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REVIEW ARTICLE

Role of NT-proBNP Level in Heart Failure in Children: A Review

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Abstract

Paediatric heart failure is associated with significant morbidity and mortality. In adult heart failure patients, the role of cardiac biomarkers has exponentially increased over the last two decades. There is enough evidence to support the use of cardiac biomarkers as an adjunctive marker in the integrated evaluation of patients with congenital and acquired heart disease to define severity and progression of heart failure as well in the monitoring of response to treatment. Cardiac biomarkers can also be used for the screening of heart failure and as a prognostic marker in children undergoing cardiac surgery. Of all the biomarkers, BNP continues to be the dominant biomarker even in pediatric heart failure. Although B-type Natriuretic Peptide (BNP), N-terminal-proBNP (NT-proBNP), and mid-regional-proANP (MR-proANP) are included in current guidelines on heart failure in adults, no guideline considering these biomarkers in pediatric heart failure is available.

Keywords: *Children, heart failure, NT-proBNP.*

Introduction

Heart failure is common among children having both congenital and acquired heart disease. Congenital heart diseases such as ventricular septal defect (VSD), atrial septal defect (ASD), and patent ductus arteriosus (PDA) are the major causes of heart failure in the paediatric age group.[1] Among the acquired heart diseases dilated cardiomyopathy, rheumatic carditis, and infective endocarditis may play a major role in inducing cardiac failure.[2] There are various symptoms of heart failure in children, which may overlap with other common diseases of childhood, particularly viral illnesses.[3] The symptoms of heart failure include respiratory distress, effort intolerance, poor sucking in neonates & interrupted feeding in older children, and poor weight gain and edema.[4] Various clinical grading systems may help to diagnose and identify the severity of heart failure in children. Many clinical scoring systems have been established based on clinical features, but sometimes, those systems lack objectivity due to the variation of features in different ages.[1] The New York Heart Association (NYHA) classification was the only system for classifying heart failure in children until 1987.[5] However, this approach was predicated on adult activity limitations, which did not translate effectively when applied to children. For this purpose, the Ross classification was first applied to children 25 years ago. The system has gone through several modificationssince then. Therefore, the modified Ross classification is most commonly used to classify heart failure severity in children. This classification provides a numeric score comparable to the NYHA heart failure classification for adults.[5] It can occasionally be difficult to determine the severity of heart failure in newborns and young children based on the amount of dyspnea, tiredness, palpitations, or chest discomfort, which form the

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basis of the NYHA/Ross classifications.[6] Thus, different cardiac biomarkers, including B-type Natriuretic Peptide (BNP) and Nterminal B-natriuretic peptide (NT-proBNP), have been studied most to assess the severity among heart failure patients.

Role of various biomarkers in the disease process

Current American Heart Association guidelines for managing heart failure recommend using cardiac biomarkers in the diagnosis, treatment, and prognosis of heart failure.[7] Several biomarkers are being studied in both adults and children with heart failure. Because of its high diagnostic accuracy, current adult "National Institute for Health and Care Excellence" (NICE) guidelines recommend evaluating NT-proBNP as the first line of investigation in suspected heart failure patients. Similarly, cardiac troponin I and T are recommended by NICE guidelines for diagnosing acute coronary syndrome and screening for chest pain.[8] Cardiac biomarkers are commonly employed in adults but not in children. This is owing to the complex, multifaceted mechanism of childhood heart failure and the scarcity of large-scale pediatric research.[9]

Natriuretic peptide

The natriuretic peptide (NP) system includes atrial NP (ANP)**;** B-type NP (BNP, also called brain NP)**;** C-type NP (CNP), dendroaspis NP (DNP) and urodilatin.[10] There are three receptors: NP receptor-A [guanylate cyclase (GC)-A or NPRA], NP receptor-B (GC-B or NPR-B), and NP receptor-C (clearance receptor or NPR-C).[11] In humans, ANP and BNP are encoded by NP precursor A (NPPA) and NPPB genes on chromosome 1, while NPPC encodes CNP on chromosome 2.[12] Cardiomyocytes, fibroblasts, endotheliocytes, immunological cells (neutrophils, T-cells, and macrophages), and immature cells (embryonic stem cells, muscle satellite cells, and cardiac precursor cells) produce and secrete NPs through specific pathways.[13] They are produced mainly by cardiac myocytes, brain tissue, and renal tissues in response to wall stretch and other causes.[10]

