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MINIREVIEWS

Cardiac biomarkers in pediatric heart disease: A state of art review

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Abstract

Every year there are more than 11000 hospitalizations related to heart failure in children resulting in significant morbidity and mortality. Over the last two decades, our understanding, diagnosis and management of pediatric heart failure is evolving but our ability to prognosticate outcomes in pediatric heart acute heart failure is extremely limited due to lack of data. In adult heart failure patients, the role of cardiac biomarkers has exponentially increased over the last two decades. Current guidelines for management of heart failure emphasize the role of cardiac biomarkers in diagnosis, management and prognostication of heart failure. It is also noteworthy that these biomarkers reflect important biological processes that also open up the possibility of therapeutic targets. There is however, a significant gap present in the pediatric population with regards to biomarkers in pediatric heart failure. Here, we seek to review available data regarding cardiac biomarkers in the pediatric population and also explore some of the emerging biomarkers from adult literature that may be pertinent to pediatric heart failure.

Key words: Pediatric heart failure; Biomarkers; Cardiac; Outcomes; Congenital heart disease

Core tip: Biomarkers such as BNP, ST2 are well established in adult heart failure. Emerging data supports the use of some of these biomarkers for diagnosis, monitoring and prognostication of pediatric heart disease. Continued research is needed to better understand these established and emerging biomarkers. Here, we review the available data regarding cardiac biomarkers in the pediatric population and also explore some of the emerging biomarkers from adult literature that may be pertinent to pediatric heart disease.

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INTRODUCTION

Pediatric acute heart failure is now being increasingly recognized as an important source of healthcare resource utilization with 11000 to 14000 heart failure related hospital admissions in the United States every year[1,2]. Additionally, pediatric heart failure is associated with significant morbidity and mortality. Over the last two decades, our understanding, diagnosis and management of pediatric heart failure is evolving. This is especially true with regards to acute heart failure. However, unlike adult heart failure, underlying mechanisms and etiology is responsible for pediatric heart failure are very heterogeneous from simple congenital heart defects, cardiomyopathies to complex palliated single ventricle patients. Similar to the underlying etiologies, management and outcomes in these groups of patients are also very variable. However, ability to prognosticate outcomes in pediatric heart acute heart failure is extremely limited due to lack of data.

In adult patients with heart failure both related to ischemic and non-ischemic cardiomyopathy, the role of cardiac biomarkers has exponentially increased over the last two decades.

Current American Heart Association guidelines for management of heart failure emphasize the role of cardiac biomarkers in diagnosis, management and prognostication of heart failure[3]. This is especially true for two biomarkers included in these guidelines *viz.* brain-type natriuretic peptide and suppression of tumorigenicity-2 (ST2)[3]. In addition to these there are several biomarkers being studied that have provided additive information beyond the well-established biomarkers. It is also noteworthy that these biomarkers reflect important biological processes that also open up the possibility of therapeutic targets.

There is however, a significant gap present with regards to biomarkers in pediatric heart failure. Here, we seek to review available data regarding cardiac biomarkers in the pediatric population and also explore some of the emerging biomarkers from adult literature that may be pertinent to pediatric heart failure.

