Paediatric heart failure-understanding the pathophysiology and the current role of cardiac biomarkers in clinical practice

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Introduction

Paediatric heart failure (HF) is defined by the International Society for Heart & Lung Transplantation (ISHLT) as "a clinical and pathophysiologic syndrome that results from ventricular dysfunction, volume, or pressure overload, alone or in combination" (1). Kantor et al describe it as "as the failure of the heart to supply blood to either systemic or pulmonary circulation at an appropriate rate of flow, or to receive venous return at an appropriate filling pressure, resulting in adverse effects on the heart, the circulation, and the patient" (2).

In high income countries, paediatric heart failure is primarily caused by congenital heart disease or cardiomyopathy. In low- and middle-income countries, rheumatic heart disease and infective endocarditis remain the most common causes of paediatric heart failure. It is important to understand the background pathophysiology to paediatric heart failure before considering the role of various plasma biomarkers in this disease process. In clinical medicine, we routinely measure various plasma components which have an active role in the body to diagnose and monitor a patient's health. In adult patients, cardiac biomarkers are recommended in the diagnosis of heart failure and to aid clinical management. However, in paediatric patients their use has remained mostly scientific as a result of differences in the underlying mechanism of cardiac dysfunction and influence of age affecting the assay levels.

This review provides a comprehensive overview of paediatric heart failure caused by congenital heart disease and cardiomyopathy and considers the available evidence for cardiac biomarkers in this complex, multifactorial condition.
A literature review was completed using MEDLINE ALL, EMBASE and PubMed on 10th November 2022. Search terms included biomarkers, heart failure, heart defects, congenital heart disease, Fontan circulation, single ventricle circulation, cardiomyopathy, and child.

Paediatric heart failure pathophysiology

Pulmonary over-perfusion

Children with significant left to right shunting of blood secondary to congenital cardiac conditions such as large septal defects and persistent ductus arteriosus may experience clinical heart failure secondary to pulmonary over-circulation. Significant valvar regurgitation may also cause increased volume overload in the left atria causing pulmonary over-circulation. For affected infants, the reduction in pulmonary vascular resistance a few weeks after birth results in symptoms of respiratory distress, failure to thrive and recurrent lower respiratory tract infections. Importantly, whilst these children may experience significant comorbidities secondary to congestive heart failure, their ventricular function is usually well preserved, and they will make a good recovery post-surgical repair (3).
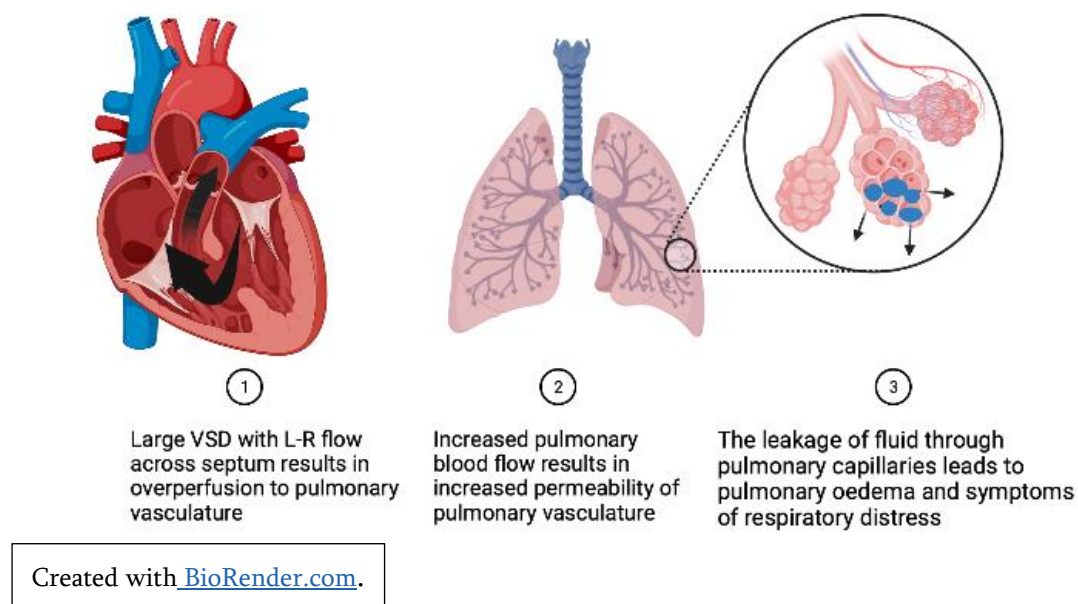
Figure 1

Pressure overload

Children with significant left sided cardiac obstructions may show signs of heart failure secondary to reduced cardiac output. Critical aortic stenosis or neonatal coarctation of the aorta both put abnormal pressure on the left ventricle, cause LV remodelling and reduced ventricular function if untreated (5). Patients with hypertrophic cardiomyopathy can develop left ventricular hypertrophy secondary to marked fibrosis and disarray of cardiac myocytes. For some patients this causes left ventricular outflow tract obstruction, subsequent pressure overload and heart failure symptoms (6).

