

Original Article

Plasma Brain Natriuretic Peptide and the Evaluation of Volume Overload in Infants and Children with Congenital Heart Disease

Yoko Kunii*, Masahiro Kamada, Shinichi Ohtsuki, Tohru Araki,
Kohichi Kataoka, Misao Kageyama, Naomi Nakagawa, and Yoshiki Seino

Department of Pediatrics, Okayama University Graduate School of Medicine and Dentistry, Okayama 700-8558, Japan

This study was designed to explore whether it was possible to evaluate the severity of VSD, PDA, and ASD by measuring brain natriuretic peptide (BNP) levels. We also investigated normal BNP levels in children to provide a baseline for our study. We measured BNP levels in 253 normal children, including 11 normal neonates, and in 91 VSD patients, 29 PDA patients, and 34 ASD patients. BNP levels showed no age-related differences in normal children (the mean value: 5.3 ± 3.8 pg/ml). In the healthy neonates, BNP levels rose from 10.4 ± 11.9 pg/ml in cord blood to 118.8 ± 83.2 pg/ml on day 0, then fell to 15.3 ± 7.8 pg/ml by day 7. In VSD and PDA patients, BNP levels correlated significantly with Qp/Qs, LVEDV, and peak RVP/LVP. In ASD patients, BNP levels correlated with Qp/Qs and RVEDV. Especially, in VSD patients, as an index corresponding to 1.5-2.0 of the Qp/Qs ratio, BNP levels of 20-35 pg/ml were found to be best with regard to both sensitivity and specificity. In the healthy neonates, BNP levels changed rapidly after birth. In VSD, PDA, and ASD patients, BNP levels were well-correlated with the severity of the disease. Especially, in VSD patients, it that appears BNP levels may be useful in evaluating surgical indications, with 20-35 pg/ml levels being the appropriate cut-off value.

Key words: brain natriuretic peptide, congenital heart disease, ventricular volume overload

It has recently been reported that changes in natriuretic peptide levels can play a role in determining the treatment strategy in adult heart failure patients [1, 2]. In adult patients, it has also been recognized that the measurement of brain natriuretic peptide (BNP) is useful as a biochemical marker of left ventricular (LV) dysfunction, acute myocardial infarction, and dilated cardiomyopathy [3, 4], and as a method of screening for cardiac function in primary care [5, 6]. However, in children with congenital heart disease (CHD), the primary complaints are ventricular volume overload and pulmonary

hypertension (PH), not cardiac dysfunction. Unfortunately, few studies have clearly examined the relationship between BNP levels and CHD in children.

Therefore, the present study was designed to evaluate the relationship between BNP levels and LV volume overload and right ventricular (RV) overload in children and infants with CHD. We focused on patients with ventricular septal defects (VSD) and atrial septal defects (ASD), trying to see if BNP levels can provide of noninvasive means of predicting the need for surgery. To provide a baseline for our study, we also investigated normal BNP values in children.

Materials and Methods

Study subjects. As a control group, we studied 253 healthy neonates, infants, and children (129 males, 124 females) ranging in age from day 0–16 years. These subjects visited our outpatient clinic because of allergic diseases or mild infectious diseases. The neonates were drawn from neonates born in our hospital and had a mean gestational age of 39.8 weeks (range: 37 weeks and 6 days to 41 weeks and 2 days) and a mean birth weight of $3,191 \pm 299$ g (range: 2,813 g to 3,690 g). None of these subjects had suffered birth asphyxia. These healthy controls were classified into the following groups: 11 neonates, 34 infants under 1 year of age, 68 children between 1 and 3 years of age, 57 children between 3 and 5 years of age, 48 children between 5 and 10 years of age, and 46 children between 10 and 16 years of age.

As an experimental group, we studied 154 patients with CHD. As a model of LV volume overload (LV volume overload group), we evaluated 91 patients with ventricular septal defect (VSD) (47 males and 44 females), aged 3 months to 12 years, and 29 patients with patent ductus arteriosus (PDA) (10 males and 19 females), aged 2 months to 11 years. As a model of RV volume overload, we evaluated 34 patients with atrial septal defect (ASD) (16 males and 18 females), aged 9 months to 10 years.