B-TYPE NATRIURETIC PEPTIDE AND N-TERMINAL SEGMENT OF PRO-B-TYPE NATRIURETIC PEPTIDE

B-type natriuretic peptide (BNP) and the N-terminal segment of pro-BNP (NT-ProBNP) are used as essential parts of adult cardiologic evaluation. BNP belongs to a larger family of titrated peptides which have a paracrine role in the body. It is primarily secreted by cardiocytes in the form of pre-pro-peptides. These pro-peptides are synthesized within the endoplasmic reticulum of the cardiac cells where they're stored as specific atrial granules. These pre-pro-peptides have a constant basal rate of release and play an important regulatory function in maintenance of salt and water homeostasis. Various stimuli such as myocardial stretch or stress can lead to a very rapid increase in the secretion of these pre-pro-peptides. Once released it undergoes conversion into pro BNP which is cleaved by serine peptidases into the active moiety BNP and inactive moiety NT-proBNP. Outside of the heart, kidneys and blood vessels are the major target organs where natriuretic peptide receptors types A, B and C are present. Once receptor bound, BNP leads to increased diuresis, natriuresis and vasorelaxation. On the cardiac sites, BNP has significant anti-proliferative and anti-hypertrophic properties mediated by the same receptor[4]. Since its first description in 1970s by de Bold[5,6], natriuretic peptides have been extensively studied in various disease conditions both cardiac and non-cardiac. It is one of the most studied biomarker for heart failure. The cumulative data has led to the recognition of its value in diagnosis, management and prognosis of heart failure by the current AHA/ACC heart failure guidelines[3].

BNP and age

BNP and NT-ProBNP levels vary with age especially in the pediatric group. Immediately after birth, BNP and NT-ProBNP are elevated and then rapidly decrease after the first week of life. Reasons for this physiologic fluctuation in the levels are unclear at this point, but hypotheses include removal of the placenta and thereby significant redistribution of blood volume to the heart causing a volume overload and an increase in the afterload at the same time. Rapid increase in pulmonary blood flow with lung expansion further adds to the stimulus. Lastly, renal immaturity may contribute to decreased clearance of the BNP during the first week of life. As a result, the BNP (and NT-proBNP) levels are significantly elevated in newborns and drop rapidly over the first two weeks of life. The BNP concentrations due appear to hold steady until 12 years of age without any differences in gender. However, in the second decade of life, higher BNP levels were seen in girls than in boys. This parallels differences in the activity of the renin-angiotensin-aldosterone system, renin levels (higher in males) as well as the influence of gonadal hormones in the second decade of life[7-10]. BNP, along with the biomarkers reviewed here are also summarized in Table 1.

BNP and congenital heart disease

Before delving into the diagnostic value of BNP, it is important to note that BNP levels are strongly method dependent. This is because different assays that are used to measure BNP use different methods and have varying sensitivities and specificities. The various com-

Table 1 Overview of cardiac biomarkers and their physiologic actions

Name of biomarker	Mechanism of action	Primary effect	Available evidence
BNP/NT-ProBNP	Activates the intracellular Guanylyl cyclase-A moieties after binding to the NPR types A, B and C	Increases diuresis, natriuresis and vasorelaxation Anti-proliferative and anti-hypertrophic properties	[4]
ST2	After binding to its TL/IL-1 receptor like family, interacts with IL-33	Anti-proliferative and anti-hypertrophic properties	[3]
CTGF	Unknown	Deposition of extracellular matrix	[43]
h-FABP	Participate in the uptake, intracellular metabolism and transport of fatty acids	Modulation of cell growth and proliferation	[48]
Pro-adrenomedullin	Releasing nitric oxide from the endothelium Inhibit nicotinic agonist-induced catecholamine secretion and synthesis and nicotinic agonist-induced Na^+ and Ca^{2+} influx	Regulation of hormonal secretion Angiogenesis proliferation Vasodilation	[50]
GDF-15	Unknown	Deposition of extracellular matrix	[55]

ST2: Suppression of tumorigenicity-2; CTGF: Connective tissue growth factor; h-FABP: Serum heart-type fatty acid-binding protein; BNP: B-type natriuretic peptide; NT-ProBNP: N-terminal segment of pro-B-type natriuretic peptide; GDF: Growth differentiation factor.

ponents of pro-BNP cleavage impact measurements to varying degree depending on the method used. Hence, the reference ranges change according to which method was used.

