Cardiac biomarkers in children with congenital heart disease

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Background: **Most congenital heart diseases (CHDs) have specific hemodynamics, including volume and pressure overload, as well as cyanosis and pulmonary hypertension, associated with anatomical abnormalities. Such hemodynamic abnormalities can cause activation of neurohormones, inflammatory cytokines, fibroblasts, and vascular endothelial cells, which in turn contribute to the development of pathologic conditions such as cardiac hypertrophy, fibrosis, and cardiac cell damages and death. Measuring biomarker levels facilitates the prediction of these pathological changes, and provides information about the stress placed on the myocardial cells, the severity of the damage, the responses of neurohumoral factors, and the remodeling of the ventricle. Compared to the ample information on cardiac biomarkers in adult heart diseases, data from children with CHD are still limited.**

Data sources: **We reviewed cardiac biomarkers-specifically focusing on troponin as a biomarker of myocardial damage, amino-terminal procollagen type III peptide (PIIIP) as a biomarker of myocardial fibrosis and stromal remodeling, and B-type natriuretic peptide (BNP)/N-terminal proBNP as biomarkers of cardiac load and heart failure, by introducing relevant publications, including our own, on pediatric CHD patients as well as adults.**

Results: **Levels of highly sensitive troponin I are elevated in patients with atrial septal defects (ASDs) and ventricular septal defects (VSDs). PIIIP levels are also elevated in patients with ASD, VSD, pulmonary stenosis, and Tetralogy of Fallot. Measurement of BNP and N-terminal proBNP levels shows good correlation with heart failure score in children.**

Conclusions: **In the treatment of children with CHD requiring delicate care, it is vital to know the specific degree of myocardial damage and severity of heart failure. Cardiac biomarkers are useful tools for ascertaining the condition of CHDs with ease and are likely to be useful in determining the appropriate care of pediatric cardiology patients.**

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Review article

Introduction

Most congenital heart diseases (CHDs) have specific hemodynamics, including volume and pressure overload, as well as cyanosis and pulmonary hypertension (PH), associated with anatomical abnormalities. These overloads can result in necrosis, apoptosis, and mechanical stressors, such as direct pressure and stretching of myocardial cells, which are believed to cause myocardial damage (Fig. 1). When the myocardium incurs the aforementioned overload, various compensatory mechanisms work to maintain cardiac function. One of these compensatory mechanisms is cardiac hypertrophy due to an increased activity of the renin-angiotensin-aldosterone (RAA) system.[1] Furthermore, myocardial damage may result in myocardial localization of inflammatory cytokines and cause activation of fibroblasts and vascular endothelial cells.[2,3] Growth signals from tissue growth factors and angiotensin-II induce the production of amino-terminal procollagen type III peptide (PIIIP), which is the most frequently and extensively studied marker of tissue fibrogenesis. PIIIP is cleaved off during conversion from type III procollagen to type III collagen in the fibroblasts, and is subsequently released into the bloodstream.[4]

Cardiac hypertrophy and myocardial fibrosis are compensatory mechanisms of heart failure (HF). In the early stage, HF is compensated by increasing cardiac output; however, persistent HF may trigger a vicious cycle in which the ventricle must work against a greater