We diagnosed all CHD patients by echocardiography and cardiac catheterization. All patients had good LV systolic function (or contraction), with ejection fractions over 0.60. Patients with one or more of the following conditions were excluded: aortic valvular stenosis, coarctation of the aorta, moderate or severe regurgitation of the semilunar and atrial-ventricular valves, and pulmonary valvular stenosis. We also excluded patients with abnormal chromosomes or with Eisenmenger syndrome. Pulmonary hypertension (PH) was defined by a mean pulmonary artery pressure > 25 mmHg during cardiac catheterization [7]. There were no ASD patients with PH.

Blood sampling and assay for BNP. In control subjects, 1 ml of peripheral venous blood was taken from the samples drawn to rule out organic lesions such as mild infections and allergic diseases. In the healthy neonates, BNP levels were measured three times: using cord blood, at day 0 (12–20 h after birth, mean 17.7 h), and at the time of discharge from hospital (6–7 days after birth, mean: 6.9 days). In patients with CHD,

blood samples were drawn from the femoral vein at the beginning of each cardiac catheterization.

Informed consent for the blood sampling was obtained from the parents of each child, and this study protocol conformed to the guidelines of the ethics committee at our institution.

Blood was immediately transferred into chilled glass tubes containing disodium EDTA (1 mg/ml) and aprotinin (500 U/ml). It was centrifuged immediately at 4 °C, and the plasma was frozen and stored at -80 °C until the assay. Plasma BNP levels were measured with specific immunoradiometric assay kits (Shiono RIA BNP assay kit, Shionogi Co., Ltd., Osaka, Japan).

Hemodynamic studies. In the neonates, we carried out echocardiography just before taking blood samples to check the patency of ductus arteriosus and to measure the left ventricular diameter (LVEDD).

All patients with CHD underwent cardiac catheterizations. The procedure included measurement of pressure and oxygen saturation in the superior vena cava, inferior vena cava, right atrium, pulmonary artery, right ventricle (RV), pulmonary vein (or pulmonary capillary wedge pressure), left ventricle (LV), and the aorta. Using these data, we calculated the following values to investigate the relations to BNP levels; pulmonary to systemic flow ratio (Q_p/Q_s), left ventricular end-diastolic volume (LVEDV), right ventricular end-diastolic volume (RVEDV), and the peak right ventricular to left ventricular pressure ratio (peak RVP/LVP). We determined Q_p/Q_s using the oxymetric principle of Fick. LVEDV and RVEDV were calculated from biplane cine-angiocardiograms using Simpson's rule method and compared with normal values expressed as a function of body surface area [8].

Statistical analysis. All data were expressed as mean value \pm standard error (SE) unless otherwise indicated. Comparison of the BNP levels between each age group of normal subjects was carried out using Mann-Whitney's *U* test. Correlation of the BNP levels with hemodynamic parameters was examined using linear regression analysis. All results were considered statistically significant at the level of $P < 0.05$. Lack of significance is indicated as $P = NS$ (not significant).

In VSD and ASD patients, in particular, we investigated whether surgical indication could be evaluated noninvasively based on plasma levels of BNP using various cut-off points. We attempted to determine which cut-off points were the most sensitive and specific.

Results

Plasma levels of BNP in healthy subjects.

Fig. 1 shows the BNP levels in healthy subjects, excluding neonates, according to age groups. There were no significant differences in BNP levels among the groups. The mean level of BNP was 5.3 ± 3.8 pg/ml. In the

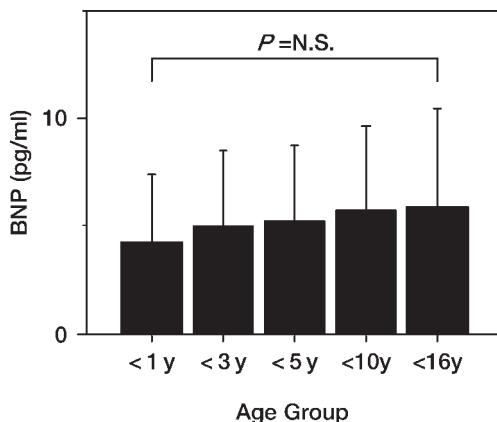


Fig. 1 Plasma BNP levels in 242 children (excluding neonates) without heart disease classified into 5 age groups. Histograms show the mean BNP level and 1 SE. No significant differences were noted between the age groups. N.S. = not significant.