BNP has utility in diagnosis of congenital heart disease (CHD) in newborns. Cantinotti *et al*[11] have shown that while there is a rapid decline in the BNP levels in normal newborns within the first few days of life, newborns with CHD maintain significantly elevated levels beyond 5 d of life. This was true across the spectrum of various congenital heart defects except those leading to volume or pressure overload on the right heart[11]. Maher *et al*[12] studied infants with left-sided obstructive lesions admitted to our center. Infants were divided into 2 groups: Group 1 was diagnosed with cardiogenic/circulatory shock at presentation, and group 2 consisted of infants with ductal-dependent systemic circulation without evidence of shock. In this group of total 122 patients, newborns with cardiogenic shock had a median BNP of 4100 pg/mL at presentation compared to a median BNP of 656 pg/mL ($P < 0.001$) for those without shock. A 100% of patients presenting with shock had significantly abnormal BNP values. They also report an incremental value of BNP such that every 100 units rise in BNP increased the odds of cardiogenic shock by 100 ($P < 0.001$)[13].

A study comparing new diagnosis of CHD in an emergency room setting evaluated the value of BNP compared to patients with diagnosis of respiratory distress due to primary respiratory illness or infection. This study found that in a cohort of critically sick patients with a heart disease, a mean BNP value of 3290 pg/mL was seen in patients with heart disease when compared to 17.4 pg/mL for the patients with respiratory illness or infection[13]. Koulouri *et al*[14] (2004) and Cohen *et al*[15] (2005) report similar findings that plasma BNP or NT-proBNP can differentiate between cardiac or pulmonary etiologies for patients presenting with respiratory distress.

Elevation of BNP/pro-B-type NP are seen due to long term exposure of right heart or left heart to volume and pressure overload. These elevations are especially seen with diseases that causes left ventricular volume overload when compared to right ventricular volume or pressure overload[16]. Furthermore, when comparing pediatric populations with complex CHD *vs* simple cardiac defects (ASD, VSD or PDA), on average, complex defects tend to have higher concentrations. Nir *et al*[9] (2004) showed that patients with higher pressure left to right shunts (VSD, PDA) have higher levels of NT-proBNP when compared to low pressure left to right shunts (ASD). BNP can be used to differentiate preemies with and without a patent ductus arteriosus (PDA) as well as potentially guide therapy. Attridge *et al*[17] showed that by using BNP, fewer doses of indomethacin were used for therapy of PDA. Of note, the pediatric heart can compensate better with pressure overload than volume overload and this can directly impact BNP secretion or level. A normal BNP reflects a compensated heart status but does not rule out heart disease.

BNP can assist in clinical decision making especially when identifying populations at high risks for outcomes after cardiac surgery. Various studies have shown that post-operative BNP, lack of decrease in BNP post-operatively were all strongly related to poor hemodynamics or adverse outcomes after a cardiac surgery[18,19]. Bobik *et al*[20] evaluated the value of NT-pro BNP in patients with atrioventricular septal defects (AVSD) preoperatively. They found that patients with complete AVSD had higher levels of BNP preoperatively compared to partial AVSD. Additionally, NT-proBNP levels predicted longer ICU length of stay, ventilator needs and inotropic support needs post-operatively[20].

For pediatric patients supported on mechanical support (ECMO), Huang *et al*[21] have suggested the utility of serial BNP monitoring before, during and after decannulation from ECMO. In their series, it was noteworthy that after coming off ECMO, BNP levels on the fourth day after removal of ECMO among the

survivors (median, 498 pg/mL) were significantly lower than those among non-survivors (median, 3900 pg/mL; $P = 0.017$)[21].

BNP and heart failure without structural heart disease

As mentioned above, majority of adults have heart failure (ischemic or non-ischemic) in the setting of structurally normal heart. In pediatric patients dilated cardiomyopathy is the most dominant etiology for heart failure[22]. Additional forms such as restrictive, hypertrophic cardiomyopathies are rare but important causes of genetic cardiomyopathies and heart failure. Amongst acquired causes, myocarditis followed by rheumatic heart disease in certain regions of the globe cause acute and chronic heart failure in children.