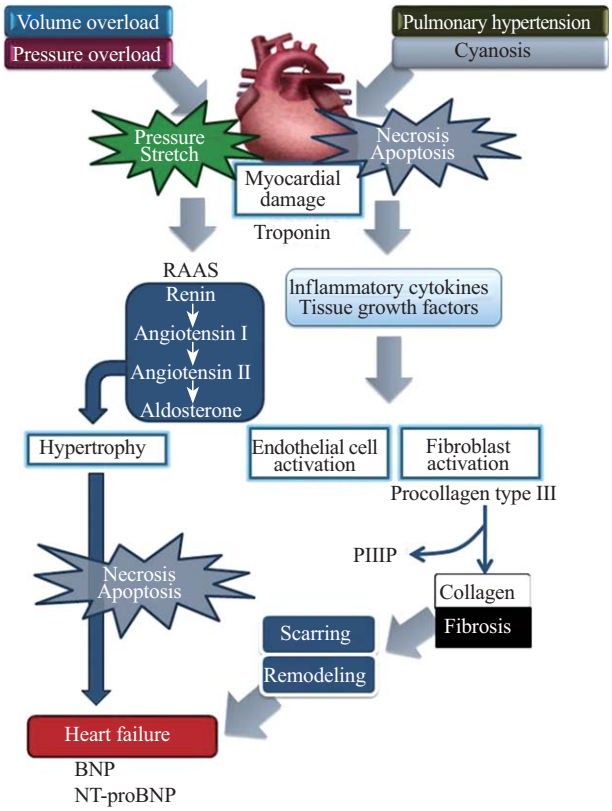

Fig. 1. Cardiac biomarkers and mechanisms of cardiac loading and hypoxia that cause heart failure in congenital heart diseases. PIIIP: procollagen type III peptide; BNP: B-type natriuretic peptide; NT-proBNP: N-terminal pro-B-type natriuretic peptide; RAAS: renin-angiotensin-aldosterone system.

load, which in turn may lead to further deterioration of ventricular function. Biomarker measurements facilitate the prediction of the pathological condition, including what stress is placed on the myocardial cells, how much damage is incurred, how neurohumoral factors respond, and how the ventricle has been remodeled.

However, information about various types of cardiac biomarkers is still limited in children with CHD as compared to that in adults. Therefore, to help deepen our understanding of cardiac biomarkers in pediatric CHD patients, we reviewed this topic—specifically focusing on 1) troponin as a biomarker of myocardial damage, 2) PIIIP as a biomarker of myocardial fibrosis and stromal remodeling, and 3) B-type natriuretic peptide (BNP)/N-terminal proBNP (NT-proBNP) as biomarkers of HF—by introducing relevant publications, including our own, on pediatric CHD patients as well as adults.

Biomarker of myocardial cell damage: troponin

Biomarkers used in the diagnosis of myocardial damage include creatine kinase (CK), creatinine kinase MB (CK-MB), myoglobin, and heart-type fatty acid-binding protein (H-FABP), all of which are present in the cytoplasm-soluble fraction, and troponin T (TnT), troponin I (TnI), and myosin light chain, which constitute myofibrils. TnT, TnI, and H-FABP are present inside the myocardial cells, but may infiltrate the bloodstream if the myocardial cells are damaged. These biomarkers, especially TnT and TnI, have high specificity, and newly developed rapid measurement kits have been recently utilized in clinical practice in the diagnosis of acute coronary syndrome and acute myocardial infarction (AMI).[5,6] The guidelines on the diagnosis of AMI published in 2010 by the American College of Cardiology/American Heart Association and European Society of Cardiology emphasize the importance of elevated troponin levels instead of elevated CK and CK-MB levels, which were previously used.[7]

TnT and TnI may be detected in the blood 3-4 hours after the onset of AMI, and may therefore be useful in the early diagnosis of AMI.[5] The recent development of a second-generation high-sensitivity troponin assay has not only increased the accuracy of AMI diagnosis, but also made it possible to diagnose slight myocardial ischemia, which has been imperceptible to date. An examination of adults revealed that blood TnT and TnI levels correlated with the degree of severity of HF and were more useful than NT-proBNP levels as prognostic factors of cardiovascular events.[8] Moreover, serum TnI levels were also found to be increased in patients without AMI or HF, and were elevated in 75% of patients who received treatment in the intensive care unit for systemic inflammatory response syndrome and sepsis.[9,10] It has been suggested that systemic inflammatory enzymes, such as tumor necrosis factor alpha (TNF-α), interleukin (IL) 6, and reactive oxygen species, may cause myocardial damage.[11] Moreover, elevated TnI levels are found in 40% of patients with acute pulmonary embolism.[12] It is assumed that myocardial damage is caused by hypoxia and a pressure overload on the right ventricle due to sudden elevated pulmonary vascular resistance. In addition, it has been reported that in patients with hypertrophic cardiomyopathy, the TnI levels significantly increase as the myocardial wall thickens.[13]