healthy neonates, the BNP levels were 10.4 ± 11.9 pg/ml in cord blood, 118.8 ± 83.2 pg/ml at day 0 (12–20 h), and 15.3 ± 7.8 pg/ml at day 7. The BNP levels changed rapidly after birth and were significantly higher on day 0 than on the following days (Fig. 2A). Echocardiography was performed on day 0 (12–20 h after birth), showed the physiological pulmonary hypertension in all neonates and the patency of the ductus arteriosus in 4, and there was a positive correlation between LVEDD and BNP ($P < 0.05$) (Fig. 2B). We performed echocardiography on day 7 to confirm the decrease in pulmonary artery pressure, closure of the ductus arteriosus, and reduced LVEDD in all neonates.

Clinical and hemodynamic characteristics.

Table 1 shows the clinical data and the cardiac catheterization data for the subjects with CHD. The BNP levels were higher in subjects with CHD than in healthy subjects.

Relation between BNP levels and hemodynamic variables.

In VSD patients, the BNP levels significantly correlated with Qp/Qs ($r = 0.75$, $P < 0.0001$), LVEDV ($r = 0.72$, $P < 0.0001$), and peak RVP/LVP ($r = 0.72$, $P < 0.0001$) (Fig. 3). In PDA patients as well, the BNP levels significantly correlated with Qp/Qs ($r = 0.89$, $P < 0.0001$), LVEDV ($r = 0.79$, $P < 0.0001$), and peak RVP/LVP ($r = 0.74$, $P < 0.001$) (Fig. 4).

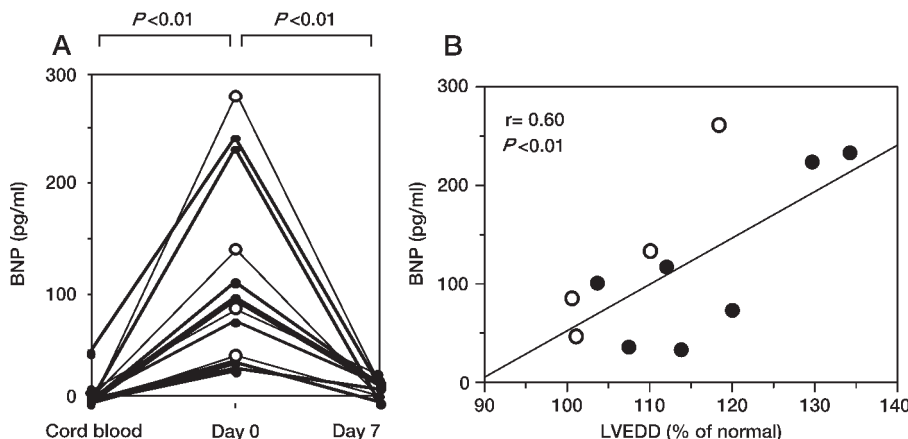


Fig. 2A Plasma BNP levels in 11 normal neonates. The BNP levels (mean \pm SE) were 10.4 ± 3.3 pg/ml in the cord blood, 118.8 ± 23.1 pg/ml on day 0, and 15.3 ± 2.2 pg/ml on day 7.

○, Patency of ductus arteriosus; ●, Closure ductus arteriosus.

Fig. 2B Correlation between BNP levels and LVEDD (compared with normal values expressed as a function of body surface area). LVEDD was measured by echocardiography on day 0.

○, Patency of ductus arteriosus; ●, Closure ductus arteriosus.