Although the overall incidence of these clinical conditions is relatively common, our understanding of BNP in these patients is not as robust. Mir *et al*[23] reported significantly higher NT-ProBNP levels in children with heart failure (from various etiologies) than health children. Ohuchi *et al*[24] showed that the BNP levels differentiated NYHA classes regardless of the underlying etiology. Law *et al*[25] in their study used two cutoff values to differentiate between a hemodynamically significant cardiologic process *vs* other disease process with a similar presentation. For neonates, a cutoff value of 170 pg/mL showed a sensitivity of 94% and a specificity of 73%. For the older age group, a cutoff value of 41 pg/mL produced a sensitivity of 87% and specificity of 70% to detect significant cardiovascular disease and related heart failure[25]. For patients presenting with acute heart failure in non-CHDs, our data (currently under review) indicated that mean BNP at presentation in this cohort is very elevated; mean of approximately 1700 pg/mL. In the outpatient setting for pediatric populations with chronic left ventricular systolic dysfunction, BNP values > 300 pg/mL have shown high sensitivity, specificity, positive and negative predictive value for the prediction of adverse cardiovascular events. Price *et al*[26] studied pediatric patients with chronic heart failure. They found that whole blood BNP concentrations were increased in patients who had a 90-d adverse cardiovascular event compared with those who did not (median, 735 pg/mL *vs* median, 37 pg/mL; $P < 0.001$). Patients with a BNP concentration > 300 pg/mL were at increased risk of death, hospitalization, or listing for cardiac transplantation (adjusted hazard ratio, 63.6; $P < 0.0001$)[26].

BNP and other diseases (post-chemotherapy, heart transplantation, Kawasaki disease, cardiac surgery)

BNP can be used to predict cardiac dysfunction in a myriad of conditions such as post-chemotherapy cancer patients, rejection from heart transplantation and Kawasaki disease. It is well known that anthracyclines exposure can lead to significant cardiac dysfunction. As such, serial measurement of BNP maybe of value to detect anthracycline induced cardiomyopathy. Studies have shown BNP to correlate with both early and late effects of anthracycline exposure, correlate well with echocardiographic findings as well as other makers of cardiac dysfunction[27].

Utility of BNP in patients with heart transplantation is being increasing explored. Lan *et al*[28] (2004 showed that BNP was elevated early on after heart transplantation however, falls exponentially early on and reached very low levels around 3 mo post-transplant. Lindblade *et al*[29] and Rossano *et al*[30] showed that BNP was significant elevated in acute rejection and had sensitivities of 96% with BNP > 100 pg/mL 1 year after transplantation. Sparks *et al*[31] have documented reduction in BNP over the first 3 mo and showed correlation it with hemodynamics. Overall, it appears that BNP correlates well with acute episodes of rejection, especially when accompanied by hemodynamic compromise.

Kawasaki disease is an acute febrile vasculitis process that may have cardiac manifestations such as myocarditis, pericarditis and coronary vasculitis leading to coronary ectasia and aneurysms. In one of the earlier studies to assess the utility of BNP in Kawasaki patients, Kurotobi *et al*[32] studied echocardiographic markers of diastolic function during acute phase of Kawasaki disease. They found that diastolic dysfunction occurs during the acute phase of the disease and BNP levels correlated well with the presence of significant diastolic dysfunction[32]. Similarly, Iwashima *et al*[33] have demonstrated the utility of BNP in identifying non-responders. They demonstrated that high level of NT-pro BNP in acute phase KD was associated with systemic inflammatory responses, elevated CRP, and increased vascular permeability. This level was particularly higher in immunoglobulin (IVIg) non-responders compared to responders (1689.3 ± 1168.8 pg/dL *vs* 844.4 ± 1276.3 pg/dL, $P < 0.001$)[33].

