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RESEARCH ARTICLE

B-type natriuretic peptide in children with atrial or ventricular septal defect: a cardiac catheterization study

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Abstract

In this study, we investigated the relationship between plasma B-type natriuretic peptide (BNP) levels and hemodynamics from cardiac catheterization in pediatric patients with atrial or ventricular septal defect. A total of 59 patients were studied including 80% of patients had Qp/Qs > 1.5 and 25% of patients had pulmonary hypertension. The mean BNP value and BNP *z*-score were 10.9 ± 11.2 pg/mL and −0.28 ± 1.7 (−2.85 to 3.29), respectively. There was a statistically significant linear correlation between BNP value and the size of defects ($r = 0.303$, $p = 0.002$) and a trend toward to positive correlation between BNP value and Qp/Qs ratio ($r = 0.183$, $p = 0.166$) among all patients. To identify patients with a Qp/Qs ratio >1.5, the sensitivity and specificity were 28%, 100% in all patients at a plasma BNP cut-off point of 15 pg/mL. We concluded that a BNP > 15 pg/mL would help identify patients who need further intervention.

Keywords: Atrial septal defect, biomarker, B-type natriuretic peptide, cardiac catheterization, ventricular septal defect

Introduction

B-type natriuretic peptide (BNP), a 32-amino acid peptide hormone secreted by the ventricular myocardium during situations of increased wall stress caused by excessive volume or pressure loading of the heart, is thought to be a sensitive and specific biomarker of heart failure and ventricular dysfunction (Nakagawa et al. 1995). Plasma BNP values, which are elevated in adults with congestive heart failure (CHF), correlate with severity of heart failure symptoms, and are predictive for morbidity and mortality (Cheng et al. 2001; Maisel et al. 2002). Plasma BNP has also been shown to increase during hemodynamic overload of the heart, and may be a useful biomarker in various other conditions such as congenital heart disease (CHD), myocardial infarction, and cardiomyopathy in adults (Mizuno et al 2000; Bolger et al. 2002; Grabowski et al. 2005). There is now increasing interest in BNP not only in adults with heart failure, but also in pediatric patients with cardiovascular diseases such as CHD, critical heart disease and Kawasaki disease (Koch et al. 2006; Takeuchi et al. 2007; Maher et al. 2008; Law et al. 2009). However, there is scant data concerning plasma BNP in pediatric populations with ventricular septal defect (VSD) or atrial septal defect (ASD), the two most common forms of CHD that occur as an isolated anomaly in 15% to 30% of all such defects (Suda et al. 2003; Ozhan et al. 2007). These defects vary in size, ranging from tiny defects without hemodynamic significance to large defects with accompanying CHF and pulmonary hypertension (PH). Closure of defect is a reasonable standard in VSD and ASD patients with conditions such as intractable CHF, growth failure, PH or significant left-to-right shunt. One of the indications of surgical intervention or transcatheter closure for ASD or VSD is patients with hemodynamically significant shunts or PH. Therefore, the purpose of the present study was to investigate the relationship between plasma BNP levels and hemodynamics from cardiac catheterization in pediatric patients with ASD or VSD. In addition, we

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wanted to determine whether rapid bedside detection of the plasma BNP value could be used to predict the severity of shunt and PH, which would indicate whether further intervention would be needed.

Methods

Patients

Pediatric patients younger than 18 years old with VSD or ASD who received cardiac catheterization before heart surgical intervention or transcatheter closure of ASD between 2008 and 2009 were enrolled in this study. All the participants or their parents signed an informed consent document for this study. The exclusion criteria for this study included patients who had congenital heart disease other than ASD or VSD, patients who had bleeding tendency or sepsis that was not suitable for cardiac catheterization, and those who did not give informed consent. This study was approved by the Committee on Human Studies (Institutional Review Board) at the Taichung Veterans General Hospital (TCVGH-IRB no.C07205).

BNP measurements

The BNP value was measured by a commercially available fluorescent immunoassay on a modular analyzer (Triage Meter Plus, Biosite Diagnostics, CA, USA). The lower limit of detection is 5 pg/mL for the assay of BNP, with an average interassay coefficient of variation of 3%. A half milliliter blood sample was drawn from a peripheral vein within 24 h before cardiac catheterization for determination of plasma level of BNP measurement. BNP standard deviation scores (SDS) were calculated according to the following formulas. Boys and girls aged 2 weeks to 10 years: BNP SDS = (natural logarithm of BNP plasma level–2.05) / 0.56; female patients older than 10 years: BNP SDS = (lnBNP–2.32) / 0.67; male patients older than 10 years: BNP SDS = (lnBNP–1.80) / 0.31 (Koch et al. 2006).

Echocardiographic study

Echocardiographic studies were performed with a Sonos 5500 ultrasound system (Philips, Andover, MA, USA), equipped with a 5 to 12-MHz ultraband sector transducer for two-dimensional and color flow Doppler mapping within 1 month before cardiac catheterization. The size of defect was detected by echocardiography using standard techniques with subcostal, precordial or apical imaging measurements of at least two cardiac cycles and the measurements were averaged. All echocardiographic studies were performed by an experienced echocardiographer who was blinded to the results of the plasma BNP measurements.