Table 1 Clinical and hemodynamic characteristics of patients with congenital heart disease

	LV volume overload VSD	RV volume overload PDA	RV volume overload ASD
Age (month)	41.2 ± 4.6	37.5 ± 6.4	69.5 ± 8.5
Body Weight(kg)	13.3 ± 1.1	13.2 ± 1.4	18.4 ± 1.7
Male: Female	47:44	10:19	16:18
Therapy			
diuretics	38 (42%)	8 (28%)	2 (6%)
digoxin	36 (40%)	7 (24%)	1 (3%)
Hemodynamic and angiographic data			
mean PAP(mmHg)	30.3 ± 2.4	28.4 ± 3.6	19.4 ± 1.2
Qp/Qs	2.0 ± 0.1	1.6 ± 0.1	2.1 ± 0.1
LVEDV(% of normal)	168.0 ± 7.2	154.4 ± 9.8	113.5 ± 4.8
RVEDV(% of normal)	126.3 ± 3.3	140.0 ± 14.1	171.1 ± 12.2
peak RVP/LVP	0.54 ± 0.03	0.43 ± 0.04	0.36 ± 0.02
BNP (pg/ml)	46.1 ± 7.3	32.8 ± 6.5	37.6 ± 8.4

ASD, atrial septal defect; BNP, brain natriuretic peptide; LVEDV, left ventricular end-diastolic volume; mean PAP, mean pulmonary arterial pressure; PDA, patent ductus arteriosus; peak RVP/LVP, peak right ventricular to left ventricular pressure ratio; Qp/Qs, pulmonary to systemic flow ratio; RVEDV, right ventricular end-diastolic volume; VSD, ventricular septal defect.

In contrast, in ASD patients, the BNP levels significantly correlated with Qp/Qs ($r = 0.69$, $P < 0.001$) and RVEDV ($r = 0.81$, $P < 0.001$), but not with peak RVP/LVP ($r = 0.003$, $P = \text{N.S.}$) (Fig. 5).

Discussion

There were 4 major findings in the present study:

- 1) There are no significant differences in BNP levels among healthy children (with the exception of neonates).
- 2) In healthy neonates, BNP levels on day 0 are significantly higher than those on other days, and a positive correlation can be observed between LVEDD and BNP levels ($P < 0.05$) on day 0.
- 3) BNP levels are elevated in patients with LV and RV volume overload.
- 4) BNP levels significantly correlate with Qp/Qs and the end-diastolic volume (LVEDV, RVEDV).

As for normal BNP levels in children, there were no significant differences in BNP levels observed among the age groups, except for neonates. The mean level of BNP was 5.3 ± 3.8 pg/ml. In the healthy neonates, BNP

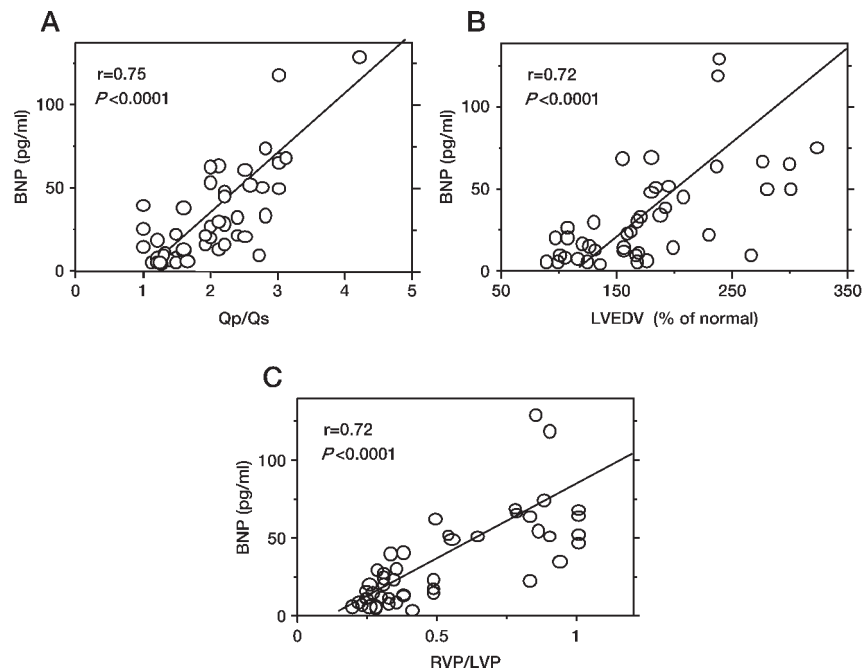


Fig. 3 (A) Correlation between BNP levels and the pulmonary to systemic flow ratio (Qp/Qs) in 91 VSD patients. (B) Correlation between BNP levels and left ventricular end-diastolic volume (LVEDV). (C) Correlation between BNP levels and the peak right ventricular to left ventricular pressure ratio (peak RVP/LVP).