Upon examining serum TnI levels in children, we found that the cutoff value in healthy children was 0.014 ng/mL, whereas the cutoff value in adults was known at 0.04 ng/mL.[14] In adults, the serum troponin level is thought to be increased by silent HF, invisible cardiovascular stress, and renal dysfunction; it is moreover known to increase with aging.[15] Furthermore, upon measuring troponin levels in pediatric patients with left-to-right shunt [atrial septal defects (ASDs) and ventricular septal defects (VSDs)],

we found significantly elevated levels of TnT and TnI. These results suggest that ventricular volume overload may cause myocardial damage. Moreover, children with VSDs were found to have much higher levels of TnT and TnI than children with ASDs, and the TnT and TnI levels showed a good positive correlation with the pulmonary-to-systemic blood pressure ratio (Pp/Ps), which suggests that, in addition to ventricular volume overload, right ventricular pressure overload may also damage the myocardium. Accordingly, Eerola et al[16] reported that in CHD, ventricular pressure and volume overload might increase the TnI levels. Moreover, it has been reported that patients with CHD-related PH have increased levels of TnT.[17] Thus, the measurement of high-sensitivity troponin facilitates the early diagnosis of AMI; meanwhile, in the field of pediatric cardiology, it may also reflect silent myocardial damage due to pressure or volume overload, and is a useful tool in the management of CHD and for ascertaining the patients' condition.

Biomarker of myocardial fibrosis and interstitial remodeling: PIIIP

In the event of ischemic myocardial necrosis and apoptosis, inflammatory cytokines and tissue growth factors activate the growth of fibroblasts, and thus collagen metabolism (Fig. 1).[18] Furthermore, physical stressors, such as that caused by myocardial pressure and stretch overload, induce the production of angiotensin II, and consequently lead to the growth of fibroblasts via angiotensin I receptors.[2] PIIIP is a protein in the blood that reflects collagen metabolism in the tissues, and its expression has long been known to be increased in patients with HF. PIIIP levels increase after treatment of HF, even in mild HF, and are thus utilized as a marker of myocardial remodeling to determine and predict prognosis.[19-21] Moreover, PIIIP has also gained attention as a marker of ventricular diastolic dysfunction.[22]

In a previous study by our group, the PIIIP level was found to be elevated owing to various hemodynamics in children with CHD.[23] In children with VSDs or ASDs exhibiting ventricular volume overload, the PIIIP level was found to correlate with the pulmonary-to-systemic blood flow ratio (Qp/Qs), whereas in children with Tetralogy of Fallot (TOF), the PIIIP level was found to correlate with the degree of cyanosis. Moreover, we also found that the PIIIP levels were inhibited by angiotensin-converting enzyme inhibitors.

Similar to adults, the RAA system in children has been reported to be involved in the development of myocardial fibrosis. Lai et al[24] reported that following surgery for TOF, a good correlation was observed between mechanical dyssynchrony of the left ventricle and PIIIP expression. The degree of diastolic dysfunction of the left ventricle and the PIIIP levels have been reported to be well correlated in children with dilated cardiomyopathy, and additional reports have indicated that the degree of coronary stenosis in the late period of Kawasaki disease and elevated PIIIP levels are correlated as well.[25,26] Accordingly, in the treatment of children with cardiovascular disease, we believe that the PIIIP level is a useful tool to ascertain the state of myocardial fibrosis and associated ventricular function.

Biomarkers of HF: BNP and NT-proBNP

The neurohumoral factors, noradrenalin, the RAA system, endothelin, IL-6, and TNF-α are activated and they play key roles in the formation of HF. However, these neurohumoral factors interrelate and are difficult to be measured, as their blood serum levels tend to change often, and as they are unstable substances. Therefore, it is not practical to use the blood serum levels of these factors for diagnosis and treatment monitoring.

Various stressors that impact myocardial cells induce the production of proBNP, which breaks down into BNP and NT-proBNP, which are in turn secreted into the bloodstream.[27] BNP is a protein responsible for inducing physiological activities such as diuretic effects, vasodilator actions, and inhibition of myocardial remodeling.[28] In contrast, NT-proBNP is a protein without any physiological activity that is highly stable, with a longer half-life than BNP (approximately 70 minutes *vs.* 5 minutes).[29] During childhood, both BNP and NT-proBNP levels decrease with increasing age, and the levels are known to be particularly high during the neonatal period.[30-33] In our previous studies, we used Ross scores instead of the New York Heart Association functional classification system used in adults to objectively evaluate the symptoms of HF in children,[34,35] excluding in neonates, and compared their sensitivity and specificity with those of BNP and NT-proBNP levels.[36] We found that, as the grade of cardiac HF progressed, the BNP and NT-proBNP levels significantly increased (Fig. 2A&B). Moreover, in the event of grade 2 or higher HF, the sensitivity and specificity of NT-proBNP were superior to those of BNP (Fig. 3A&B). The receiver operating characteristic curves for the BNP and NT-proBNP levels with respect to grade 2 and higher congestive HF are shown in Fig. 3. The reasons for why the NT-proBNP level is associated with a larger area under the curve than BNP are likely differences in metabolism, stability, and