Coarctation may occur anywhere along the descending aorta. Common sites include the isthmus where the ductus arteriosus connects.

Coarctation of aorta may be associated with other congenital heart conditions including a bicuspid aortic valve

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Figure 2

Pump Failure

Ventricular dysfunction can result from ischaemic injury, arrhythmias and myocardial failure which leads to systemic and/or pulmonary hypoperfusion. Ischaemic myocardial injury in children is caused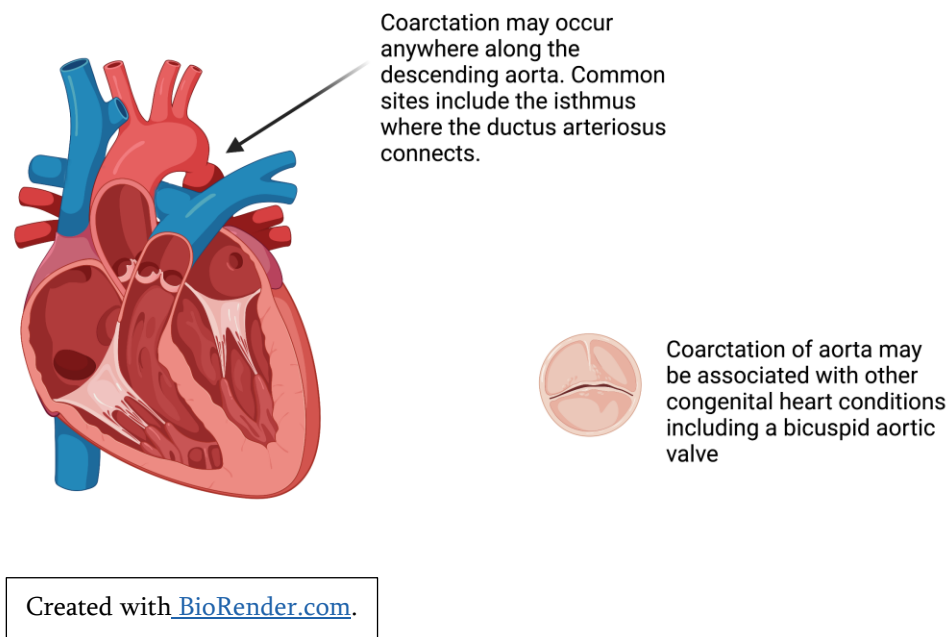 by conditions such as myocarditis, Kawasaki disease and abnormalities of the coronary arteries. Ischaemia causes ventricular remodelling and reduced pumping function.

Children with single ventricle physiology may also experience pump failure during their staged palliation or following the completion of Fontan circulation. This is a result of reliance on the morphological right ventricle to maintain the systemic circulation and subsequent ventricular dysfunction over time.

