQR: 16.0 Median: 2.2; IQR: 1.2 Median: 2.0; IQR: 1.3
Caselli et al. [22]	hs-cTnI architect	Newborns: <1 month; n=24 Infants: 1–12 months; n=26 Children: 1–12 years; n=19 Adolescents: 13–18 years; n=26	Median: 9.3; 25–75th perc: 3.3–93.8 Median: 13.5; 25–75th perc: 4.6–52.1 Median: 11.5; 25–75th perc: 4.0–48.1 Median: 2.6; 25–75th perc: 2.1–3.9
Bohn et al. [23]	hs-cTnT ECLIA	0–6 months; n=55 6–12 month; n=44 1–19 years; females; n=249 1–29 years; males; n=249	97.5th perc: 83 (CI: 69–96); 99th perc: 93 (CI: 78–108) 97.5th perc: 19 (CI: 12–22); 99th perc: 21 (CI: 17, 24) 97.5th perc: 6 (CI: 5–13); 99th perc: 11 (CI: 5, 13) 97.5th perc: 11 (CI: 7–5); 99th perc: 14 (CI: 7, 17)
Karlén et al. [24]	hs-cTnT ECLIA	Cord blood; n=105 Newborn: 2–5 days; n=73	Median: 34; 25th per: 26; 75th perc: 44; 99th perc: 88 Median: 93; 25th perc: 54; 75th perc: 158; 99th perc: 519
Lam et al. [26]	hs-cTnT ECLIA	0–6 months; n=64 6 months to 1 years; n=45 1–19 years; n=131	97.5th perc: 78 (CI: 68–87); 99th perc.87 (CI: 76–97) 97.5th perc: 34 (CI: 28–42); 99th perc.21 (CI: 32, 47) 97.5th perc: 6 (CI: 6–11); 99th perc.11 (CI: 11, 14)
Mondal et al. [27]	hs-cTnI architect	Cord blood all data; n=256 Cord blood only full-term	Median: 6; 90th perc: 27.4; 95th perc: 54.3; 99th perc: 172.1 Median: 6; 90th perc: 19.8; 95th perc: 41.5; 99th perc: 166.3

IQR, interquartile range; CI, 90% confidence interval.

Table 2: Analytical characteristics and distribution parameters for some hs-cTnI and hs-cTnT methods.

hs-cTnI methods	LoD, ng/L	LoQ 10%, ng/L	Median, ng/L, 25–75th percentiles	99th percentile URL, ng/L	Number of subjects
ARCHITECT	1.3	4.7	1.8 (1.2–2.8)	18.9	1,463
ACCESS DxI	1.3	5.3	2.7 (1.9–4.0)	16.8	1,460
ADVIA CENTAUR XPT	2.2	8.4	3.3 (1.8–4.9)	46.9	1,411
hs-cTnT method					
ECLIA	3.0	8.0	4.4 (3.0–6.8)	13.1	1,600

LoD, limit of detection [1]; LoQ 10%, limit of quantitation, which is the cTn concentration measured with an error of 10% [1]. 99th percentile URL, the 99th percentile values for hs-cTnI methods were evaluated in an Italian reference population of apparently healthy individuals of both sexes (women/men ratio 0.95, age range 18–86 years, mean age 51.5 years, SD: 14.1 years) [1, 16, 39]. The 99th percentile for the cTnT method was evaluated as previously reported [20]. Analytical parameters and median (interquartile range) values for hs-cTnI methods were evaluated according to previous studies [1, 16, 40], those for the cTnT method were reported in previous studies [20].

or exercise duration [66]. hs-cTn release might be related to a temporary mismatch between oxygen delivery and consumption, and the degree of training may influence hs-cTn increase [66].

The transient hs-cTn elevation usually represents a physiological phenomenon, but can unmask a subclinical cardiac disease [2, 3, 7, 43]. The influence of different confounders (age, sex, sport type/intensity/duration, and training level) should be better clarified to establish individualized normal ranges for post-exercise hs-cTnI and hs-cTnT elevation [42, 67–75]. Both in well-trained athletes and in healthy subjects free of cardiovascular disease, hs-cTnI and hs-cTnT levels show only a moderate increase

