Volume Overload and Pressure Overload due to Left-to-Right Shunt-Induced Myocardial Injury

– Evaluation Using a Highly Sensitive Cardiac Troponin-I Assay in Children With Congenital Heart Disease –

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Background: Cardiac troponin I (cTnI) is currently considered to be the most sensitive and specific biochemical marker of acute coronary syndrome and acute myocardial infarction. However, few reports have described the use of cTnI assays for evaluating abnormal hemodynamic load in children with congenital heart disease (CHD). It was hypothesized that significant hemodynamic overload due to a left-to-right shunt induces myocardial injury.

Methods and Results: A highly sensitive cTnI assay was used to measure the serum cTnI levels in 30 children with atrial septal defect (ASD), 32 children with ventricular septal defect (VSD), and 350 healthy children. Cardiac catheterization was performed in the children with ASD and VSD to determine the ratio of pulmonary to systemic blood flow, the ratio of pulmonary to systemic arterial pressure (Pp/Ps), the pulmonary vascular resistance index, and the right and left ventricular end-diastolic volume. Serum cTnI levels in both the ASD and VSD children were significantly higher than those in healthy children ($P<0.05$ and $P<0.01$, respectively). Furthermore, serum cTnI levels significantly correlated with Pp/Ps ($r=0.745$, $P<0.001$) in VSD children.

Conclusions: Significant volume and pressure overload due to a left-to-right shunt induce myocardial injury and might eventually cause irreversible myocardial remodeling in children with CHD. The serum cTnI level is a useful biomarker for evaluating myocardial damage associated with pulmonary hypertension in VSD children. (*Circ J* 2011; **75**: 2213–2219)

Key Words: Congenital heart disease; Myocardial injury; Pulmonary hypertension; Troponin I

Cardiac troponins I (cTnI) and T (cTnT) are currently considered to be the most sensitive and specific biochemical markers of acute coronary syndrome and acute myocardial infarction (AMI).^{1,2} cTnI is found in the atrial and ventricular walls and contains an immunologically distinct N-terminus of the amino acid chain.³ cTnI is released into the circulation in response to ischemic and non-ischemic cardiac injury.⁴ An assay for serum cTnI that facilitates the measurement of clinically-relevant cTnI levels is useful for the diagnosis of myocardial injury in adults.^{3,5–7} In 2000, the European Society of Cardiology and the American College of Cardiology also advocated that a serum troponin level that exceeded the 99th percentile of a reference population is a specific biochemical marker of AMI.⁸ Moreover, elevated serum troponin levels have been reported in several cohorts of patients with heart failure, and the magnitude of the elevation correlated with the severity of the heart disease.⁹

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The first-generation troponin assay has some limitations. These limitations include antibody specificity, assay imprecision, lack of standardization, and the relatively late increase in circulating troponin levels after the onset of ischemia. Recently, a second-generation cTnI assay (Centaur TnI-Ultra assay) has become available.^{10–12} This group of sensitive troponin assays might further enhance the accuracy of the diagnosis of myocardial ischemia, and could therefore offer improved diagnostic sensitivity and specificity, even in patients presenting early after the onset of chest pain.^{13,14}

In congenital heart disease (CHD), anatomical anomalies of the heart are generally associated with abnormal hemodynamic load and neurohumoral activation. Brain natriuretic peptide (BNP) and its N-terminal prohormone fragment (NT-

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Table 1. Characteristics of Healthy Controls and Patients With CHD

	Healthy group	CHD	
		ASD group	VSD group
N	350	30	32
Age (years)	3.9±3.7	3.4±4.2	1.0±1.3*
Gender, male	174 (49.7%)	12 (40.0%)	13 (40.6%)
NT-proBNP (pg/ml)	98.8±92.8	304.1±370.3	1,181.0±1761.9*
Medications			
Diuretics (%)		6 (20.0%)	27 (84.3%)
Hemodynamics			
Qp/Qs		2.3±1.0	2.4±1.1
Pp/Ps		0.3±0.1	0.8±0.3**
Rpl		1.0±0.6	2.2±1.2**
%RVEDV		151.1±46.2	158.7±47.3
%LVEDV		100.3±14.5	163.3±46.0**

Data are the mean±SD or the number of patients.

CHD, congenital heart disease; ASD, atrial septal defect; VSD, ventricular septal defect; NT-proBNP, N-terminal prohormone fragment of brain natriuretic peptide; Qp/Qs, ratio of pulmonary to systemic blood flow; Pp/Ps, ratio of pulmonary to systemic arterial pressure; Rpl, pulmonary vascular resistance index; RVEDV, right ventricular end-diastolic volume; LVEDV, left ventricular end-diastolic volume.