Cardiomyopathies in children cause atrial and ventricular remodelling which in turn affects pump function (7). Dilated cardiomyopathy (DCM) may be inherited, acquired, or associated with autoimmune and metabolic conditions (8). DCM is characterised by ventricular remodelling and haemodynamic overload as a result of reduced sarcomere contractility and increased ventricular volumes to maintain cardiac output. This progressive ventricular dilatation leads to tricuspid and mitral valve insufficiency which further reduces systolic function, increases ventricular wall stress and myocardial injury, and contributes to ventricular dysfunction and pump failure (9).
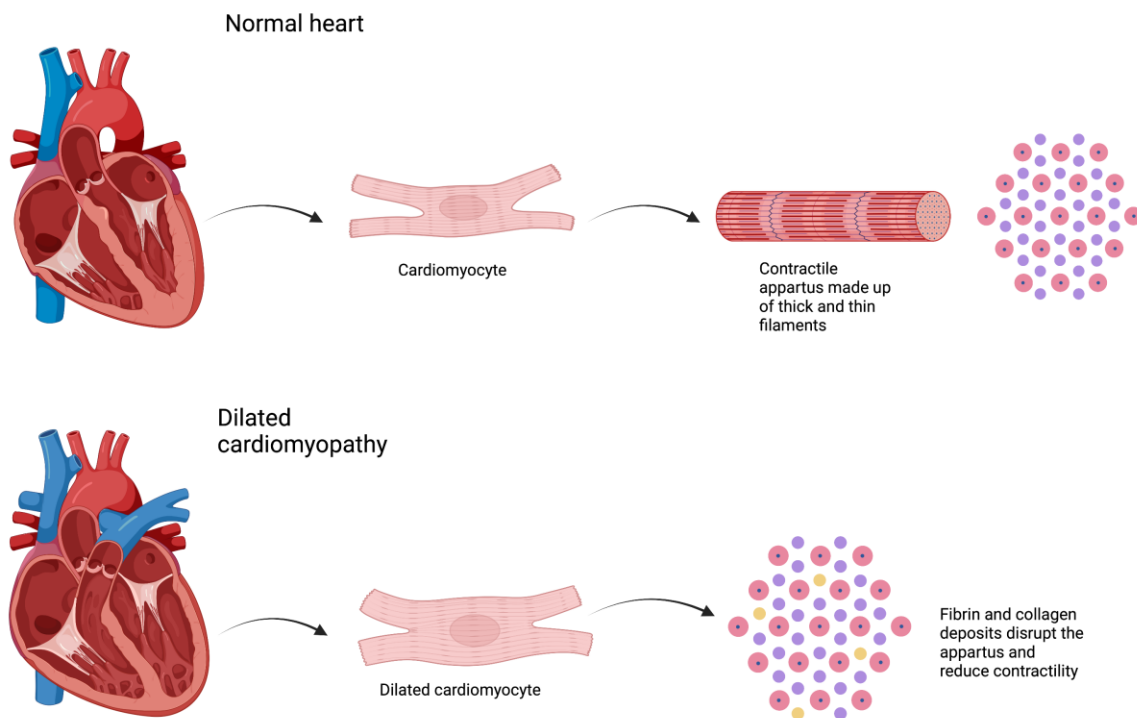
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Figure 3

Role of biomarkers

Current adult NICE guidelines advise measuring NT-proBNP as the first line investigation in suspected heart failure because of its high diagnostic accuracy. Similarly, cardiac Troponin I and T are recommended by NICE for diagnosis of acute coronary syndrome and screening of chest pain. However, the current ISHLT paediatric guidelines advise BNP/NT-proBNP can be used as an adjunctive marker in the integrated evaluation and monitoring of children with known HF but should not be used as a stand-alone test for diagnosis (1). Therefore, cardiac biomarkers are routinely used in adults but not in paediatric patients. This is due to the complex multifactorial mechanism of heart failure in children and the limited number of large paediatric research studies. Given that heart failure may be the first presentation of structural heart disease in children (10), and is often a complicated clinical state to monitor, a widely available blood biomarker to aid diagnosis and prognosis would improve outcomes in paediatric patients as it has in adults.

Natriuretic peptides

Atrial Naturetic Peptide (ANP) and Brain Naturetic Peptide (BNP) are primarily produced in cardiac cells, namely atrial and ventricular cardiomyocytes. The cardiac natriuretic hormones are synthesised by cardiomyocytes as prohormones i.e., proANP and proBNP. They are then split into two fragments at the point of secretion: the inactive precursor i.e., NT-proANP and NT-proBNP, and the active hormone i.e., ANP and BNP (11).

The main mechanical stimulus for ANP and BNP secretion is atrial and ventricular distension respectively, although studies suggest multiple other proteins/hormones can promote secretion including endothelin-1, α-adrenergic agonists, and angiotensin II, glucocorticoids, vasopressin, growth factors and cytokines (12).

Both ANP and BNP bind to natriuretic peptide receptor-A (NPR-A or guanylyl cyclase-A). They exert similar effects within target tissues namely they reduce vascular tone, increase electrolyte and water excretion, functionally antagonise the renin angiotensin aldosterone system (RAAS) and have antifibrotic and antihypertrophic effects (13).

BNP and NT-proBNP

Early studies of paediatric heart failure in CHD and cardiomyopathy focused on BNP measurements but this has been widely overtaken by focusing on BNP's precursor NT-proBNP given its longer half-life and stability (14).