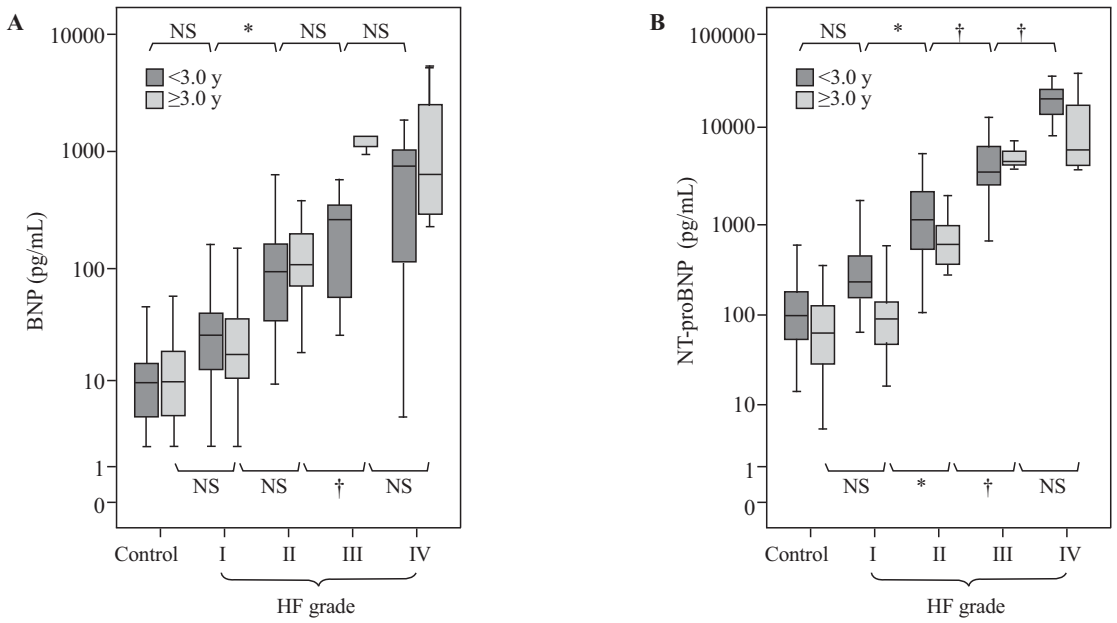

Fig. 2. The B-type natriuretic peptide (BNP) (**A**) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) (**B**) levels in the control group and in the four different heart failure (HF) grades on a logarithmic scale. In each of the HF grades, the left boxes indicate ages younger than 3 years and the right boxes indicate ages 3 years or older. The bars represent the median, 5th, 25th, 75th, and 95th percentiles. *: $P< 0.05$; †: $P< 0.01$. NS: not significant.