*P<0.05 vs. healthy group, **P<0.05 vs. ASD group.

proBNP) found in the circulation are mainly expressed by ventricular cardiac myocytes in response to ventricular volume and pressure overload.^{15,16} However, few reports have described the use of serum cTnI levels for evaluating hemodynamic overload in children with CHD.¹⁷ Therefore, we hypothesized that significant hemodynamic overload due to a left-to-right shunt can induce myocardial injury. In this study, we measured serum cTnI levels using a highly sensitive assay and compared the levels observed in children with atrial septal defects (ASD) or ventricular septal defects (VSD) to those observed in healthy children without a history of heart disease.

Methods

Patients and Healthy Volunteer Children

From November 2005 to May 2010, we prospectively enrolled 412 clinically stable subjects, consisting of 30 children with ASD (ASD group), 32 children with VSD (VSD group) and 350 healthy volunteer children (healthy group). They ranged between 2 months and 16.8 years of age. All of the children in the ASD and VSD groups were admitted to the Department of Pediatrics of Asahikawa Medical University Hospital. We assessed the characteristics of this population, including current medication use and representative parameters that reflected the hemodynamics as examined by cardiac catheterization. The ratio of pulmonary to systemic blood flow (Qp/Qs) was derived by oxymetric measurement with the use of Fick's principle. Also, the ratio of pulmonary to systemic arterial pressure (Pp/Ps), the pulmonary vascular resistance index (Rpl, WU/m²), the right ventricular end-diastolic volume (RVEDV) and the left ventricular end-diastolic volume (LVEDV) were determined by blood pressure measurement and ventriculography. Deviations in RVEDV and LVEDV from the normal values were calculated as follows:

$$\%RVEDV = RVEDV / (75.1 \times BSA^{1.43}) \times 100$$

$$\%LVEDV = LVEDV / (72.5 \times BSA^{1.43}) \times 100$$

where the terms $75.1BSA^{1.43}$ and $72.5BSA^{1.43}$, which represent normal RVEDV and normal LVEDV, respectively, are a function of the body surface area (BSA) in children with

normal hearts.¹⁸

The children in the healthy group were admitted to an affiliated general hospital between November 2005 and January 2010. When they enrolled in this study, they had fully recovered from either a respiratory tract infection, asthma, or epilepsy after receiving medical treatment.

No children had a history of cardiac ischemia. All of the children and their parents were fully informed about the procedures, risks, and benefits of the study, and written informed consent was obtained before the study. This study was approved by the Ethics Committee of Asahikawa Medical University Hospital.

Measurement of NT-proBNP and cTnI

Blood samples were taken from the superior vena cava or the antecubital vein. The samples were centrifuged immediately after collection and were subsequently stored at -21°C until being assayed. Serum NT-proBNP levels were measured by an Elecsys 2010 analyzer with a chemiluminescent immunoassay kit (Roche Diagnostics; Mannheim, Germany). Serum cTnI levels were measured by a 3-site sandwich immunoassay technique using an ADVIA Centaur analyzer (TnI-Ultra/Siemens Medical Solution Diagnostics; Tarrytown, NY, USA). In this assay, the lower limit of detection is 0.002 ng/ml, and the lowest concentration at which the coefficient of variation (CV) was <10% was 0.03 ng/ml and the %CV was 4.82.¹⁹ Further details are available in previously published reports.^{10,11,20}

Statistical Analysis

A least-squares regression line was fitted to the cTnI level vs. age plots for the healthy group. The Spearman's rank correlation coefficient was calculated to assess the correlations between various parameters. We used the Kruskal-Wallis analysis of variance (ANOVA), a non-parametric method, to examine overall differences between the healthy, ASD, and VSD groups because the cTnI levels and the composition of the 3 groups were not always distributed normally. If ANOVA findings were found to be statistically significant, then the statistical significance of the differences between the groups was estimated using the Steel-Dwass test. A multi-

variate stepwise linear regression analysis was performed to test the effects of age and hemodynamic load on serum cTnI levels. Correlations between continuously distributed variables were tested by linear regression analysis. A P value <0.05 was considered to be statistically significant. All statistical analyses were performed with the use of a commercially available statistical software package (SPSS for Windows, Version 18.0).

Results

The characteristics of the children in the 3 groups are shown in **Table 1**. The mean age in the VSD group was significantly lower than that in the healthy group (P<0.05). The mean NT-proBNP level in the VSD group was significantly higher than that in the healthy and ASD groups (P<0.05). Six children (20.0%) in the ASD group and 27 children (84.3%) in the VSD group received diuretics at the time of enrollment in this study, but no one received a cardiac medication such as digoxin or β -blockers.