NT-proBNP is the most widely studied cardiac biomarker in paediatric heart failure and although it is influenced by age, sex and underlying cardiac condition, it appears to be the most sensitive and specific biomarker of cardiac dysfunction available. In healthy children NT-proBNP levels are highest in the first year of life and then decrease steadily throughout childhood (15)(16). Roche have generated reference values (see table 1) for NT-proBNP based on the Albers et al study published in 2006 which included 408 participants. These values can be applied to healthy children with structurally normal hearts to aid interpretation of NT-proBNP levels. The LIFE Child study included 2522 children aged 3 months to 18 years and determined reference ranges based on 97.5th percentiles for healthy children. They also compared these to the study by Albers et al (16). They supported the previous findings that NT-proBNP is elevated in the first year of life and demonstrated a steady decrease in NT-proBNP levels during childhood to adult levels as the child reaches puberty. Given their larger sample population, they had less variability than Albers et al and may therefore be worth considering as the most accurate reference ranges for 97.5th percentiles of NT-proBNP in healthy children based on age.
Both Albers et al and the LIFE child study highlight that females have higher baseline NT-propBNP than males of the same age.

Table 1

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

Whilst it is useful to establish reference ranges for NT-proBNP in healthy children based on age and sex, we must consider the impact of congenital cardiac disease on baseline levels of NT-proBNP. This is because studies suggest that the presence of structural cardiac disease impacts baseline NT-proBNP levels for individual patients and therefore the healthy children reference ranges cannot be relied on for similarly aged children with a structural abnormality.

To improve our understanding of how to interpret NT-proBNP levels in paediatric patients we must first consider the clinical indication or need for this biomarker. In adult patients, elevated NT-proBNP levels aid diagnosis of heart failure in primary and secondary care. In children, heart failure is multi-factorial and may mimic other pathologies e.g. respiratory or infectious conditions. Therefore NT-proBNP needs to be used with a clear clinical question before it can be considered as a diagnostic tool in paediatric heart failure. For example, one of the benefits of NT-proBNP in paediatrics is aiding diagnosis of heart failure at initial presentation. BNP and NT-proBNP are both significantly elevated in paediatric patients with respiratory distress secondary to cardiac disease compared to respiratory distress secondary to respiratory disease and healthy controls (17)(18)(19). Therefore, it could be used as a screening tool in the assessment of suspected heart failure in children who present with respiratory symptoms.

In congenital cardiac disease, BNP/NT-proBNP is proven to correlate to symptoms of heart failure through Ross and/or NYHA classification systems (14)(20)(21). Importantly, NT-proBNP also correlates to objective measures of ventricular function on echocardiogram (22)(23)(24). A higher BNP/NT-proBNP is associated with increased symptoms of HF and reduced EF suggesting an increased likelihood of adverse outcomes.

However, because of the small number of paediatric patients who have been studied, there is not a clear definitive BNP/NT-proBNP assay level that could be used as a reference value to diagnose HF in children with an underlying cardiac condition. As previously discussed, BNP/NT-proBNP reference ranges based on age and sex are useful but we must consider if reference ranges for children with congenital cardiac disease and other comorbidities can be developed.

Salem et al, in their paper published in 2021, suggested on-admission BNP at a cut-of-point 507.13 pg/ml has 95.5% sensitivity and 88% specificity for in-hospital mortality (25). Despite lack of assay cut-off values in congenital cardiac disease, this suggests BNP/NT-proBNP may be utilised as a prognostic indicator in known cardiac disease to aid earlier identification of patients most at risk of adverse outcomes.

Similarly, an elevated BNP/NT-proBNP preoperatively is associated with increased adverse events and/or increased circulatory support requirement post operatively (26)(27). One study of 86 patients with complex cardiac disease scheduled for biventricular repair, of which most had evidence of mild HF symptoms, had preoperative BNP levels measured before surgical intervention. They found that a preoperative BNP level >60.9pg/ml was associated with increased risk of an adverse event (26). This suggests BNP has the potential to identify higher risk patients for adverse outcomes even if they are clinically stable preoperatively.

However, postoperative BNP/NT-proBNP levels appear to be less useful in predicting adverse events and postoperative prognosis. This is likely because of the influence of acute cardiomyocyte injury causing an acute BNP/NT-proBNP assay level rise which will recover and is an inaccurate assessment of potential ventricular failure in this period (28)(29).

Role of NT-proBNP in single ventricle physiology
BNP/NT-proBNP is significantly elevated in patients with HF secondary to single ventricle physiology compared to children with similar anatomy who are not clinically in HF (30)(31)(32). Studies have found that BNP/NT-proBNP baseline levels reduce with each subsequent stage of palliative surgery regardless of heart failure status (33). It has been suggested that once children have undergone their Fontan procedure, if they do not clinically have signs/symptoms of HF, there is no difference in their BNP/NT-proBNP levels compared to a healthy age matched control (34). Ghelani et al report a negative correlation between ejection fraction on cardiac MRI and NT-proBNP in Fontan patients in NYHA Class I-II. They suggested NT-proBNP >150pg/ml may be used as an indicator of ventricular dysfunction (35). Similarly, a study of 133 Fontan patients with a median age of 13.2yrs found that the 27% of patients who had an adverse cardiac outcome, had significantly higher NT-proBNP levels at recruitment and their NT-proBNP level correlated with severity of event (36).
This highlights the potential role of NT-proBNP as a prognostic indicator in Fontan patients given that it is elevated prior to clinical symptoms or signs of ventricular dysfunction and correlates to cardiac MRI findings.

