How to interpret cardiac biomarkers in children?

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Abstract:

Cardiac biomarkers are used as first line diagnostic tools in suspected myocardial injury and heart failure in adult patients. Their use in paediatric patients has been limited by variability caused by age, gender and presence of an underlying congenital cardiac condition. There are established reference ranges for both NT-proBNP and Troponin in healthy children, but these cannot be applied to all paediatric patients because of limited large studies focusing on children with congenital heart disease and/or cardiomyopathy.

This article will focus on the pathophysiology of myocardial injury and heart failure in children and the subsequent cardiac biomarker correlation. It will explain how to interpret the biomarker assay levels obtained for both Troponin and NT-proBNP and highlights the importance of a clear clinical question prior to requesting a cardiac biomarker assay level. Clinical cases outline scenarios that may prompt consideration of biomarker analysis in children and aims to equip the reader with an understanding of how to interpret the results.

Introduction

There are two common cardiac biomarkers used in adults with suspected cardiac disease. Troponin to diagnose or exclude acute coronary syndrome in adults, and NT-proBNP/BNP to aid diagnosis and monitoring of congestive cardiac failure. Both biomarkers have been extensively studied, validated, and recommended by the National Institute for Health and Care Excellence (NICE). There is ongoing paediatric research and increasing evidence for the use of Troponin and NT-proBNP to aid assessment of cardiac disease in children.

In the 1960s, aspartate aminotransferase (AST) was found in elevated levels in acute myocardial infarction. Following this, Creatine Kinase (CK) and lactate dehydrogenase (LDH) became the preferred biomarkers for acute myocardial injury and were used for clinical diagnosis (1). However, given their lack of cardiac specificity, they were replaced when a sensitive and reliable radioimmunoassay was developed to detect serum troponin (2).

Natriuretic peptides were first discovered in mouse atrial myocardium (3). Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) were then identified and their roles in natriuresis and diuresis studied. Following the 'Breathing Not Properly' study in 2002, there was clinical evidence for BNP in the diagnosis of acute heart failure in adults (4).

Physiological Background

Troponin

The contractile apparatus of cardiomyocytes is known as the sarcomere and is comprised of actin (thin filaments) and myosin (thick filaments) proteins. The thin filaments also contain Troponins which are essential for striated muscle contraction (5). There are three subunits of the troponin complex: Troponin T, Troponin I and Troponin C (Figure 1). Troponin T and Troponin I are cardiac specific isoforms, whereas Troponin C is also present within thin filaments of skeletal muscle. Troponin T binds the troponin components to tropomyosin, Troponin I inhibits the interaction of myosin with actin, and troponin C exhibits a binding site for Ca^{2+}, which is required during excitation-contraction coupling (6). When cardiomyocytes become damaged, troponin protein is released into the blood stream and this can be detected almost immediately following cardiac injury, including an ischaemic or hypoxic event (7). Common cardiac manifestations that can lead to elevated blood troponin levels are described in Table 3. There are also non-cardiac causes for a blood troponin rise including, but not limited to, carbon monoxide poisoning, asphyxiation, renal failure and infection/fever (8). Therefore all elevated troponin levels must be considered within their clinical context.

Figure 1: Troponin structure

NT-proBNP

BNP is a cardiac natriuretic hormone synthesised predominantly by cardiomyocytes as a preprohormone, pre-proBNP. Subsequent removal of the signal peptide forms proBNP. ProBNP is cleaved into two peptides at the point of secretion: the inactive precursor NT-

proBNP and the active hormone BNP (Figure 2). ProBNP, NT-proBNP, and BNP can be detected in the circulation. Routine diagnostic measurement of NT-proBNP has largely overtaken BNP given its longer half-life and stability. The main mechanical stimulus for BNP secretion is ventricular distension, although studies suggest multiple other proteins/hormones can promote secretion including endothelin-1, α-adrenergic agonists, angiotensin II, glucocorticoids, vasopressin, growth factors and cytokines. Elevated levels of BNP are found in adults with heart failure. It is understood to work within target tissues to reduce vascular tone, increase electrolyte and water excretion and functionally antagonise the renin angiotensin aldosterone system (RAAS) (9).

