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Biomarkers in pediatric heart failure: Their role in diagnosis and evaluating disease progression

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ABSTRACT

Biomarkers have established an important role in the diagnosis and prognosis of heart failure in adults. Several biomarkers of different classes have also demonstrated a practical or potential role in managing patients with heart failure. In the pediatric population, objective assessment of severity and disease progression is apt to be more difficult. Therefore, biomarkers may represent an objective tool to confirm functional status and echocardiographic indices of left ventricular dysfunction in children with heart failure. Since early detection of remodeling is vital to preemptive management, biomarkers may also serve to gauge the severity of the ventricular remodeling process in several different diseases. Thus far, B-type natriuretic peptide levels have been found to be associated with the severity and outcome of heart failure in children, correlating with symptom severity, functional status and degree of left ventricular remodeling. They have been found to predict cardiovascular events, and may guide medical treatment decisions in symptomatic heart failure. High-sensitivity C reactive protein, cytokines, cytokine receptors, cardiac troponins and gene expression profiling are all emerging as a useful assessment tools in adults with heart failure. Further study is required to validate the role of these measures in children with cardiomyopathies and with heart failure.

1. Introduction

Heart Failure remains an important cause of morbidity and mortality in children. Registry based data suggests that 50% of pediatric heart transplants are a direct result of cardiomyopathy, presumably representing end-stage heart failure [1]. To some extent, the progression of heart failure is delayed by surgical palliation of congenital heart disease lesions, but seldom completely abrogated. The eventual consequences of single ventricle physiology, or of a right ventricle in the systemic position typically become evident from the third decade onwards[2]. In a child or young adolescent, the clinical syndrome of heart failure often presents in an advanced state as acute decompensated heart failure: regardless of the underlying etiology, management at this stage of disease is a formidable challenge, with death or cardiac transplantation being a frequent outcome [3].

Against this backdrop, what is the value of biomarkers? Conventional wisdom has offered tenuous support for additional diagnostic tests in a disease process that is so readily evident. A brief overview of currently proposed biomarkers is illustrated in Table 1. For clarity, these are grouped according to the pathophysiologic process, which they represent in the progression of heart failure. Recalling the primary roles of biomarkers as enunciated by Morrow[4] and others, they should offer additional diagnostic or prognostic information not otherwise readily evident, and potentially support treatment decisions. This paper will review the evidence both supportive and otherwise, that biomarkers are in fact useful in pediatric heart failure. In so doing we will examine the evidence for the use of natriuretic peptides (the established standard for heart failure biomarkers) and explore the potential value of other markers likely to be implicated based on their role in tissue injury, inflammation and remodeling. We will touch briefly on the relative value of multiple versus single markers.

1.1. The natriuretic peptides and heart failure diagnosis

The pathophysiology of symptomatic heart failure is closely mirrored by the production and metabolism of the natriuretic peptides. Natriuretic peptides (type A and type B) are released into the blood stream by myocardial tissue in response to atrial and ventricular wall stretch, thereby reflecting the mechanical stress that accompanies volume loading. These peptides derive from the splitting of an inactive precursor molecule: from the left ventricle (LEFT VENTRICLE), proBNP is cleaved into BNP (the active component) and NT-proBNP which is inactive[5]. NT-proBNP has a longer half-life, is more stable at room temperature and after freezing has less intrinsic assay variability than BNP, making it a more convenient molecule to work with in laboratories[6] . Both BNP and NT-proBNP levels are far

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Table 1
Currently proposed biomarkers relevant to heart failure severity and prognosis. There are relatively few biomarkers in current clinical use. These can be nominally assigned to one of several pathophysiologic processes (as indicated here). Other novel biomarkers are reviewed elsewhere.

Current molecular biomarkers of heart failure		
Biomarker	Description	Current use
A. Ventricular Loading		
B-type Natriuretic Peptide (and NT- proBNP)	Responds to mechanical loading stress, results in ventricular/vascular relaxation, natriuresis, counteraction of the renin–angiotensin–aldosterone axis.	Well established validity, with numerous applications in Pediatrics.
B. Myocardial Injury		
Troponin T and I	Not biologically active, released with myocyte necrosis.	High sensitivity assays validated in adult heart failure trials.
C. Myocardial Inflammation		
C-reactive protein	Hepatic derived protein, binds to damaged tissue antigens and activates complement.	Validated as a prognostic tool in adult population-based trials. Additive prognostic value with BNP.
D. Myocardial Matrix remodelling		
Matrix metalloproteinases (MMP)	Multiple (>25) proteases which regulate turnover of cardiac (and other) connective tissue	Highly dynamic process, with complex signaling, best defined in experimental post-MI models. Limited data to support use as a heart failure biomarker, remains investigational.
Tissue inhibitors of Metalloproteinases (TIMPs)	Inhibits the activity of the MMPs	Stoichiometric balance of MMP-TIMP determines tissue activity. Variable data noted following VAD placement, complicates interpretation.
Collagen proPeptides	Increased circulating levels during active remodeling	Use remains investigational.

higher in newborns and infants, decreasing to more stable level after 3 years of age[7], 12).