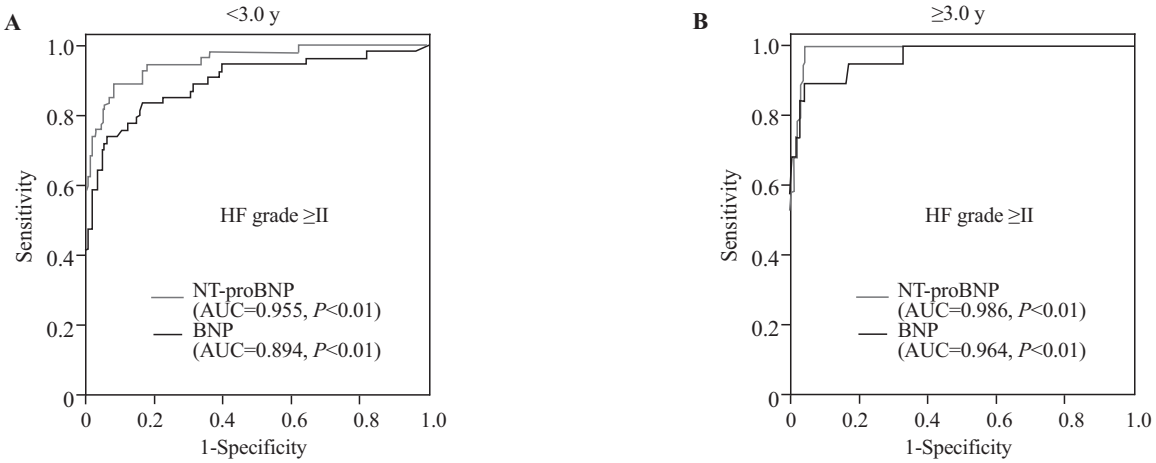

Fig. 3. Receiver operating characteristic curves of the B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in grade 2 and higher heart failure (HF) in patients younger than 3 years (**A**) and in those 3 years or older (**B**). AUC: area under curve.

influence by renal function between the two markers. Because renal function is closely associated with HF, NT-proBNP may indicate severity more subtly.[37]

Several reports[38-40] have compared elevated BNP and NT-proBNP levels according to different CHDs. In heart disease due to a left-to-right shunt, such as ASDs and VSDs, NT-proBNP levels are high when the Qp/Qs is high, and the fact that this decreases after surgery indicates that congestive HF due to volume overload may result in increased NT-proBNP levels.[41-43] Moreover, right ventricular volume overload due to pulmonary regurgitation after surgery for TOF also leads to increased NT-proBNP levels.[44,45] NT-proBNP levels have been reported as a useful marker of HF in patients with single ventricular circulation after Fontan surgery.[46-48] Accordingly, in the treatment of CHD, measurement of BNP and NT-proBNP levels is a useful tool to evaluate HF, to determine the effectiveness of therapeutic agents, and to identify the need for surgical intervention.

Other possible biomarkers of HF, such as fraction of exhaled nitric oxide (FENO), a well-established biomarker of airway inflammation and response to pharmacological treatment in patients with asthma,[49] and

F2, isoprostanes are known to be reliable biomarkers of oxidative stress;[50] they should also be studied in children with CHD. Increased FENO concentrations after exercise in adult patients with chronic systolic HF associated with pulmonary hypertension[51] as well as increased urinary F2-isoprostane concentrations in patients with non-ischemic congestive HF have been reported.[52]

Others: PH markers associated with CHD

CHD may be accompanied by PH due to anatomical abnormalities, and several attempts have been made to evaluate PH by using biomarkers.[53] Sanli et al[54] measured homocysteine and asymmetric dimethyl arginine levels in 30 children with PH associated with CHD. However, although both biomarkers were elevated in patients with PH, they did not correlate with the pulmonary artery pressure determined via echocardiography and catheterization. Moreover, many reports[55,56] have indicated that BNP and NT-proBNP levels are elevated in adult patients with PH, and recent reports[57] similarly indicate that children with CHD-induced PH also have elevated NT-proBNP levels. Van Albaba et al[58] examined 29 children with PH and reported that NT-proBNP, uric acid, adrenalin, and noradrenalin levels were all useful in determining the therapeutic outcomes and in evaluating the prognosis. We have previously reported that TnI levels and Pp/Ps correlated well; however, our results may have included right ventricular pressure overload and left ventricular volume overload, as patients with VSDs and PH had high TnI levels (Fig. 3).[14] A biomarker that can be used directly to detect the high resistance of the pulmonary vascular bed is being investigated; however, at present, no innovative markers have been found, and further developments are anticipated.

Conclusions

Most CHDs present specific hemodynamics, including volume and pressure overload, as well as cyanosis and PH, associated with anatomical abnormalities. While these hemodynamics may be evaluated by using various imaging tests and cardiac catheterization, the measurement of serum biomarkers has recently played an important role in the evaluation of hemodynamics. The benefits of biomarkers are as follows: 1) they can be objectively evaluated as numerical values; 2) they have high reproducibility; 3) they can be repeatedly measured; 4) they do not require expert skills in diagnostic techniques; 5) they are less invasive and more safe compared to diagnostic methods that subject patients to radiation exposure; and 6) they can be easily measured without expensive specialized equipment or facilities. Accordingly, the measurement of biomarkers is likely to become more common in the treatment of CHD.

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