ST2

ST2 receptor is a member of toll like/IL-1 receptor family. It interacts with IL-33, a cytokine synthesized by cardiac fibroblasts leading to a cardioprotective stress-induced signaling that produces both antihypertrophic and antifibrotic cell signaling. ST2 is present in a membrane bound and soluble form. Soluble ST2 (sST2) may prevent the binding of IL-33 to a membrane-bound receptor version of ST2. The soluble ST2 has been shown to be of significant value in diagnosis and prognosis of heart failure. One of the key initial studies looked at myocyte stretch induced marked upregulation of myocardial *ST2* gene expression[34,35]. This was followed by multiple, large studies which have corroborated the importance of ST2 in heart failure. An analysis of the patients enrolled in the PRIDE study showed that elevated ST2 levels at presentation to the emergency room with dyspnea was a very strong predictor of death at one year. This was true for both patients with dyspnea as well as those with acute heart failure[36]. In a recent study, Parikh *et al*[37] studied population of

community-dwelling older individuals enrolled in the Cardiovascular Health Study. They found that soluble ST2 levels were significantly associated with incident heart failure, cardiovascular death and that greater ST2 level was continuously associated with increasing hazard for cardiovascular death[37]. Various studies have documented the incremental value of addition of ST2 to pre-existing predictive models of heart failure[37,38]. Accumulation of these data have led the ACC/AHA guidelines to recommend ST2 measurement for additive risk stratification in patients with acute or chronic ambulatory heart failure[3]. Normal concentration of ST2 in adults is less than 18 ng/mL, with a level greater than 35 ng/mL generally accepted as a predictor of morbidity and mortality.

Data regarding pediatric application of ST2 is extremely limited. Meeusen *et al*[39] evaluated healthy children between 2-17 years of age and measured their soluble ST2 levels using the Presage ST2 quantitative assay (Critical Diagnostics, San Diego, CA, United States). The median value for the entire cohort was 21 ng/mL (range: 6 to 122 ng/mL). They found that the ST2 levels normally increase with age, was slightly higher in males and that the central 95th percentile reference interval was 9-50 ng/mL[39].

Mathews *et al*[40] report analysis of patients with heart transplantation and small bowel transplantation and present relationship between soluble ST2 and episodes of rejection. ST2 levels are significantly elevated at the time of acute rejection (cellular and or antibody mediated) in pediatric heart transplant patients. During an episode of biopsy proven rejection, serum sST2 was elevated compared to rejection-free time points (1714 ± 329 pg/mL *vs* 546.5 ± 141.6 pg/mL; $P = 0.0002$). The authors found that, a level of > 600 pg/mL could discriminate time points of acute rejection and nonrejection [area under the curve (AUC) = 0.724 ± 0.053; $P = 0.0003$][40]. Additive value of ST2 as a marker for rejection needs to be validated.

In pediatric patients with idiopathic or primary pulmonary hypertension, Chida *et al*[41] studied the utility of ST2, BNP and other cardiac biomarkers. They report finding to statistically significant relationship between ST2 levels and functional class in these patients. Additionally, ST2 levels along with BNP levels were predictive of poor outcomes. On AUC analysis, a cutoff value of 11.1 ng/mL was identified for mortality prediction, with an AUC of 0.830. The authors conclude that ST2 and BNP levels correlate with clinical status and our predictive of outcome in pediatric patients with pulmonary hypertension[41].

To date, there has been only one published study looking at the utility of ST2 in pediatric heart failure. Hauser *et al*[42] evaluated 114 patients (and 89 controls) with heart failure due to various etiologies, analyzed for different biomarkers along with BNP for diagnostic utility. In this study, MR-proANP was the only novel biomarker that performed in a comparable manner to BNP as far as diagnostic utility was concern. ST 2 levels were not statistically different between controls and heart failure patients[42]. However, it is noteworthy that only 17/114 (15%) of patients with heart failure were in class Ⅲ or class Ⅳ heart failure. The rest of the patients were categorized as class Ⅰ or Ⅱ heart failure. It is therefore not surprising that majority of the levels were not different compared to the controls. Subgroup analysis of the 17 patients with class Ⅲ or class Ⅳ heart failure is not available. Our experience with a pilot group of 15 pediatric heart failure patients was more favorable. In our patients, the ST2 levels ranged from 14 to > 1000 ng/mL, with a mean of 229.7 ng/mL. BNP values ranged from 217 to 18216 pg/mL with a mean of 4179.5 pg/mL. There was a very strong and statistically significant correlation between ST2 and BNP levels in this cohort. We could not establish correlation between functional status or ventricular function (ejection fraction) and ST2 levels probably due to a small sample size (unpublished data).