Cardiac catheterization study

Routine hemodynamic measurements, including values of pressure and oxygen saturation of blood, were obtained. Flow was calculated by use of the Fick formula: Pulmonary blood flow (Qp) is equal to VO_2 divided by ($C_{PV} - C_{PA}$); Systemic blood flow (Qs) is equal to VO_2 divided by ($C_{AO} - C_{MV}$), where flows are in L/minute, VO_2 is oxygen consumption (mL/min), C is oxygen content (mL/L) at various positions, and PV, PA, AO and MV are pulmonary vein, pulmonary artery, aorta, and mixed systemic venous blood, respectively. Normal pulmonary-to-systemic blood flow ratio (Qp/QS ratio) is 1, and a ratio of greater than 1.5 usually indicates significant left-to-right shunt with volume overload. The diagnosis of PH is made when the mean pulmonary artery pressure is larger than 25 mmHg measured directly in the cardiac catheterization laboratory.

Statistical analysis

Categorical variables were summarized as frequencies with percentages and continuous variables as means ± standard deviation. SPSS, version 15.0 for windows (SPSS, Chicago, IL, USA) was used for the statistical analysis. The plasma BNP values and BNP SDS were compared with size of defects by echocardiography and hemodynamic data from cardiac catheterization by regression line and plotting scattergrams. Pearson's correlation coefficients were also calculated. Cut-off points for receiver operating characteristic curve analyses, expressing sensitivity, specificity, and positive and negative predictive values, were determined. The chi-square test or Student's *t* test according to unequal or equal variance was used to compare the data between patients with ASD and VSD. A level of $p = 0.05$ was used for hypothesis testing.

Results

A total of 59 patients (23 male and 36 female) with a mean age of 7.2 ± 6.1 years who had ASD or VSD were studied. Among these patients, 34 patients were diagnosed as having isolated ASD (3 ostium primum, 31 ostium secundum) and 25 patients had isolated VSD (2 supracristal and 23 perimembranous). The demographic data and clinical laboratory features are shown in the Table 1. Among the 59 patients, 46% had cardiomegaly estimated by cardiothoracic (CT) ratio in CxR, including 50% of patients with ASD and 40% of those with VSD. Forty-seven (80%) patients had Qp/Qs ratio values higher than 1.5, including 32 (94%) patients with ASD and 15 (60%) with VSD. A total 15 of patients had PH, including 5 (15%) patients with ASD and 10 (40%) patients with VSD. The mean BNP value was 10.9 ± 11.2 pg/mL, with a range between <5 pg/mL and 49.1 pg/mL. BNP *z*-score was –0.28 ± 1.7, with a range between –2.85 and 3.29. Although the patients with VSD had a higher plasma BNP level, higher mean pulmonary artery pressure, and lower Qp/Qs ratio than those patients with ASD, the difference was not statistically significant among the demographic and laboratory data except in pulmonary artery pressure ($p = 0.005$) in this study. Among all patients, BNP level or BNP z-score had a statistically poor correlation with age, body surface area, CT ratio in CxR, mean right atrial pressure

Table 1. The demographic and laboratory features of patients with ASD or VSD.

	Total ($n=59$)	ASD ($n=34$)	VSD ($n=25$)	p value
Gender	23M / 36F	15M / 19F	8M / 17F	0.891
Age (y/o)	7.2 ± 6.1 (0.5–17.8)	9.2 ± 5.7 (2.0–17.8)	4.6 ± 5.6 (0.5–16.3)	0.264
Body length (cm)	114 ± 33 (63–171)	125 ± 30 (86–171)	99 ± 31 (63–161)	0.872
Body weight (kg)	28 ± 23 (6–88)	32 ± 22 (11–84)	23 ± 23 (6–88)	0.603
Body surface area (m^2)	0.91 ± 0.49 (0.3–1.91)	1.07 ± 0.47 (0.5–1.91)	0.7 ± 0.45 (0.3–1.85)	0.200
CxR/echocardiography				
CT ratio (%)	54 ± 6 (40–69)	53 ± 5 (40–61)	57 ± 6 (44–69)	0.217
Size of defects (mm/m^2)	17.1 ± 10.6 (2.5–56.5)	17.2 ± 9.3 (4.6–40.6)	17.1 ± 12.3 (2.5–56.5)	0.357
Cardiac catheterization				
Qp/Qs	2.1 ± 0.8 (1.1–4.9)	2.4 ± 0.9 (1.2–4.9)	1.8 ± 0.6 (1.1–3.5)	0.307
RAp (mmHg)	6 ± 2 (2–10)	6 ± 2 (2–10)	6 ± 2 (2–10)	0.609
PAp (mmHg)	22 ± 8 (12–56)	20 ± 6 (12–38)	25 ± 11 (13–56)	0.005*
BNP level (pg/mL)	10.9 ± 11.2 (<5–49.1)	10.6 ± 9.3 (<5–36.7)	11.4 ± 13.5 (<5–49.1)	0.343
BNP z-score	−0.28 ± 1.70 (−2.85–3.29)	−0.32 ± 1.62 (−2.85–2.77)	−0.22 ± 1.84 (−2.10–3.29)	0.426