after endurance exercise and usually return to pre-exercise values within 24–48 h [41, 66–74]. On the contrary, the kinetic curve of cTn concentrations in patients with MI is much longer (from 4 to 10 days) and may cover several orders of magnitude (from 100 to 100,000 ng/L) [1–3, 13–15, 18, 44–46]. Furthermore, circulating forms of cTnI and cTnT measured after an intense exercise could differ from those found in patients with cardiac or renal disorders [42, 67–75]. Indeed, degraded fragments (molecular weight, MW, of 14–18 kDa) are the main circulating forms after strenuous exercise [68]. These lower molecular forms of cTnT seem more similar to those observed in patients with end-stage renal disease (ESRD) [67–69]. Conversely,

the intact cTnT (MW about 40 kDa) is measured during the first hours of an MI, while in the following days some degraded form with lower MW (14–20 kDa) are predominantly detected [67, 68]. Therefore, hs-cTnI and hs-cTnT elevation due to physical exercise can be easily distinguished due to their shorter kinetics and lower MW isoforms of biomarker [42, 67–75].

Application of cardiac troponin assay in pediatric cardiology

As in adult patients, the combined elevation in natriuretic peptide and hs-cTn indicates both hemodynamic overload and myocardial injury, respectively, and can be found for example in neonates, infants or children with bronchiolitis or sepsis [76]. Patients with both cardiac-specific biomarkers increased have usually a worse prognosis [76, 77]. These data have been recently confirmed in adult and pediatric patients with SARS-CoV-2 [78]. Cardiac disease is an important cause of morbidity and mortality also in the pediatric age [79, 80]. In particular, chest pain is frequent in children and adolescents, but the incidence of MI is much lower than in adults [7, 8, 81–83]. In adults, only 25–30% of patients with a hs-cTn value over the URL have a MI [2, 3, 83–85]. Unfortunately, only few retrospective studies have assessed the usefulness of cTnI and cTnT assay in the differentiation of cardiac involvement in pediatric patients [7–12, 43].

Literature search

On August 4, 2021, a search for “troponin” OR “cardiac troponin” AND “pediatric” OR “children” OR “infants” OR “adolescents” retrieved 216 PubMed entries. Most of these articles included adult patients or populations of both pediatric and adult patients, or focused on specific cases. Other articles were experimental or pharmacological studies in animals or humans. hs-cTn methods were used in a minority of studies (usually those published after 2012 for cTnT or after 2015 for cTnI). Some articles were discarded because the analytical characteristics and performance of cTnI or cTnT assay were not well specified; while the analytical characteristics of the hs-cTnI and hs-cTnT methods, reported in Table 3 were described in details in other articles [1, 40, 98, 99]. Only 12 articles were finally selected [7, 86–97] (Table 3). Notably, these studies might not be representative of hs-cTnI use in a real-world setting as several recent articles do not clearly report the analytical

characteristics of cTnI methods used [100–104]. Moreover, only two studies using hs-cTn methods [93, 96] evaluated pediatric populations including more than 60 subjects, and some recent multicenter studies provided pooled results for hs-cTnI and hs-cTnT [105, 106]. Only one article using a hs-cTnI method was ultimately included [97].

General population

Yoldaş and Örün evaluated the most common causes of cTnI elevation in children and adolescents [81]. Patients with hs-cTnI above the 60 ng/L cut-off between 2007 and 2018 were retrospectively evaluated [81]. Patients undergoing cardiac surgery and those with severe congenital heart disease were excluded. The Authors evaluated 759 patients (58% males; median age four years, range 3 days to 17 years) [81]. The most frequent causes of elevated cTnI were myopericarditis (22%), drug intoxication (11%), carbon monoxide poisoning (10%), peri-myocarditis (9%), and intensive use of inhaled β agonists (9%) [81].

Dionne et al. [7] performed a retrospective evaluation of 1,993 subjects aged 0–21 years without known cardiac disease with cTnT assay measured during outpatient or inpatient evaluation for any cause from 2005 to 2018. Biomarker was considered to be elevated (using a cut-off of 100 ng/L) in 182 patients (9%). Cardiac disorders were more often diagnosed in patients with increased cTnT ($n=109$, 60%) [7]. The positive predictive value (PPV) of elevated cTnT for a cardiac disorder was 60% for the entire cohort and 85% for patients with a cardiac presentation. The negative predictive value (NPV) of cTnT under the cut-off was 89% for the entire cohort and 96% in patients without a cardiac presentation. Interestingly, considering the 404 patients with initial cTnT <100 ng/L who underwent serial measurements, an elevation above the cut-off value was found in 80 (20%), of whom 15 (19%) had a cardiac disease diagnosed. The optimal cTnT cut-off to differentiate cardiac from non-cardiac disorders was higher in children <3 months (45 ng/L) than in those ≥ 3 months (5 ng/L) [7]. Therefore, the cTnT assay can be useful to evaluate children when the differential diagnosis includes cardiac disorders [7]. Serial measurements were not helpful when troponin was elevated at baseline, but may be considered when the first level is not elevated and cardiac involvement is suspected [7].