Figure 2: NT-proBNP is predominantly produced by cardiomyocytes

Technological Background

A small volume of blood should be obtained for laboratory analysis - it is advised to check with each local laboratory regarding minimum volume required. The analysis of Troponin or NT-proBNP can be carried out on either serum or plasma, though it is recommended not to use different sample types interchangeably for the same patients as variations have been reported between serum and plasma (10).

Troponin as a marker of cardiac ischaemia in children and neonates

Troponin concentrations above the 99th percentile, along with clinical evidence of acute ischaemia, are indicative of myocardial infarction in the adult population (10). There are validated clinical practice guidelines for the diagnosis and exclusion of myocardial infarction

in adults. The gender-specific 99th percentiles for the hsTnT assay in healthy adults are; less than or equal to 9 ng/L for females and less than or equal to 17 ng/L for males.

Currently there are no validated guidelines for how to interpret Troponin in children. Troponin levels vary with age and gender making their interpretation challenging. The current best data regarding paediatric normal ranges of Troponin come from the CALIPER study of over 1400 healthy children aged 0-19 years (Table 1). Myocardial ischaemia in children is rare compared to adults. In children ischaemic injury tends to be as a result of myocarditis/perimyocarditis, coronary artery abnormalities or secondary to drug ingestion which induces vasospasm (11). An elevated troponin aids diagnosis in these clinical presentations but is unable to predict prognosis and therefore clinicians rely on echocardiogram and cardiac MRI for monitoring.

Serial Troponin measurements can also be useful in the neonatal setting. Neonatal myocardial infarction, whilst uncommon, can be caused by perinatal asphyxia, congenital heart disease, myocarditis, and congenital diaphragmatic hernias (12). As in older children there is variability in normal troponin levels in healthy neonates. Serial measurements, under specialist guidance, can be useful but there are no agreed guidelines or cut-offs in widespread use for preterm or low birth weight infants (13).

Table 1: Summary of 99th percentile upper limit cut-off for normal ranges in healthy children for Troponin using various assays (14).

Assay	*Age (years)*	*Sex*	*99th percentile cut off (ng/L)*
Abbott TnI	1-19 years	Male and female	21
Roche Elecsys Troponin T hs	0-6 months	Male and female	87
Roche Elecsys Troponin T Gen 5 STAT assay	0-6 months	Male and female	93
Roche Elecsys Troponin T hs	6months-1year	Male and female	39
Roche Elecsys Troponin T Gen 5 STAT assay	6 months-1 year	Male and female	21
Roche Elecsys Troponin T hs	1 year-19years	Male and female	11
Roche Elecsys Troponin T Gen 5 STAT assay	1-19 years	Male only	14
Roche Elecsys Troponin T Gen 5 STAT assay	1-19years	Female only	11

NT-proBNP as a marker of congestive cardiac failure in children

The International Society for Heart and Lung Transplantation guidelines on heart failure advise that BNP/NT-proBNP may be used to monitor paediatric patients with established heart failure but should not be used as a sole diagnostic test (15). This may be because there are no established reference ranges for congenital heart disease conditions and thus each result for these patients must be considered in the clinical context. Serial monitoring of NT-proBNP in patients with complex congenital heart disease can be useful for identifying early indicators of ventricular dysfunction before evident on 2D echocardiogram, to aid risk stratification preoperatively and to maximise medical management. NT-proBNP levels are influenced by age and gender in healthy children and are highest in the first year of life. The recommended age-dependent reference ranges for healthy children aged between 1 and 18 years are shown in the Table 2.

Table 2: Roche Cobas® derived NT-proBNP concentrations in a paediatric population aged between 1 and 18 obtained using the Elecsys proBNP assay (16).