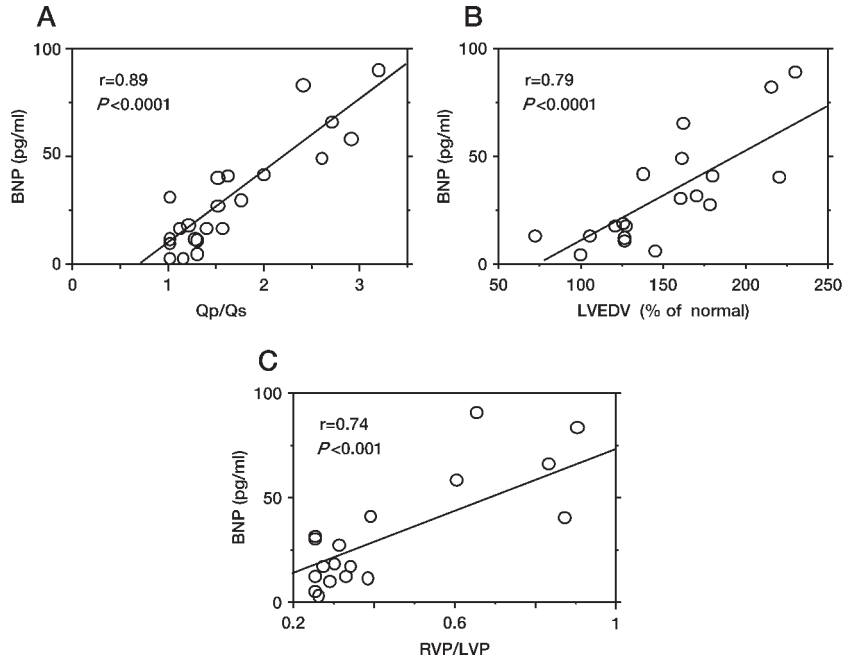


Fig. 4 (A) Correlation between BNP levels and Qp/Qs in 29 PDA patients. (B) Correlation between BNP levels and LVEDV. (C) Correlation between BNP levels and peak RVP/LVP.

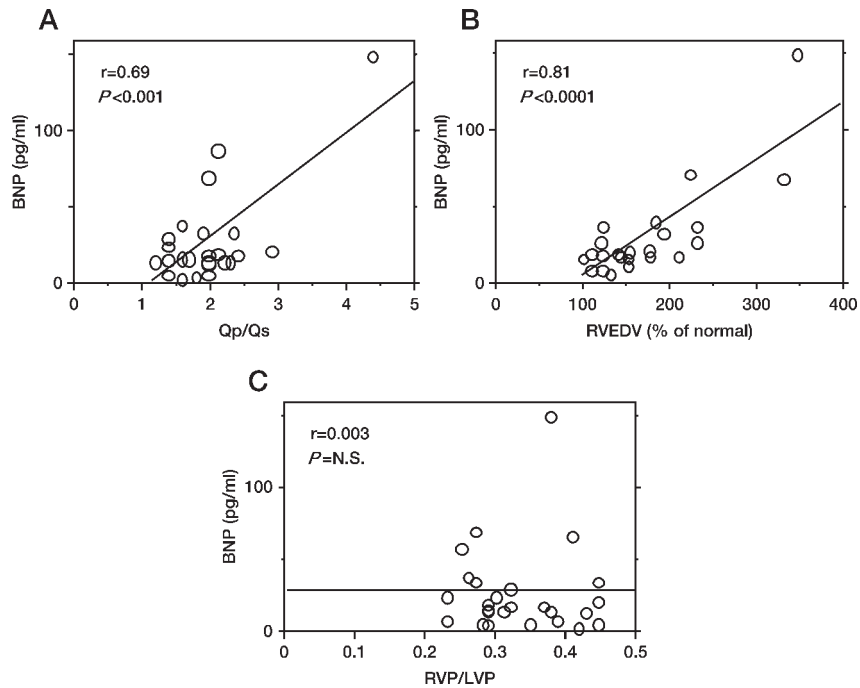


Fig. 5 (A) Correlation between BNP levels and Qp/Qs in 34 ASD patients. (B) Correlation between BNP levels and right ventricular end-diastolic volume (RVEDV). (C) Correlation between BNP levels and peak RVP/LVP.

levels changed rapidly after birth and were significantly higher on day 0 than on other days (Fig. 2A); in addition, 45% of 11 neonates had BNP levels above 100 pg/ml, as also reported by Yoshiyoshi *et al.* [9].