The Qp/Qs ratios in the ASD and VSD groups (2.3 $\pm$ 1.0 and 2.4 $\pm$ 1.1, respectively) were not significantly different. The Pp/Ps ratio and Rpl in the VSD group were significantly higher than those in the ASD group (P<0.05 and P<0.05, respectively). There was no significant difference in %RVEDV between the ASD and VSD groups (151.1 $\pm$ 46.2% and 158.7 $\pm$ 47.3%, respectively). The mean %LVEDV in the VSD group (163.3 $\pm$ 46.0%) was significantly higher than that in the ASD group (100.3 $\pm$ 14.5%).

Figure 1 shows the relationship between the serum cTnI level and age in the healthy group (aged 2 months to 16.8 years). cTnI levels were relatively constant with respect to age. A diagnostic threshold for cTnI that was indicative of an abnormal condition was chosen to be the 99th percentile cutoff in the healthy group. The value of this threshold was determined to be 0.014 ng/ml, which was higher by 1 order of magnitude than the minimum quantity that could be measured by the cTnI assay used in this study.

Table 2. Univariate and Multivariate Analyses of cTnI Levels: Comparison of Age and Hemodynamic Parameters in the VSD Group				
	Univariate analysis		Multivariate analysis	
	r	P value	SE	P value
Age	−0.522	0.001		
Qp/Qs	0.571	<0.001		
Pp/Ps	0.745	<0.001	0.745	<0.001
Rpl	0.309	0.043		
%RVEDV	0.553	0.001		
%LVEDV	0.066	0.359		

cTnI, cardiac troponin I; SE, standardized partial regression coefficient. Other abbreviations see in Table 1.

Figure 2 shows the cTnI levels in the 3 groups. The differences in the cTnI levels between the ASD and healthy groups and between the VSD and ASD groups were significant ($P<0.05$ and $P<0.01$, respectively). The median (25th–75th percentiles) cTnI level in the VSD group was significantly higher than those in the healthy and ASD groups [0.029 ng/ml (0.008–0.081), 0.000 (0.000–0.002) and 0.002 (0.000–0.009) respectively].

Table 2 shows the results of univariate and multivariate analyses of the effects of age and hemodynamic parameters on the serum cTnI level in the VSD group. In stepwise multivariate analyses, the serum cTnI level correlated only with the corresponding Pp/Ps as a statistically significant independent predictor ($P<0.001$). This analysis was highly accurate ($r=0.745$, ANOVA $P<0.001$), the Durbin–Watson ratio (2.534) was acceptable, and there was no other parameter for which the predicted value was beyond ± 3 SD.

The relationship between the serum cTnI level and Pp/Ps in the VSD and ASD groups is shown in **Figure 3A**. In the VSD group, cTnI levels significantly correlated with Pp/Ps levels [$cTnI=0.0006 \times e^{5.0082(Pp/Ps)}$ ($r=0.745$, $n=32$, $P<0.001$)]. The relationship between the serum cTnI level and other parameters in the VSD and ASD groups are shown in **Figures 3B–F**.

Discussion

This study evaluated serum cTnI levels in healthy children and children with CHD, and is the first to show an increased serum cTnI level in children with CHD. The cTnI levels in pediatric patients with ASD and VSD were significantly higher than those in healthy children. In particular, patients with VSD had significantly elevated cTnI levels that were related to pulmonary hypertension. Furthermore, we determined a clinically relevant threshold for the serum cTnI level that can be used to identify myocardial injury in a pediatric population.

In recent years, atrial natriuretic peptide and BNP have been used as clinical markers for the evaluation of heart failure.^{21–23} In particular, in our previous study, we established that the serum NT-proBNP level is a marker of congestive heart failure in children.²⁴ In contrast, cTnT and cTnI are clinical markers of myocardial injury and are associated with a variety of heart abnormalities such as hypertension, cardiomyopathy, myocarditis, myocardial necrosis, and apoptosis.^{3,5,7,9} In addition to its usefulness as a marker of myocardial injury, an increase in circulating cTnI levels correlates with the severity of heart failure.^{23,25,26}

A highly sensitive and specific cTnI assay has been developed to detect very low levels of cTnI,¹¹ even trace leakages from the unbound cytosolic pool in the circulation.²⁷ Such low serum cTnI levels might reflect early myocardial cell death as well as reversible injury,²⁸ including transient damage after strenuous endurance exercise.²⁹ Thus, the cTnI assay is a very useful tool for detecting subclinical heart disease at the initial presentation in hospitals and for evaluating the severity of cardiac decompensation in emergency cases.^{30,31}

Hemodynamic overload in the ASD group was attributable only to right heart volume overload. However, hemodynamic overload in the VSD group included not only volume overload but also right ventricular pressure overload. As a result of **Figure 1**, we consider that age would not affect the level of cTnI in ASD and VSD groups as well as in the control group. In this study, there was a significant difference in the cTnI levels between the ASD and healthy groups, which

suggests that a volume overload can cause myocardial injury. Furthermore, the finding of a significantly increased cTnI level in the VSD group suggests that a ventricular pressure overload, in addition to volume overload, apparently induces myocardial injury.