An important limitation of these two retrospective studies is the time period spanning several years [7, 81]. Indeed, the analytical performance of cTnI and cTnT assays significantly and progressively improved during the study periods, possibly affecting the diagnostic accuracy of hs-cTnI and hs-cTnT methods [1, 42, 44, 45].

Table 3: Summary of analytical and clinical of studies using hs-cTnI and hs-cTnT methods.

Study	Biomarker	Population	Clinical data
Dyer AK et al. [86]	cTnT	Mean age 11 years Range 1–18 years n=42	Cardiac transplantation
Mavinkurve-Groothuis AM et al. [87]	cTnT	Children n=60	Cardiotoxicity by anthracycline therapy
El-Khuffash AF et al. [88]	cTnT	Infants n=30	Patent ductus arteriosus ligation syndrome
Sankar J et al. [89]	cTnT	Median age seven years IR 1.5–14 years n=56	Fluid refractory septic shock
Rady HI et al. [90]	cTnT	Median age 5.5 months Interval 3.25–21 months n=16	Myocarditis
Yildirim A et al. [91]	cTnT	Newborns n=30	Perinatal asphyxia
Asrani P et al. [92]	cTnT	Infants <34 weeks n=60	Hemodynamically significant patent ductus arteriosus
Wilkinson JD et al. [93]	cTnT	Mean age 13.6 years SD 2.66 years n=246	Perinatal HIV infection
Rodriguez-Gonzalez M et al. [94]	cTnT	Age <19 years Median age eight years IR 1.5–12 years n=42	Myocarditis
Dionne A et al. [7]	cTnT	Mean age 8.4 years SD 5.8 years Age range 0–21 years n=1993	Detection of heart disease
Nlemadin AC et al. [95]	cTnT	Age range 5–17 years n=34	Sickle cell anaemia and myocardial ischaemia
Cattalini M et al. [96]	cTnT	Median age three years IT 1–6 years n=149	Kawasaki disease and pediatric inflammatory multisystem syndrome associated to SARS-CoV-2 infection

Table 3: (continued)

Study	Biomarker	Population	Clinical data
Sanil Y et al. [97]	cTnI	Mean age 6.8 years SD 4.4 years n=54	COVID-19 infection

IR, interquartile range; SE, standard error; SD, standard deviation; cTnI, the biomarker was measured with the hs-cTnT Access method (Beckman Coulter Diagnostics); the analytical characteristics of this laboratory test were previously reported in detail [1, 40, 98]; cTnT, the biomarker was measured with the ECLIA method (Roche Diagnostics); the analytical characteristics of this laboratory test were previously reported in detail [1, 99].

Emergency setting

The measurement of hs-cTnI or hs-cTnT in adult patients presenting to the emergency department (ED) with chest pain is strongly recommended by international guidelines [2]. In pediatrics, suspicion of acute myocardial infarction or other underlying cardiac pathology in patients with chest pain is low, and thus the utility of hs-cTnI or hs-cTnT in this scenario is still controversial. In pediatric patients admitted to the ED, the most common cardiac diagnoses included myocarditis, cardiomyopathy and arrhythmias [7, 9–11, 43, 81, 107–120]. At present, measuring hs-cTnI and hs-cTnT in children presenting with nonspecific chest pain is not recommended [43]. Indeed, some Authors believe that hs-cTnI and hs-cTnT screening in pediatric patients admitted to ED may provide minimal benefit while increasing costs and resource utilization, unless patients have constitutional symptoms, such as fever and/or electrocardiographic abnormalities [12]. Nonetheless, this opinion relies on studies using methods with lower analytical performance than commercially available hs-cTn assays. Other Authors believe that the screening with hs-cTnI and hs-cTnT assay in children presenting with chest pain can be useful to identify underlying cardiac disorders, especially in the presence of clinical suspicion or an abnormal ECG [43]. Prospective cohort studies are needed to evaluate the benefits of screening in pediatric patients admitted to ED using the hs-cTnI and hs-cTnT methods and standardized serial testing algorithms [43].