We also tried to determine how differences between fetal and transitional circulation are related to the rapid increase in BNP levels. In humans, pulmonary arterial pressure falls rapidly to only half-systemic by 24 h of age [10]. In our study, BNP levels on day 0 were much higher than those obtained from the umbilical veins or those on day 7. Therefore, physical pulmonary hypertension in fetal life apparently does not raise BNP levels. In addition, the positive correlation between LVEDD and BNP ($P < 0.05$) (Fig. 2B) and the closure of the ductus arteriosus in all subjects on day 7 suggest that the LV volume overload by the PDA is the cause of high BNP levels on day 0. Studies suggesting that BNP is a hormone that is synthesized primarily in the ventricular myocardium in response to stretch stimuli [10] also support the above hypothesis.

Previous studies have demonstrated that BNP levels are elevated in patients with LV dysfunction, including myocardial infarction, severe valve regurgitation, and muscle hypertrophy due to hypertension [3, 4]. However, little information has been available regarding BNP levels in patients with LV volume overload without ventricular dysfunction, especially in children. In our study, all patients had good ventricular systolic function, and the BNP levels showed a good positive correlation with the Qp/Qs and the end-diastolic volume. These results support the hypothesis that BNP levels are influenced by the ventricular volume overload itself.

These findings suggest that it may be possible to use BNP levels to estimate the severity of the ventricular volume overload, and to determine the indications for surgery in CHD patients. In many institutions, surgery or coil embolization are favored for even small PDA in order to prevent infectious endocarditis. We therefore looked closely at whether analysis of BNP levels would be a useful, noninvasive diagnostic technique in VSD and ASD patients.

Recently, many institutions have been using surgery to treat VSD and ASD patients with Qp/Qs ratios over 1.5 or 2.0 [12, 13]. When we looked at the relationship between the Qp/Qs ratio and BNP levels in VSD patients, we found that a Qp/Qs ratio of 1.5 corresponds to a BNP level of approximately 20.3 pg/ml. Likewise, a Qp/Qs ratio of 2.0 corresponds to a BNP level of 35.5

pg/ml. On the basis of this value, we assumed several cut-off points and estimated the sensitivity and the specificity of BNP values (Table 2-1). As a result, we found that the sensitivity and the specificity are best with BNP levels of 20–35 pg/ml.

In contrast, in ASD patients, a Qp/Qs ratio of 1.5 was found to correspond to BNP levels of approximately 11.7 pg/ml. In these patients, the sensitivity and specificity are best with a BNP level of 11 pg/ml (75.0%, 50.0%) (Table 2-2). However, these levels are in a normal range, and the specificity was lower than in VSD patients. These findings demonstrate that in ASD patients it is difficult to evaluate surgical indications using BNP levels.

Our study does have one limitation: the relationship between pulmonary hypertension and BNP levels. In

Table 2-1 The cut-off point of BNP corresponds to Qp/Qs = 1.5 and 2.0 in VSD patients

BNP (pg/ml)	Qp/Qs = 1.5			
	Sensitivity (%)	Specificity (%)	False positive (%)	False negative (%)
15	86.7	68.9	31.1	13.3
20	81.7	86.7	13.3	18.3
25	75.0	91.1	8.9	25.0

BNP (pg/ml)	Qp/Qs = 2.0			
	Sensitivity (%)	Specificity (%)	False positive (%)	False negative (%)
30	81.2	79.5	20.5	18.8
35	80.6	83.3	16.7	19.4
40	88.8	76.0	24.0	11.1

Table 2-2 The cut-off point of BNP corresponds to Qp/Qs = 1.5 in ASD patients

BNP (pg/ml)	Qp/Qs = 1.5			
	Sensitivity (%)	Specificity (%)	False positive (%)	False negative (%)
11	75.0	50.0	50.0	25.0
15	65.0	50.0	50.0	35.0

VSD and PDA patients, the BNP levels were significantly correlated with peak RVP/LVP, and BNP levels may have been influenced by pulmonary hypertension. But pulmonary hypertension usually reflects the LV volume overload in VSD and PDA patients [12]. Further studies will be necessary to clarify the influence of PH on BNP levels, especially about PH group without ventricular volume overload, for example, primary pulmonary hypertension.