In experimental models, angiotensin II has been reported to induce necrosis and apoptosis of neonatal and adult ventricular myocardial cells.^{32,33} Another factor, catecholamine, secreted at the time of congestive heart failure might contribute to myocardial injury.³⁴ We did not measure the blood levels of angiotensins or catecholamines in this study because of the difficulty of taking blood for plasma in this population. However, these mechanisms could account for the increase in cTnI levels observed in the enrolled children with CHD.

In the clinical setting, it has been found that serum cTnI levels are increased in patients with non-ischemic heart disease or those without heart failure. cTnI levels are elevated in 75% of patients who are treated in intensive care units for sepsis or systemic inflammatory response syndrome.³⁵ The elements of systemic inflammation including tumor necrosis factor alpha, interleukin 6 and reactive oxygen species might lead to direct myocardial injury through an immunological reaction.²⁷ In addition, cTnI levels are elevated in up to 40% of patients with acute pulmonary embolism.^{36,37} It is known that right ventricular pressure overload due to increased pulmonary arterial resistance leads to a decrease in myocardial perfusion and the oxygen supply, which results in right ventricular dysfunction in patients with pulmonary embolism.³⁸ In patients with hypertrophic cardiomyopathy (HCM), the cTnI levels were found to be significantly higher in the area where the left ventricular wall was the thickest.³⁹ Petersen et al reported that patients with HCM had a reduced myocardial perfusion reserve that was in proportion to the magnitude of hypertrophy.⁴⁰ Both ventricular hypertrophy and myocardial extension due to left-to-right shunting can inhibit myocardial perfusion. An increase in intrawall pressure due to extension can disturb the coronary microcirculation.⁴¹ In addition, cardiac enlargement as a result of volume overload increases the oxygen demand of the myocardium, which also results in relative hypoperfusion of the myocardium.²⁷ In this study, cTnI levels significantly correlated with Pp/Ps, but not with Rpl (**Figure 3**). cTnI levels of a few patients with idiopathic pulmonary arterial hypertension, not including those in this study, were normal. These results suggest that cTnI reflects not only pulmonary hypertension without the influence of pulmonary arterial resistance but also myocardial stretch due to volume overload. Monasky et al reported that myocardial stretch causes an increase in the phosphorylation of cTnI in rabbits.⁴² Therefore, we speculate that the right ventricular pressure overload and ventricular volume overload in children with VSD synergistically induces myocardial injury associated with myocardial perfusion.

In our previous study, we reported that both volume overload and pressure overload in children with CHD elevated the serum levels of procollagen type III N-terminal peptide, which is a marker of myocardial remodeling.⁴³ Myocardial cells are finally differentiated cells and do not have the potential to divide. In addition, the reproduction of myocardial cells from stem cells and progenitor cells is extremely limited. Apoptosis and necrosis of cardiac myocytes results in myocardial remodeling, leading to a decrease in cardiac contractility and heart failure. Our results support the notion that significant pressure overload due to a left-to-right shunt promotes myocardial injury and might eventually cause irreversible myocardial remodeling in children with CHD.

A strong correlation was observed between the cTnI and NT-proBNP levels ($r=0.728$; **Figure 3**). This correlation also indicates that myocardial injury is associated with congestive heart failure exaggerated by pressure overload in addition to volume overload in this population. The use of cTnI as a biomarker might aid in the earlier detection of myocardial injury in patients with CHD. Further studies are required to validate the use of cTnI and NT-proBNP as biomarkers of pulmonary hypertension in patients with VSD. And, additional studies involving larger populations are necessary to validate the effectiveness of cTnI monitoring in children with CHD.

Conclusion

This study clearly demonstrated that the serum cTnI levels in children with ASD and VSD were significantly higher than that in healthy children. These results suggest that significant volume and pressure overload due to a left-to-right shunt induces myocardial injury and might eventually cause irreversible myocardial remodeling in children with CHD. The serum cTnI level is a useful biomarker for evaluating myocardial damage associated with pulmonary hypertension in VSD children.

Study Limitations

The present study has 2 limitations. **Figure 1** shows the relationship between serum cTnI levels and age in the healthy group (from 2 months to 16.8 years of age). The data from children less than 2 months of age were excluded from the overall analyses because Bader et al reported that serum cTnI levels abruptly increase immediately after birth, followed by a gradual decrease in the neonatal period.⁴⁴ Therefore, our results are not representative of infants aged less than 2 months. The second limitation is that the subjects in the VSD group were younger than those in the other 2 groups. This difference is not due to a selection bias because the patients with VSD were diagnosed on average at an earlier age and were surgically treated sooner compared to patients with ASD.

Disclosures

We hereby confirm that there are no known conflicts of interest associated with this research and there has been no significant financial support for this work that could have influenced its outcome.

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