Age (Years)	*Number*	*NT-proBNP (ng/L)*	
		75th percentile	97.5th percentile
1-3	13	231	320
4-6	21	113	190
7-9	32	94	145
10	11	73	112
11	69	93	317
12	21	95	186
13	23	114	370
14	18	68	363
15	24	74	217
16	24	85	206
17	24	71	135
18	12	53	115

Scenarios

In this section we present some common paediatric scenarios and discuss the role of Troponin and NT-proBNP testing.

Is there benefit in sending a Troponin in all children with chest pain?

Scenario

You are the paediatric registrar on-call in and receive a phone call from A&E regarding Abdul a 14-year-old boy who presents with a history of non-exertional central chest pain for the past week. He states it started after he was lifting weights. The pain can be associated with feeling a little short of breath, but he denies palpitations, syncope or presyncope. He has a normal cardiovascular examination, vital signs and ECG. He is slightly tender on palpation over his midsternum. The A&E registrar tells you she thinks his pain is likely musculoskeletal in origin and suggests discharging him home with safety net advice about red flag symptoms but asks you if there is a benefit in sending a troponin prior to discharge to help exclude a cardiac cause.

Outcome

Troponin should only be used if the clinician suspects an ischaemic heart condition in children as a tool for diagnosis and monitoring (see Table 3). A troponin level is not indicated in this case of musculoskeletal chest pain. The most useful tool to decipher if the pain may be cardiac in nature is a detailed clinical history. Chest pain is a very common presentation in children and in only 5% of patients there is an underlying cardiac cause (17). If a mildly elevated troponin level is obtained in a low-risk healthy child, it may lead to further unnecessary invasive investigations and stress for the patient and their families which could have been avoided. If you suspect a cardiac cause of the patient's chest pain

following a comprehensive history, clinical examination, and an ECG; discussion with the local paediatric cardiology team is appropriate for further management.

Can NT-proBNP be used to diagnose congestive cardiac failure?

Scenario

Angela is a 4-month-old girl with Trisomy 21 and diagnosed atrioventricular septal defect (AVSD). Her father tells you she has been struggling to gain weight over the past month and is now feeding less than half of her usual bottle volumes. He thinks she is breathing faster and is worried she is also sweating more. Her older sister Edith currently has a cold at home. On examination she weighs 4.8kg, is warm and well perfused. She has normal heart sounds and a pansystolic murmur radiating to her back. There is 3cm liver palpable. You note her respiratory rate is 66 and oxygen saturations are 92% in room air.

Outcome

Angela is experiencing symptoms of congestive cardiac failure secondary to her AVSD. It is also important to consider other non-cardiac causes of her symptoms such as respiratory illness or sepsis. Congestive cardiac failure is a clinical diagnosis and management is guided by clinical features not NT-proBNP levels. NT-proBNP values need to be interpreted in conjunction with the medical history, clinical findings and other information (e.g. imaging, laboratory findings, accompanying disorders, treatment effects) and should only be used under specialist supervision. NT-proBNP can be useful to monitor heart failure in certain settings but in this case a clinical diagnosis is the priority given that Angela has a clear cause of her symptoms and a one-off NT-proBNP level wouldn’t change management.

Are cardiac biomarkers useful in suspected myocarditis?

Scenario

Fatima is a 15-year-old previously healthy girl who has had temperatures, chest pain and fatigue for four days. She describes the pain as worse lying flat and feels sharp and stabbing in nature. Fatima feels generally unwell and looks miserable. Her temperature is 37.9^{o}C, heart rate 140bpm, blood pressure 90/58mmHg and oxygen saturations 96% in room air. She has normal heart sounds and a soft ejection systolic murmur audible. The remainder of her examination is unremarkable. A chest x-ray indicates cardiomegaly. You suspect she may have myocarditis and consider the role of cardiac biomarkers in this setting.