Role of NT-proBNP in cardiomyopathy
A longitudinal study of paediatric patients with dilated cardiomyopathy (DCM) found that NT-proBNP was useful in identifying the patients at recruitment who were most likely to deteriorate over time. In addition, within the group that would deteriorate, it was able to distinguish between those who would experience adverse events (heart transplant or death) and those who did not (37).
Studies show higher BNP/NT-proBNP levels in children with HF secondary to DCM compared to CHD. This may be partly because of the increased prevalence of HF in the DCM subgroup

and the associated systolic impairment which causes elevated BNP/NT-proBNP compared to the effect of volume overload as seen in the CHD subgroups. (21)(22)(38).

Role of NT-proBNP in haemodynamically significant shunts
In infants and young children, septal defects causing pulmonary overperfusion may result in symptomatic HF.   NT-proBNP has been shown to positively correlate to shunt size in atrial and ventricular septal defects and to fall following closure correlating to reduced symptoms of heart failure (39)(40)(41)(42)(43)(44). NT-proBNP has also been reported to be positively correlated with symptoms of HF and in-hospital mortality in haemodynamically significant shunts (45). Clinically, NT-proBNP may be used to aid risk stratification and identification of children with more haemodynamically significant left to right shunts in known septal defects.

Correlation to imaging
An advantage of NT-proBNP would be if it could identify cardiac dysfunction or improvement before evident on imaging. Yet few studies have monitored serial BNP/NT-proBNP levels in children with HF and compared them with cardiac function on echocardiogram. One study of 30 children which identified elevated NT-proBNP levels in children with HF secondary to dilated cardiomyopathy showed there was a significant difference in NT-proBNP levels following 1 week of medical heart failure therapy despite a non-significant change in echo findings. (46) Another small study which used tissue doppler echocardiogram imaging in children with cardiomyopathy secondary to ectopic atrial tachycardia, concluded that tissue doppler imaging correlates better to elevated NT-proBNP levels than standard 2D echocardiogram parameters in terms of identifying early diastolic dysfunction (47). This highlights the potential role of BNP/NT-proBNP in identifying myocardial changes and function before evident on 2D-echocardiography and the importance of larger scale research in this area.

ANP

ANP/MR-proANP has shown similar results in paediatric HF diagnosis and prognosis as BNP/NT-proBNP. ANP appears to be significantly elevated in patients with HF compared to healthy controls, and increased in a stepwise manner to reflect increasing Ross or NYHA class of HF. Studies show that as patients received treatment and their NYHA score improved, their ANP assay level reduced in keeping with similar studies focusing on BNP(48)(49)(50)(51). ANP values were found to be highest amongst children with cardiomyopathy compared to congenital heart disease (50). When ANP and BNP are compared directly in assessment of paediatric heart failure, the changes noted in BNP/NT-proBNP are reflected by ANP/MR-proANP (21)(23)(52)(53)(54). This supports the belief that naturetic peptides have a role in paediatric heart failure diagnosis and monitoring but that BNP/NT-proBNP and ANP/MR-proANP perfom similarly and there is therefore little merit in pursuing both as a biomarker of heart failure.

Troponin

Troponins are cardiac specific proteins which make up thin filaments, which along with thick filaments, form the sarcomere which is the contractile apparatus of cardiomyocytes (55). When cardiomyocytes are damaged, troponin is released into the blood stream and can be detected almost immediately following an ischaemic or hypoxic event (56). Transient levels are also detected in chronic conditions which are understood to be secondary to necrosis. Chronic kidney disease is associated with increased serum troponin levels in the adult population due to reduced renal clearance and continuous myocardial damage from exposure to uraemic and other renally cleared toxins (57).

Troponin I (TnI) and Troponin T (TnT) are established highly sensitive biomarkers of acute myocardial injury and are used widely in the diagnosis and monitoring of acute coronary syndrome in the adult population (56)(58). TnI and TnT perform similarly in adult studies assessing acute myocardial events (59) and are both used in the paediatric studies in this review.