Our findings indicate that BNP levels reflect the severity of disease in patients with left and right ventricular volume overload, and that a BNP level of 20–35 pg/ml is useful as one indicator of surgery in VSD patients. By combining the BNP measurement with echocardiography, we believe it will be possible to determine whether or not surgery should be performed in CHD patients. Monitoring BNP levels is also useful for determining the timing for such surgery. Most importantly, monitoring BNP levels is a noninvasive technique and therefore minimizes trauma to the patient. Thus, we conclude that analysis of BNP levels in blood samples is a useful, noninvasive indicator of volume overload in infants and children with congenital heart disease and will thus be useful in clinical pediatric practice.

Acknowledgments. We would like to acknowledge Shionogi Medical Laboratories, Osaka, Japan, for their measurement of plasma BNP levels.

References

1. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG and Richards AM: Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. *Lancet* (2000) 355: 1126–1130.
2. Sagnella GA: Measurement and significance of circulating natriuretic peptides in cardiovascular disease. *Clin Sci* (1998) 95: 519–529.
3. Muders F, Kromer EP, Griese DP, Pfeifer M, Hence HW, Riegger GA and Elsner D: Evaluation of plasma natriuretic peptides as markers for left ventricular dysfunction. *Am Heart J* (1997) 134: 442–449.
4. Tsutamato T, Wada A, Maeda K, Hisanaga T, Maeda Y, Fukai D, Ohnishi M, Sugimoto Y and Kinoshita M: Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: Prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. *Circulation* (1997) 96: 509–516.
5. McDonagh TA, Robb SD, Murdoch DR, Morton JJ, Ford I, Morrison CE, Tunstall-Pedoe H, McMurray JJV and Dargie HJ: Biochemical detection of left ventricular systolic dysfunction. *Lancet* (1998) 351: 9–13.
6. Cowie MR, Struthers AD, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA and Sutton GC: Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* (1997) 350: 1349–1353.
7. Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Koerner SK, Levy PC, Reid LM, Vreim CE and Williams LW: Primary pulmonary hypertension. A national prospective study. *Ann Intern Med* (1987) 107: 216–223.
8. Nakazawa M, Marks RA, Isabel-Jones J and Jarmakani JM: Right and left ventricular volume characteristics in children with pulmonary stenosis and intact ventricular septum. *Circulation* (1976) 53: 884–890.
9. Yoshiyayashi M, Kamiya T, Saito Y, Nakao K, Nishioka K, Temma S, Itoh H, Shirakami G and Matsuo H: Plasma brain natriuretic peptide concentrations in healthy children from birth to adolescence: Marked and rapid increase after birth. *Eur J Endocrinol* (1995) 133: 207–209.
10. Moss AJ, Emmanouilides G and Duffie ER Jr.: Closure of the ductus arteriosus in the newborn infant. *Pediatrics* (1963) 32: 25–30.
11. Yasue H, Yoshimura M, Sumida H, Kikuta K, Kugiyama K, Jougasaki M, Ogawa H, Okumura K, Mukoyama M and Nakao K: Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. *Circulation* (1994) 90: 195–203.
12. Emmanouilides GC, Riemenschneider TA, Allen HD and Gutgesell HP: Moss and Adams Heart Disease in Infants, Children, and Adolescents Including the Fetus and Young Adult. 5th Ed, Baltimore, Williams & Wilkins (1995) pp 724–746.
13. Emmanouilides GC, Riemenschneider TA, Allen HD and Gutgesell HP: Moss and Adams Heart Disease in Infants, Children, and Adolescents Including the Fetus and Young Adult. 5th Ed, Baltimore, Williams & Wilkins (1995) pp 687–703.