Brain natriuretic peptide (BNP) and N terminal pro-BNP (NT-proBNP)

Cardiomyocytes synthesize the cardiac natriuretic hormones as prohormones such as proANP and proBNP. The precursor pro-BNP is a 108-amino acid (aa) protein that is cleaved by a circulating endoprotease known as Corin into two polypeptides.[14] ProBNP is enzymatically cleaved to form NT-proBNP, a 76-aa N-terminal peptide, and B-type natriuretic peptide (BNP), a 32-aa COOH-terminal peptide (Fig.-1). NT-proBNP is the inert form, whereas BNP is biologically active. NT-proBNP has a longer plasma half-life of 1-2 h, compared to BNP's half-life of 15-20 min, and so has a greater plasma concentration.[15]

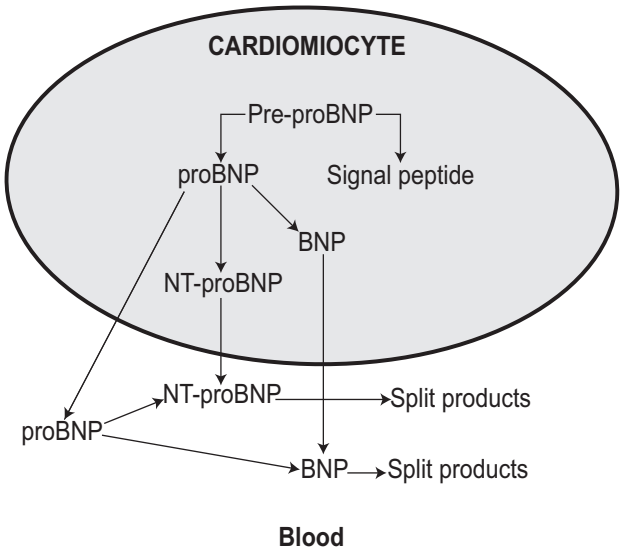

Fig.-1 *Production pathways of B-type natriuretic hormone and its related peptides*[15]

Plasma BNP concentrations are very high during the first 4 days after birth, and values decrease rapidly during the first week, with a further slow reduction until the first month of life.[15]

Mechanism of action of natriuretic peptide

Circulating ANP and BNP can bind to natriuretic peptide receptor-A (NPR-A) in various tissues, including the vascular and renal. NPR-A is connected to the cellular membrane's particulate guanylyl cyclase (GC). GC activation results in the production of cGMP from GTP. The cGMP acts as a second messenger for the cellular activities of NPs. Neutral endopeptidase (NEP, also known as neprilysin) is a circulating enzyme that breaks down natriuretic peptides. As a result, inhibiting this enzyme (for example, with sacubitril) raises circulation levels of natriuretic peptides and enhances their effects.[16]

Effects of natriuretic peptide

There are two major pathways of NP actions: 1) vasodilator effects and 2) renal effects. NPs immediately dilate veins and lower central venous pressure, lowering cardiac output by decreasing ventricular preload (Fig. 2). NPs also dilate arteries, reducing systemic vascular resistance and arterial pressure. Systemic vasodilation is caused by NP receptor-mediated increases in vascular smooth muscle cGMP and reduced sympathetic vascular tone. This latter approach may include inhibiting norepinephrine release by sympathetic nerve terminals.

NPs influence the kidneys by raising the glomerular filtration rate and filtration fraction, resulting in natriuresis (increased salt excretion) and diuresis. A second renal function of NPs is to reduce renin release, which reduces circulating levels of angiotensin II and aldosterone. This further causes increased natriuresis and diuresis. Natriuretic peptides act as a counter-regulatory system for the renin-angiotensin-aldosterone system.[16]

Table I

Causes of increased natriuretic peptide

Cardiac:

- Heart failure
- Congenital heart disease
- Valvular heart disease
- Myocarditis
- Arrhythmias
- Left ventricular hypertrophy
- Acute coronary symptoms
- Hypertrophic or restrictive cardiomyopathy
- Surgical procedures involving the heart

Noncardiac:

- Renal dysfunction
- Liver dysfunction
- Pulmonary hypertension
- Chronic obstructive pulmonary disease
- Ischemic stroke
- Subarachnoid hemorrhage
- Anemia
- Severe infections
- Severe metabolic and hormonal abnormalities (e.g., diabetic ketosis, thyrotoxicosis)