This biomarker therefore warrants more studies in the pediatric heart failure population to establish its value in diagnosis and prognosis.

CONNECTIVE TISSUE GROWTH FACTOR /CCN2

In addition to the myocardial remodeling seen in heart failure, the role of extracellular matrix is being increasingly recognized. The ultrastructural changes in the extracellular matrix contribute towards both functional as well as structural changes that take place in acute and chronic heart failure. Enhanced collagenous deposition and fibrosis are some of the key changes in the extracellular matrix in CHF. Various mediators and matri-cellular proteins in the extracellular matrix are being increasingly looked at as biomarkers for heart failure. Connective tissue growth factor (CTGF) is one such matri-cellular protein that is involved in pathologic process of fibrosis in addition to other physiologic conditions such as endochondral ossification, vascular growth, cellular growth. Recently CTGF plasma levels have been investigated in patients with chronic and acute heart failure[43]. Koitabashi *et al*[44] studied CTGF levels along with other cardiac biomarkers as well as markers of fibrosis in 52 patients with chronic heart failure. In this study plasma CTGF levels were significantly elevated in patients with symptomatic heart failure and strongly correlated with plasma BNP, TGF beta, matrix metalloproteinase levels. Plasma CTGF levels also correlated with E/E' ratio[44].

Behnes *et al*[45] studied CTGF levels in 212 patients enrolled in the Mannheim NT-proBNP study including 66 patients with acute heart failure. This study showed that CTGF levels were significantly elevated (median 93.3 pg/mL) in patients with heart failure with reduced ejection fraction as well as in patients with acute heart failure (median 77.3 pg/mL) when compared to those with normal heart function (median 25.9 pg/mL). In

addition, CTGF significantly improved the diagnostic capacity of NT proBNP for acute heart failure. There is limited data in pediatric heart failure[45]. Li *et al*[46] studied CTGF and BNP levels in 61 children including 41 with heart failure. They report that CTGF levels were significantly increased in patients with heart failure and that the levels correlated with the severity of heart failure. Addition of CTGF levels to NT-proBNP levels also improved ability to diagnose heart failure in children[46]. The same group has also shown significant correlation of CTGF levels with pulmonary arterial hypertension associated with CHD in children[47].

SERUM HEART-TYPE FATTY ACID-BINDING PROTEIN

The serum heart-type fatty acid-binding protein (h-FABP) is an intracellular transport protein mainly involved in transport of fatty acids. When compared to skeletal muscle, it is highly expressed (about 10 ×) in cardiac muscle. H-FABP has a very strong specificity for diagnosing myocardial injury since it has a small size and so rapidly appears in the blood stream and no isotype mismatch between different types of FABP. Sun *et al*[48] showed both h-FABP and BNP concentrations have good correlation with the degree of heart failure in patients with CHF. In their study, they also evaluated the effects of therapy with carvedilol and found that initiation of carvedilol was associated with decrease in h-FABP and BNP levels. They concluded that h-FABP can be used as biomarkers to evaluate the severity of heart failure in children[48]. In a different study, the group has also demonstrated the utility of h-FABP as a marker of cardiac involvement in patients with Kawasaki disease[49].