In paediatric patients, ischaemic cardiac disease is rare and caused by inflammatory and structural abnormalities rather than atherosclerosis of the coronary arteries. Therefore, troponin has a role in aiding diagnosis of suspected inflammatory conditions e.g. pericarditis or myocarditis but the role in heart failure is less clear. Although troponin is not recommended as a biomarker for diagnosis of HF in adults in NICE guidelines, studies in adults suggest that increased TnT levels are associated with greater risk of developing HF. Models using both BNP and TnT are better at predicting future adverse events than BNP alone as they can identify evidence of myocyte damage in addition to myocyte stretch (56). Bohn et al performed TnT measurements using Roche on 598 serum samples from healthy children aged 0-19 years. They found that TnT levels initially increased from 0-6 months of age and then decline steadily after 1 year old until adulthood (60). The gender-specific 99th percentiles from 1 to <19 years were 14 ng/L for males and 11 ng/L for females. They proposed reference ranges for healthy children without structural cardiac disease based on these results (see Table 2)(60).

It appears that children with CHD have a higher baseline troponin level than healthy children regardless of heart failure status (61). Studies of children with heart failure secondary to biventricular physiology have found a correlation between troponin levels and clinical and/or echocardiogram evidence of heart failure, yet when compared to BNP, troponin remains diagnostically and prognostically inferior (25)(62). A small study of single ventricle patients which compared those with clinical evidence of HF to those without, found that cTnI was unable to distinguish clinical HF in this cohort (31).

Studies have also focused on troponin in children with evidence of pressure or volume overload. They describe that a rise in troponin levels is evident before changes on conventional or 2D-STE derived strain echocardiogram (63)(64) and that troponin levels were more elevated in the children with pressure overload syndromes compared to volume overload (65). Whilst this suggests a potential role for troponin in identifying myocardial damage before evident on echocardiogram, it isn't clear if this has clinical impact.

Troponins have been measured in the perioperative period to assess short- and long-term outcomes for children with CHD who undergo surgery. Studies suggest that preoperative

troponin levels can be used as an adverse outcome indicator (26), and patients with higher troponin levels are at an increased risk of adverse outcomes in the immediate postoperative period. Serial monitoring of postoperative troponin levels found that troponin levels correlated to degree of myocardial damage and were significantly higher in the immediate postoperative period, and in patients requiring increased levels of respiratory and inotropic support (66)(67)(68)(69)(70)(71). It may be that a degree of this troponin rise is because of surgical manipulation on the myocardium.

Similarly, the available studies were unable to find a correlation between immediate postoperative troponin levels for children with CHD, and long-term outcomes. This would suggest a degree of myocardial remodelling in children, and that even patients with severe

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

ischaemic injury may recover some function if they survive the immediate postoperative period (72)(73)(74).

Table 2

MR-proADM

Adrenomedullin (ADM) is a peptide hormone secreted by endothelial and vascular smooth muscle cells. There are ADM receptor and binding sites throughout the body, but they are particularly concentrated in the heart and lungs. MR pro-ADM is the stable inactive prohormone which is enzymatically converted to the biologically active ADM-amide and mid-regional pro-adrenomedullin (MR-proAM)(75).

ADM's roles involve vasodilation and maintenance of endothelial integrity to reduce vascular leakage. Studies demonstrate high levels of circulating levels of ADM in adult

patients with volume overload secondary to sepsis and acute heart failure. There are currently small clinical trials studying the effect of adrenomedullin as a novel therapy in adult congestive heart failure using Adrecizumab a humanized, monoclonal, non-neutralizing antibody against the N-terminus of ADM (54). There is promising evidence it may improve haemodynamic and hormonal outcomes for adult patients with volume overload.

There are few paediatric studies which study the role of MR pro-ADM in diagnosis and prognosis of heart failure. It appears to have a limited role, performing less well than NT pro-BNP or MR-proANP in children with heart failure secondary to CHD or cardiomyopathy (21). However, one small study of 53 patients found it was significantly raised in children with failing Fontan circulation, correlated to NYHA score, and was more reliable than NT pro-BNP in identifying failing Fontan circulation (76). MR pro-ADM may have a role in monitoring heart failure in the Fontan population given venous return relies on peripheral muscle pump function in this cohort.