Both BNP and NT-proBNP have been used to identify the presence and determine the severity of heart failure in several pediatric studies [8–14]: although these studies are limited in sample size and portray heterogeneous pediatric heart disease, the evidence appears on the whole consistent. Regardless of whether the etiology of heart failure is a congenital malformation, a metabolic disorder, an inflammatory, ischemic or a primary myopathic disorder, natriuretic peptides rise in proportion to the symptomatic severity and the degree of remodelling.

In children natriuretic peptides levels have been able to differentiate dyspnea due to cardiac versus pulmonary causes[15,20,21]. Of particular interest, a prospective study conducted by Law et al. [16] reported the utility of a single BNP measurement in diagnosing significant cardiac diseases in a pediatric acute care setting. The patients presenting with symptom suggestive of cardiac disease were divided into a neonatal group (≤7 days of age) and children up to 19 years of age. The median BNP for neonates with confirmed cardiac disease was 526 pg/ml versus 96 pg/ml, for those without disease, ($p<0.001$). The median BNP for the older age group with disease was 122 pg/ml versus 22 pg/ml, for those without disease, ($p<0.001$). A cut-off point of 170 pg/ml in neonates up to 7 days old had a sensitivity of 94%, and a specificity of 73%. In children up to 19 years of age a cut off point of 41 pg/ml had a sensitivity of 87%, a specificity of 70%.

In patients with left to right shunt lesions, BNP has been studied as a potential tool to determine the time and indication for surgery. Kunii et al. [17]evaluated the possibility of using BNP to determine the severity of shunt in 154 children with one of the following lesions: ventricular septal defect (VSD), patent ductus arteriosus (PDA) or atrial septal defect (ASD). BNP showed to correlate with pulmonary to systemic flow ratio (Qp/Qs) in all 3 defects: r 0.75, r 0.89, r 0.69, respectively (P 0.0001). BNP showed good correlation with LEFT VENTRICLULAR end diastolic volume in VSD and PDA patients (r 0.72, r 0.79, P 0.0001) and with right ventricular end diastolic volume in patients with ASD (r 0.81, P 0.001). A BNP of 35 pg/ml can identify a Qp/Qs of 2.0 with a sensitivity of 80.6% and specificity of 83.3%. Similarly Suda et al. [18] in 59 children with VSD showed that plasma BNP significantly positively correlated with Qp/Qs ($r=0.65$) and mean pulmonary artery pressure ($r=0.72$); also BNP of 20 pg/mL or more identified children with mean pulmonary artery pressure of 20 mmHg or greater with a sensitivity of 82% and a specificity of 89%.

In the setting of dilated cardiomyopathy, children attending an outpatient heart failure clinic with left ventricular systolic dysfunction have a risk for deterioration while on standard therapy. Price et al. [19]reported that point of care BNP levels ≥ 300 pg/mL were predictive of an adverse cardiovascular event (typically admission with worsening symptoms) within 90 days of testing with a sensitivity of 93% and specificity of 95%.

1.2. Natriuretic peptides and heart failure symptoms

In a retrospective study of 36 children with dilated cardiomyopathy, Rusconi [20] and co-workers examined the association between left ventricular remodeling, symptom severity and NT-proBNP levels. Measurement of NT-proBNP occurred within 7 days of echocardiographic and functional class assessments, and were repeated serially. An increase in NT-proBNP levels was associated with a decrease in left ventricular ejection fraction (LVEF) and shortening fraction (LVSF)-z score, and with an increase in the systolic dimension (LVSD)-z and diastolic dimension (LVDD)-z ($p<0.001$). A ten-percent decline in EF was found to be associated with a 10 fold rise in NT-proBNP. For individual patients there was also a clear association between the changes in NT-proBNP and their functional class: therefore the authors showed that in a hypothetical patient with a baseline NT-proBNP plasma level of 660 pg/ml, an acquired 10 fold increase in NT-proBNP would increase the probability of that patient being in NYHA/Ross functional class III–IV by 85.5 fold ($P<0.001$)). By subgroup analysis, this study determined that an NT-proBNP level greater than 1000 pg/mL identified children constantly or intermittently in functional class III–IV with 95% sensitivity and 80% specificity. It therefore appears that NT-proBNP has a high negative predictive value, although also an important false positive rate, with some patients maintaining a high NT-proBNP despite remaining minimally symptomatic. Therefore in children with NT-proBNP between 450 and 1000 pg/ml at least 3 serial measurements of NT-proBNP may be necessary for a reliable prediction of their true functional class.

Similar data to the above emerged when Mangat et al. [14] studied 48 children with heart failure secondary to left ventricular systolic