PRO-ADRENOMEDULLIN

The adrenomedullin protein (ADM) is protein is cleaved to form adrenomedullin and proadrenomedullin (proADM). This protein has several functions including regulation of hormonal secretion, promotion of angiogenesis, antimicrobial activity and vasodilation. CHF is a complex multifactorial process and since there is neurohormonal activation playing quite an important role in HF, ADM can be implicated in this process. Gegenhuber *et al*[50] found that ADM was found to be elevated and comparable to BNP in patients with acute decompensated heart failure. They also found that high concentrations of ADM predicted 1-year all-cause mortality[50]. Furthermore, ADM may not only be used to evaluate the severity of HF but also a prognostic indicator of this syndrome. In a study by Khan *et al*[51] looking at the value of proADM in heart failure patients post-myocardial infarction, they found that proADM was an excellent predictor of mortality. Additionally, proADM provided further risk stratification in those patients who had NTproBNP levels above the median and therefore could be of additive value[51].

Due to the implication of fluid distribution and vasodilatory properties, this biomarker has been used to predict response to treatment in patients with postural orthostatic tachycardia syndrome (POTS). Zhang *et al*[52] have shown that the levels of midregion-proADM are elevated in patients with POTS and that midodrine responsive patients had higher levels compared to non-responders. ROC analysis showed that a cutoff value for MR-proADM of 61.5 pg/mL produced both high sensitivity (100%) and specificity (71.6%) in predicting the efficacy of midodrine hydrochloride therapy for treating POTS[52].

GROWTH DIFFERENTIATION FACTOR

Growth differentiation factor (GDF-15) is a member of the TGF-B cytokine family that is implicated in the stress response. Unlike h-FABP that is expressed by the myocardium, GDF-15 is not. However, GDF-15 expression is induced in the heart in response to inflammation, tissues injury, ischemia, pressure overload. It is known that GDF-15 is elevated in the setting of left ventricular overload but may also be in response to right ventricular pressure changes as seen in pulmonary embolism. Kempf *et al*[53] found that GDF-15 can provide prognostic information in patients with heart failure. They found that GDF-15 was significantly increased in these patients. They however, concluded that since GDF-15 is non-specific for cardiac myocytes and is involved in stress overload pathways, GDF-15 would need to be compared to specific cardiac makers to get a complete prognostic assessment[53,54]. Raedle-Hurst *et al*[55] found that GDF-15 levels are significantly associated with NYHA functional class and heart function of patients after completing the Fontan procedure for single ventricle. Since Fontan physiology is not a good model of pressure overload on the single ventricle, they found that NT-proBNP failed to be directly related to the echocardiographic measures of heart function. They concluded that GDF-15 is an early marker of decreased heart function in this cohort while NT-proBNP appear to be late markers when clinical heart failure is already present. They used a cutoff of > 613 pg/mL to suggest further cardiac evaluation may be indicated to assess for impaired ventricular function[55]. A recent meta-analysis has found that increased levels of GDF-15 were associated with increased mortality in patients with heart failure (HR of 1.86, 95%CI: 1.37-2.52), although cautions about heterogeneity in the studies as well as potential publication bias[56]. Overall, it appears that GDF-15 studies focused on specific pediatric patient populations (volume load, pressure load) may clarify its role in diagnosis and prognosis of pediatric heart failure.

CONCLUSION

As our understanding of the pathobiology of heart

disease evolves we continue to identify important biomarkers responsible for the same. These biomarkers are indicative of the cascade of events resulting in various forms of heart failure and heart disease. Elucidation of these processes is extremely important as they have the potential to identify new therapeutic targets. Specifically, biomarkers therefore play a vital role in diagnosis, management and prognosis of heart failure. Of all the biomarkers reviewed, BNP continues to be the dominant biomarker even in pediatric heart failure. Our understanding of the role of these novel biomarkers, some of which have already established a role in adult heart failure, will improve with further research. There is therefore an intermediate and an urgent need for undertaking biomarkers research in pediatric heart failure to enable us to improve care of these patients.

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