MR pro-ADM has also been studied in the perioperative period. One small study, focusing primarily on vasoactive inotropic scores following cardiac surgery, found that including postop MR pro-ADM levels didn't aid predictive value to their score (72). However, other studies concluded that both pre and postoperative MR pro-ADM levels correlated to length of mechanical ventilation and PICU stay (77)(78). One study of postoperative MR pro-ADM levels suggested a cut off value of MR pro-ADM of 1.223nmol/L may indicate higher likelihood of mechanical ventilation requirement post operatively (79).

sST2

Soluble suppression of tumorigenicity-2 (sST2) is a circulating form of suppression of tumorigenicity-2 (ST2) glycoprotein. ST2L is a receptor for interleukin-33 (IL-33) and the interaction of IL-33 and ST2L is cardioprotective by reducing fibrosis and cardiomyocyte hypertrophy in experimental models. When sST2 is released in response to cardiomyocyte stretch, it binds with IL-33, ST2L is blocked and the IL-33/ST2 system disrupted, resulting in elimination of the cardioprotective effects and associated inflammation. Elevated sST2 serum levels are associated with increased heart failure and mortality in adult patients with heart disease (80)(81)(82)(83).
There are a limited number of studies focusing primarily on paediatric heart failure and serum levels of sST2, and not all results are consistent.

In a small study comparing biomarker levels in children and adults pre and post ventricular assist device insertion, it was found that sST2 levels were significantly higher in children with heart failure than healthy children with no underlying CHD. They also found that sST2 levels were higher in children compared to adults at all timepoints. (84). However, a prospective study of participants with heart failure secondary to CHD and cardiomyopathy which compared to healthy controls, found that sST2 was unable to show a significant difference between patients with heart failure and healthy controls (21).

A longitudinal study of patients with Fontan circulation found that higher baseline sST2 levels were associated with increased likelihood of adverse events but no cut-off values

were proposed (36). Ghelani et al found ST2 negatively correlated to ejection fraction in clinically stable Fontan patients but it was not statistically significant and performed worse than NT-proBNP and troponin (35).

sST2 may have a role in diagnosis and monitoring of paediatric heart failure, but given the difference in pathophysiology compared to adults, this may be limited and warrants further studies before routine use.

Galectin-3

Galectin-3 is a member of the galectins which are evolutionarily conserved proteins with the ability to bind β-galactosides through characteristic carbohydrate-recognition domains (85)(86). Galectin-3 is highly expressed in myeloid, epithelial, endothelial cells and fibroblasts. It can be located both intracellularly in the cytoplasm, nucleus and membranes, and in the extracellular matrix.

Galectin-3 is a multifunctional protein which affects cell growth, differentiation, apoptosis, angiogenesis, inflammation, tumour growth and fibrogenesis. It is widely distributed in tissues throughout the human body and although its baseline expression levels vary between organs, it is inducible by cardiac injury. Because of its expression in activated macrophages and damaged cardiomyocytes, it induces fibroblast proliferation and collagen deposition which eventually leads to reduced cardiac function (87)(88).
Studies of children with heart failure suggest that Galectin-3 levels are positively correlated to both clinical signs of heart failure and ejection fraction on echocardiogram. One study of children experiencing congestive heart failure secondary to left to right shunt physiology, highlighted that there was positive correlation between Ross score and Galectin-3 levels. Galactin-3 showed a better diagnostic value than Ross HF classification score in early diagnosis of HF in this cohort (89). Similarly, in a cross-sectional study of children and adults with HF, NYHA score was positively correlated with Galectin-3 levels and Galectin-3 was negatively correlated to ejection fraction and positively correlated with NT-proBNP (90).

However, Galectin-3's role in determining long term prognosis is uncertain as some studies did not find significant correlation between baseline Galectin-3 levels and long-term outcomes and mortality (36)(89)(91). Similarly, a longitudinal multicentre study conducted of 133 patients post Fontan found that whilst NT-proBNP and sST2 correlated with patient outcomes, Galectin-3 did not (7). This is contraindicated by a study of adult Fontan patients which concluded that Galectin-3 is elevated in Fontan patients compared to healthy controls, and that there is an independent association between elevated Galectin-3 and adverse outcomes, but they did not directly compare to NT-proBNP levels. (92).

Galectin-3 may have a role in monitoring response to medical management of heart failure. One study noted that Galectin-3 levels for children with HF were lower in those treated with spironolactone, presumably because of improved cardiac function. A study of adults and children with HF suggested that adults with lower Galectin-3 levels treated with statins had a better response to those with higher levels and Galectin-3 could be used to better guide medical management in early HF (90)(93).

The current evidence suggests that Galectin-3 may have a role in diagnosis and monitoring of HF in children and could guide medical management. It may be superior to sST2 despite both being associated with myocardial fibrosis (80). However, further large studies which compare Galectin-3 levels and NT-proBNP in established paediatric heart failure are needed to consider if it has any role above that established by NT-proBNP.