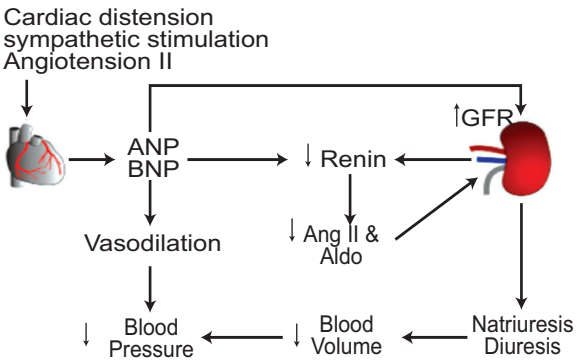

Fig.-2: *Effects of natriuretic peptides*

So, the final effects are natriuresis, diuresis, inhibit renin, decrease circulating angiotensin II, decrease circulating aldosterone, systemic vasodilation and arterial hypotension.

Causes of increased natriuretic peptide[17]

Both cardiac and non-cardiac diseases can increase natriuretic peptide levels (Table I).

BNP and heart failure with structural heart disease

BNP concentrations are high in neonates and children with CHD and are higher in those with left ventricular volume overload as compared to those with right ventricular volume or pressure overload.[18] Furthermore, BNP values are higher in diseases characterized by left ventricular pressure overload than in diseases with right ventricular pressure overload. In diseases with volume overload, BNP values are generally positively correlated with the magnitude of left-to-right shunt, pulmonary artery pressure, pulmonary vascular resistance, and end-diastolic volume.[19] Paediatric patients with complex CHD show significantly higher BNP concentrations compared with those with simple cardiac defects, such as patent ductus arteriosus and atrial or ventricular septal defects.[20] A few studies were conducted to see the role of NT-proBNP as a cardiac biomarker to diagnose and assess the severity of heart failure. In 2023, Chowdhury et al[1] conducted a study in India on 80 children aged 1 month to 5 years with CHD to determine the diagnostic efficacy of NT-proBNP as a marker of severity of heart failure. The study showed that NT pro-BNP levels gradually increased with the severity of heart failure and could be utilized as a measure of the severity of heart failure in children with CHD.

BNP and heart failure without structural heart disease

In pediatric patients dilated cardiomyopathy is the most dominant etiology for heart failure.[21] There are limited data regarding BNP values in children with various cardiomyopathies. BNP values are usually higher with decreased ejection fraction, enlarged left ventricular dimensions, and abnormal diastolic indices assessed by echocardiography.[22] In children with hypertrophic cardiomyopathy, BNP values were able to predict disease severity, independently correlated with various echocardiographic parameters including indices of diastolic function and maximal left ventricular wall thickness.[23] In a study considering children with heart failure of various etiologies, including 14 cases of dilated cardiomyopathy, NT-proBNP levels were significantly higher than in controls and showed correlation with the ejection fraction and with the clinical heart failure score. Children with dilated cardiomyopathy appeared to have higher BNP values than those with hypertrophic and restrictive forms[24] and in those with iron-overload cardiomyopathy in beta thalassemia major.[25] In 1 study, patients with acute Kawasaki disease had higher BNP levels than patients with acute viral illness and patients with Kawasaki disease in the convalescence phase.[26]

Cutoff values of BNP

The established cut-off values for BNP and NT-proBNP in adults are crucial for accurately diagnosing, monitoring, and determining the appropriate timing for intervention in congestive heart failure. However, interpreting these biomarkers in children requires a different approach due to the wide variation in normal levels throughout childhood and the different etiologies of heart failure in pediatric patients. Chowdhury et al[1] determined that the cutoff value of NT-proBNP to diagnose heart failure was 520.2pg/ml. A study by Jittham et al[4] done in Thailand in 2019, included 180 children (aged 1-15 years) with underlying heart disease. The study found that NT-proBNP level of more than 400 pg/ml predicted cardiac failure. Another study by Rajan et al[3] was conducted on 74 patients diagnosed with heart failure by modified Ross criteria. The study found LVEF and NT pro-BNP showed a significant negative correlation (r=-0.789, p=0.003). Law et al[27] in their study used two cutoff values to differentiate between a hemodynamically significant cardiologic process *vs* other disease process with a similar presentation. Paediatric 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.

Conclusion

NT-proBNP can be used as adjunctive markers in the integrated screening, diagnosis, management, and follow-up of children with heart failure caused by various acquired, congenital heart disease and after cardiac operation in children.

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