Outcome

Myocarditis is typically associated with ECG changes mimicking acute myocardial infarction and cardiomegaly on chest x-ray. Cardiac biomarkers have an important role in the diagnosis of suspected myocarditis as both troponin and NT-proBNP will be elevated secondary to myocardial inflammation and dysfunction. Of note, inflammatory markers such as CRP will also be elevated in myocarditis (18). Diagnosis is confirmed with echocardiography and/or cardiac MRI. As myocarditis is usually caused by viral or rheumatological conditions, it is seen in previously healthy children and therefore the reference ranges based on age and gender in Tables 1 and 2 may be used. Troponin and NT-proBNP may also be used in confirmed myocarditis to monitor treatment response and identify relapses over time.

Are cardiac biomarkers useful in PIMS-TS?

Paediatric Inflammatory Multisystem Syndrome (PIMS-TS) is associated with evidence of myocarditis, valvular regurgitation and reduced cardiac function in children with previously healthy hearts. PIMS-TS is an inflammatory multisystem condition believed to be associated with previous COVID-19 infection in the preceding weeks/months. Studies of PIMS-TS/MIS-C state that troponin and NT-proBNP are elevated in children with PIMS-TS (19) and correlate to evidence of myocarditis and shock (20). Clinicians should use both biomarkers to aid diagnosis and prognosis in suspected PIMS-TS.

Table 3: Indications and limitations of cardiac biomarkers in cardiac manifestations

Elevated Troponin	**Causes**
Myocarditis	Viral infections PIMS-TS/MIS-C* Immune mediated e.g. Kawasaki Disease Autoimmune e.g. sarcoidosis Drug ingestion
Pericarditis	Viral infections Bacterial infections (rare) Acute rheumatic fever Tuberculosis Postoperative
Coronary artery abnormalities	Congenital e.g. aberrant or single coronary artery or coronary artery fistula

Coronary artery vasospasm	Drug use e.g. cocaine

Elevated NT-proBNP	**Causes**
Congestive cardiac failure	Congenital heart disease Cardiomyopathy Acquired heart diseases e.g. following myocarditis or Rheumatic heart disease Metabolic abnormalities

*= Paediatric Inflammatory Multisystem Syndrome (PIMS-TS)/Multisystem Inflammatory Syndrome in Children (MIS-C)

Clinical Bottom Line

Cardiac biomarkers may have a role in assessment of children and young people presenting with conditions including ischaemic heart disease and heart failure. There is increasing evidence that they can be used for diagnosis and monitoring of these conditions but reference ranges for healthy children should be used with caution in children with suspected/confirmed congenital heart disease or cardiomyopathy. A focused history, clinical examination and basic investigations including ECG and/or 2D echocardiogram remain gold standard in assessment of children presenting with possible cardiac conditions. Cardiac biomarkers are useful in individual cases when clinicians understand their benefits and limitations.