Myocarditis

Myocarditis is classically defined as an “inflammatory disease of the heart muscle which is diagnosed by

established histological, immunologic, and immune-histological criteria” [121]. The true incidence of myocarditis in the general population is difficult to ascertain due to the high-frequency of sub-clinical presentations; however, autopsy studies have reported the incidence to be approximately 0.12–12% [122, 123]. Myocarditis is probably the most frequent cardiac disease in pediatric patients [7, 9–11, 81, 90, 94, 102, 104, 107–120]. It accounts for 22% of cases of hs-cTnI elevation [81] and has a poorer prognosis in children aged <2 years than in older children [124].

A recent systematic review [125] reports that COVID-19 infection in childhood is less common and with milder symptoms than in adults. However, the risk of cardiac involvement, especially on the background of congenital heart disease, should not be underestimated [125]. Previous cardiac surgery is related with the risk of a more severe disease, admission to intensive care unit (ICU), and need for intubation and mechanical ventilation [125]. Based on a few studies, hs-cTn increase is a marker of myocardial injury in children [78, 96, 97, 106, 119, 120, 125–127].

Congenital heart disease (CHD)

CHD is the most common congenital defect, affecting nearly 10–12 per 1,000 liveborn infants (1–1.2%) [128], and its incidence is apparently increasing because of better screening [129]. The utility of natriuretic peptides for neonatal screening and risk stratification was clearly demonstrated [43, 130, 131]. Even the usefulness of cardiac biomarkers in screening, diagnosis and evaluation of postoperative risk, particularly in neonatal and pediatric patients with CHD, has been reported in several studies using conventional cTn assays [43, 88, 132–153]. In 69 neonates undergoing arterial switch operation for transposition of the great arteries, Christmann et al. [145] reported that postoperative higher TnT has limited predictive value on the early postoperative course. In 2020, Kojima et al. [151] measured cTnI in 65 consecutive patients, undergoing cardiac surgery for CHD. cTnI on postoperative day 1 was positively correlated with the duration of catecholamine infusion after the intervention. In addition, a higher cTnI level was associated with a lower urine volume and higher lactate level 24 h after ICU admission [151]. The cTnI level on postoperative day 1 was a predictor of the duration of catecholamine use and ICU stay [151]. The results from the reported studies are difficult to compare due to large differences in number, age, and clinical conditions of pediatric patients, as well as heterogeneous experimental protocols [132–153]. Furthermore, only the most recent studies used hs-cTnI and hs-cTnT

methods. Therefore, further studies are needed to confirm the usefulness of hs-cTnI and hs-cTnT assays for prognostic evaluation during the ICU stay and after discharge.

Sepsis and septic shock

Sepsis is the most important clinical condition causing an increase in morbidity, mortality, and healthcare utilization in pediatric patients [154–156]. An estimated 22 cases of sepsis in pediatric age per 100,000 person-years and 2,202 cases of neonatal sepsis per 100,000 live births occur worldwide [156]. More than 4% of all hospitalized patients aged <18 years and around 8% of patients admitted to pediatric ICU in high-income countries have sepsis [156]. Mortality for sepsis in the pediatric age ranges from 4 to 50% due to large variations in illness severity, risk factors, and geographic location among studies [156]. The majority of children dying of sepsis suffer from refractory shock and/or multiple organ dysfunction syndrome, with the highest frequency of deaths within the first 48–72 h of treatment [156]. Early identification and appropriate resuscitation and management are critical to improve outcomes of children with sepsis [156, 157].

Some studies have shown that admission cTnI and BNP are associated with myocardial dysfunction in pediatric patients with sepsis [158, 159]. These biomarkers are also useful prognostic measures. In a prospective observational study, Fenton et al. [160] observed increased cTnI in more than 50% of children with septic shock upon hospital admission, which was associated with disease severity. More recently, Zhang et al. [161] evaluated BNP and cTnI levels in 120 pediatric patients. Both biomarkers were associated with sepsis severity in pediatric patients.

Even if COVID-19 is less common in the pediatric age and with milder symptoms than in adults, it carries a risk of cardiac involvement, especially in children with CHD [125–127]. Some children with severe multisystem inflammatory syndrome associated to COVID-19 may show very elevated inflammatory and cardiac biomarkers and may need an intensive care support [161–163]. Cardiac-specific biomarkers could be used for early detection of cardiac involvement in pediatric patients with COVID-19 and to predict related morbidity and mortality [162–164].