GDF-15

Growth Differentiation Factor-15(GDF-15), also known as macrophage inhibitory cytokine (MIC-1), is a member of the growth factor beta cytokine superfamily. In normal physiological state it is expressed in low amounts in many tissues except for placental and prostate tissue in which it is found in higher concentrations. In heart tissue it is found to rapidly increase with inflammation and ischaemia. It is also noted to increase with advancing age which is likely due to oxidative stress. High levels of circulating GDF-15 have been associated with cardiovascular disease, cancer, renal dysfunction, and diabetes mellitus (94). Elevated GDF-15 has been associated with children experiencing failure to thrive (FTT) (95) and is significantly higher in children with FTT and CHD compared to CHD alone (96).

In adult heart failure studies, GDF-15 levels correlate to NYHA class and can differentiate between clinical HF staging. This is regardless of whether ejection fraction is reduced or preserved which may suggest a role above that of NT-proBNP which tends to be lower in patients with preserved EF compared to reduced EF in HF (97).

A study of young adult Fontan patients which assessed GDF-15 levels in relation to NYHA score, echo findings and NT-proBNP levels concluded that GDF-15 was more useful than NT-proBNP in this cohort at identifying reduced ejection fraction and deteriorating NYHA class. They found that NT-proBNP was only weakly correlated to ejection fraction and that neither NT-proBNP or GDF-15 were significantly related to diastolic dysfunction measures. They have suggested a GDF-15 level of 613pg/ml to predict EF <50% with a sensitivity of 90% and specificity of 85.7% (98). This was supported by a similar study focusing on GDF-15 levels in adult CHD patients with evidence of HF. They found GDF-15 levels correlated to NT-proBNP levels, lower exercise tolerance and increasing NYHA class. They commented that participants with single ventricle physiology had higher GDF-15 levels than those with biventricular physiology (99).

In children with HF secondary to biventricular CHD physiology, GDF-15 levels were increased with increasing Ross classification and severity of heart failure. Elevated GDF-15 levels can be used to accurately identify participants at highest risk of adverse cardiac events or death (36)(100)(101). GDF-15 levels correlated positively with NT-proBNP levels, and one study highlighted that when used in combination with NT-proBNP and hsTnT it could be used to identify those participants at highest risk of adverse events compared to using NT-proBNP alone (102).
However, as only some of the studies directly compared diagnostic accuracy of NT-proBNP and GDF-15 in paediatric HF, it would appear that NT-proBNP remains more sensitive and specific for those with HF and biventricular physiology (21).

Conclusion

Paediatric heart failure is a complex physiological state which is influenced by underlying cardiac condition, age of patient and surgical and/or medical management. The current literature has not identified one sole biomarker which is useful in diagnosing and monitoring heart failure in all affected children. There is evidence that NT-proBNP correlates closely to echocardiogram findings and functional status for children with biventricular physiology. Yet, the literature has described a range of diagnostic NT-proBNP cut off values in this group, so it would require caution for use as a screening tool. It appears to be less reliable in cardiomyopathy and single ventricle physiology and therefore larger longitudinal paediatric studies are required to incorporate these patient groups and determine if biomarkers which reflect changes in systolic function and pressure overload are more suitable than NT-proBNP.

Biomarker	Role in diagnosis	Role in prognosis	Advantages	Limitations
BNP/NT-proBNP	Elevated in HF secondary to cardiomyopathy and CHD	-Correlates to signs/symptoms -Correlates to LVEF -May be useful in identification of patients at risk of adverse events	-Most evidence available -Easy to access assay -May indicate early diastolic dysfunction before evident on echo	-Elevated in first year of life in healthy children -No validated reference values for CHD and CM patients
ANP/MR-proANP	Elevated in HF secondary to cardiomyopathy and CHD	Correlates to both signs/symptoms and LVEF	Few	Similar results to BNP/NT-proBNP and less readily available
MR-proADM	Limited	May correlate better to HF than NT-proBNP in Fontan cohort	May have therapeutic role as monoclonal antibody	Limited paediatric studies
Troponin	Limited	May be useful in postoperative period to indicate risk of adverse events	Easy to access	-Limited paediatric studies -Elevated in healthy children in first year of life -No reference ranges available for CHD/CM
sST2	Limited	Limited	Associated with fibrosis	Limited paediatric studies
Galectin-3	Limited	Correlates to signs/symptoms and LVEF in HF	May reflect improvement from medical management	Limited paediatric studies
GDF-15	Limited	Correlates to signs/symptoms and LVEF in Fontan patients	Can be used in addition to NT-proBNP and troponin to identify those at risk of adverse events	Limited paediatric studies Less useful than NT-proBNP in biventricular physiology

Table 3: Summary of cardiac biomarkers and their current role in paediatric heart failure assessment

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