References

1. Jacob R, Khan M. Cardiac Biomarkers: What Is and What Can Be. *Indian J Cardiovasc Dis Women WINCARS.* 2018 Dec;3(4):240-244. DOI: 10.1055/s-0039-1679104.
2. Garg P, Morris P, Fazlanie AL et al. Cardiac biomarkers of acute coronary syndrome: from history to high-sensitivity cardiac troponin. *Intern Emerg Med.* 2017;12(2)147-155. DOI: 10.1007/s11739-017-1612-1.
3. de Bold AJ, Borenstein HB, Veress AT, Sonnenberg H. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. *Life Sci*. 1981 Jan 5;28(1):89-94. doi: 10.1016/0024-3205(81)90370-2.
4. McCullough PA, Nowak RM, McCord J, Hollander JE, Herrmann HC, Steg PG, Duc P, Westheim A, Omland T, Knudsen CW, Storrow AB, Abraham WT, Lamba S, Wu AH, Perez A, Clopton P, Krishnaswamy P, Kazanegra R, Maisel AS. B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: analysis from Breathing Not Properly (BNP) Multinational Study. *Circulation*. 2002 Jul 23;106(4):416-22. doi: 10.1161/01.cir.0000025242.79963.4c.
5. Immer FF, Stocker F, Seiler A et al. Troponin-I for prediction of early postoperative course after pediatric cardiac surgery*. J Am Coll Cardiol.* 1999;33(6). DOI:10.1016/S0735-1097(99)00061-3.
6. Katrukha IA. Human cardiac troponin complex. Structure and functions. *Biochemistry (Mosc).* 2013 Dec;78(13):1447-65. DOI: 10.1134/S0006297913130063.
7. Nagy ZL, Collins M, Seiler AM et al. Effect of Two Different Bypass Techniques on the Serum Troponin-T Levels in Newborns and Children. *Circulation*. 2003;108(5). DOI:10.1161/01.CIR.0000081779.88132.74.
8. Yoldaş T, Örün UA. What is the Significance of Elevated Troponin I in Children and Adolescents? A Diagnostic Approach. *Pediatr Cardiol*. 2019 Dec;40(8):1638-1644. DOI: 10.1007/s00246-019-02198-w.
9. Shah A, Feraco A, Harmon C et al. Usefulness of Various Plasma Biomarkers for Diagnosis of Heart Failure in Children With Single Ventricle Physiology*. J Am Coll Cardiol*. 2009;104(9). DOI:10.1016/j.amjcard.2009.06.046.
10. Krintus M, Panteghini M. *Clin Chem Lab Med*. 2020;58:1773–1783
11. Thankarel P et al, Elevated troponin levels in in previously healthy children: value of diagnostic modalities and importance of a drug screen. *Cardiology in the Young* 24(2), 2014. DOI: 10.1017/S1047951113000231
12. Papneja K, Chan AK, Mondal TK, Paes B. Myocardial Infarction in Neonates: A Review of an Entity with Significant Morbidity and Mortality. *Pediatr Cardiol.* 2017 Mar;38(3):427-441. DOI: 10.1007/s00246-016-1556-7.
13. Ottinger D, Nash P. Troponin. *Neonatal Netw.* 2013 Sep-Oct;32(5):365-8. DOI: 10.1891/0730-0832.32.5.365.
14. Bohn MK, Higgins V, Kavsak P et al. High-Sensitivity Generation 5 Cardiac Troponin T Sex- and Age-Specific 99th Percentiles in the CALIPER Cohort of Healthy Children and Adolescents. *Clin Chem*. 2019;65(4). DOI:10.1373/clinchem.2018.299156.
15. FDA-NIH Biomarker Working Group. *BEST (Biomarkers, EndpointS, and other Tools) Resource.[Internet]* Silver Spring (MD): Food and Drug Administration (US); Bethesda (MD): National Institutes of Health (US); 2016 Jan 28 [Updated 2021 Jan 25].

16. Roche Cobas® Elecsys proBNP II assay insert (2020-06 V3.0). https://www.rochecanada.com/content/dam/rochexx/roche-ca/products/docs/package_inserts/ElecsysproBNPII-07027664190-EN-CAN.pdf
17. Collins S, Griksaitis M, Legg J. 15-minute consultation: a structured approach to the assessment of chest pain in a child. *Arch Dis Child Educ Pract Ed*. 2014 Aug;99(4):122-6. DOI: 10.1136/archdischild-2013-303919.
18. Pomiato E, Perrone MA, Palmieri R, Gagliardi MG. Pediatric Myocarditis: What Have We Learnt So Far? *J Cardiovasc Dev Dis*. 2022 May 3;9(5):143. DOI: 10.3390/jcdd9050143.
19. Hoste L, Paemel RV, Haerynck F et a., Multisystem inflammatory syndrome in children related to COVID-19: a systematic review. *Eur J Pediatr.* 2021;180(7). DOI:10.1007/s00431-021-03993-5.
20. Abrams JY, Oster ME, Godfred-Cato ES et al. Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: a retrospective surveillance study. *Lancet Child Adolesc Health.* 2021;5(5). DOI:10.1016/S2352-4642(21)00050-X.