Kawasaki disease (KD)

KD is an acute, self-limiting febrile illness that predominantly affects children <5 years [43, 165]. The diagnosis of KD is based on clinical features and lacks a diagnostic

biomarker [43, 165]. KD leads to coronary artery aneurysms in $\approx 25\%$ of untreated cases [165]. BNP and NT-proBNP may be elevated in some patients with KD, but the discriminative ability to differentiate KD, and cut-point values for a positive result have not been clearly defined [164, 166, 167]. Xue and Wang [168] evaluated 102 children with KD and found that fever duration, NT-proBNP, cTnI, ESR and CRP were predictors of coronary artery lesions [168].

Other clinical conditions

Heart failure (HF) in children may manifest at birth (because of fetal disease) or can develop at any stage of childhood due to progression of a cardiac disease [169]. Primary cardiomyopathies and CHD are the main causes of HF in pediatric patients in the developed countries [169]. As in adult patients, it is conceivable that the cardio-specific biomarkers may be useful to detect pediatric patients with cardiac disease at high risk for rapid progression to symptomatic HF, facilitating early diagnosis and accurate risk prediction [43]. In particular, cardiac troponins can be elevated in some cardiomyopathies with increasing levels correlating with disease severity [169–173].

Acute rheumatic fever (ARF) is a major cause of HF in children and continues to be an important cause of morbidity, particularly in developing countries [174]. Approximately 60% of ARF patients develop rheumatic carditis, progressing to rheumatic heart disease [173]. Several studies, published from 2001 to 2011, evaluated cTnI or cTnT levels, measured with non-hs-cTn methods, in pediatric patients with ARF [175–179]. No clinically significant differences in biomarker levels were found between ARF patients with rheumatic carditis compared to those without active carditis, and also with patients with scarlet fever, or healthy control children [43, 175–179].

Some expert documents [180–182] have recently recommended the routine use of hs-cTnI and hs-cTnT assays for evaluation of risk progression to symptomatic HF in cancer adult patients on chemotherapy. A similar clinical practice should be adopted for monitoring cardiotoxicity in pediatric patients after cancer treatment [43]. Due to a lack of specific studies reporting cut-off values in pediatric patients, more evidence is required to determine the accuracy of cTnI and cTnT as a marker for cardiotoxicity and cardiac damage in children [43].

Future perspectives

The volume of blood samples required for biomarker measurement is often an important limitation, especially

in neonates and infants. Indeed, the different hs-cTnI and hs-cTnT laboratory tests using fully automated platforms require from 100 to 500 μL of serum or plasma for the assay even if special adapters can be used to decrease the volume needed for the assay. Some point-of-care-testing (POCT) methods can measure biomarkers using only a drop of whole blood for the assay. The POCT methods for cTnI and cTnT available until recently did not have the quality specification required for hs-cTn methods [183]. However, very recent studies suggest that some POCT methods for cTnI may provide comparable analytical performance than standard hs-cTn assays [184]. In 2019, Sorensen et al. [185] reported the clinical results obtained with the PATHFAST POC hs-cTnI assay using the PATHFAST immune-analyzer system, which is a POCT method with analytical performance equivalent to a hs-cTn assay. In 2020, Boeddinghaus et al. [186] reported that the POC-hs-cTnITriageTrue assay provided high diagnostic accuracy in adult patients with suspected MI with a clinical performance comparable to that of the best-validated central laboratory assays [186]. More recently, Apple et al. [187] reported that another POCT method named POC Atellica® VTLi hscTnI assay meets the designation of a hs-cTn assay according to the criteria recommended by current international guidelines [18]. Very recently, Gopi et al. [188] investigated the agreement between plasma and whole blood hs-cTnI by using the PATHFAST POC hs-cTnI assay. Whole blood can be used interchangeably with plasma for a more convenient and less time- and labor-consuming testing of hs-cTnI on the PATHFAST analyzer [188]. These recent data [185–188] indicate that some POCT methods for the assay of hs-cTnI are now available, which can accurately measure the cardio-specific biomarkers using a drop of blood. Accordingly, the new hs-cTnI POCT assays may allow a “decentralized” diagnosis of myocardial injury, even in primary care or PICU in neonates or infants by means of a common capillary puncture on the heel or the finger.

Conclusions

The experimental and clinical evidence summarized in this review indicates that hs-cTnI and hs-cTnT methods may be valuable to detect myocardial injury in the pediatric age. The most important limitation of hs-cTnI and hs-cTnT assays in the pediatric age is the lack of reference intervals specific for age groups in neonates and children, and also for sex throughout the adolescence. Further studies are needed to fill this gap.

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