Note: ASD, atrial septal defect; BNP, B-type natriuretic peptide; CxR, chest roentgenography; CT ratio, cardiothoracic ratio; Qp/QS, the ratio of pulmonary to systemic blood flow; RAp, PAp, and LAp, mean pressures of the right atrium, pulmonary artery, and left atrium; VSD, ventricular septal defect.
In the p value column, the comparisons were undergone between patients with ASD and VSD. *$p<0.5$.

and mean pulmonary arterial pressure. However, there was a statistically significant linear correlation between BNP level and the size of defects ($r=0.303$, $p=0.002$) and a trend toward a positive correlation between BNP level and Qp/Qs ratio ($r=0.183$, $p=0.166$) among all patients. There was a statistically powerful linear correlation between BNP level and Qp/Qs ratio, the size of defects ($r=0.483$, $p=0.014$; $r=0.598$, $p=0.002$, respectively) among VSD patients. The correlations between BNP level and Qp/Qs ratio, size of defects were plotted and are shown in the Figures 1–3. According to receiver operating characteristic curve analysis, using BNP value of 15 pg/mL to determine the cut-off point to identify patients with Qp/Qs ratio >1.5, the sensitivity, specificity and positive predictive values were 28%, 100%, 100% in all patients, 27%, 100%, 100% in ASD patients and 27%, 100%, 100% in VSD patients, respectively.

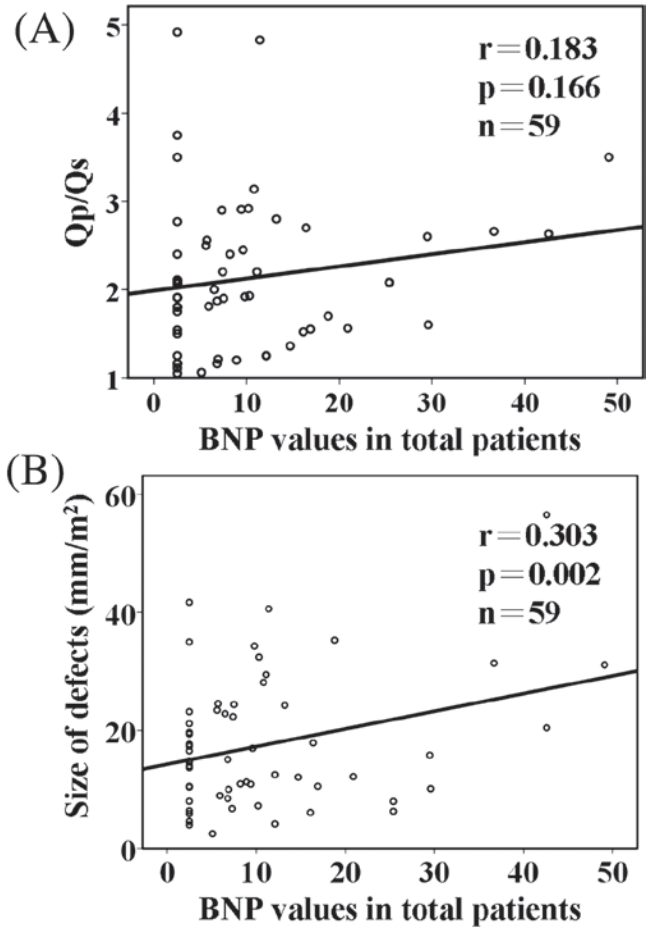

Figure 1. Scatter plot of the correlations between plasma BNP levels in total patients and pulmonary-to-systemic flow (Qp/Qs) ratio (A), and size of interseptal defects (B) with a regression line.

Discussion

One of the indications for closure of ASD or VSD by surgery or catheter-delivered device includes patients with hemodynamically significant intracardiac shunts or pulmonary hypertension. With the precise delineation of anatomic defects by current echocardiography, noninvasive quantification of Qp/Qs ratio and pulmonary artery pressure derived from pulsed-wave Doppler echocardiography in patients with ASD or VSD, diagnostic cardiac catheterization is now rarely necessary. However, the quantification of intracardiac shunt and pulmonary artery pressure with echocardiographic pulsed-wave Doppler method using the QP/QS ratio remains difficult and may induce false quantification of pulmonary pressure and output because this established method requires calculation of aortic and pulmonary orifice areas and the Doppler velocity waveform integrals by manual procedure. Thus, errors can occur in the measurement of the pulmonary ring diameter and the mean velocity from the Doppler spectral tracing, and these may induce false quantification of pulmonary pressure and flow (Cloez et al. 1998; Mansencal et al. 2005). Therefore, cardiac catheterization is still the

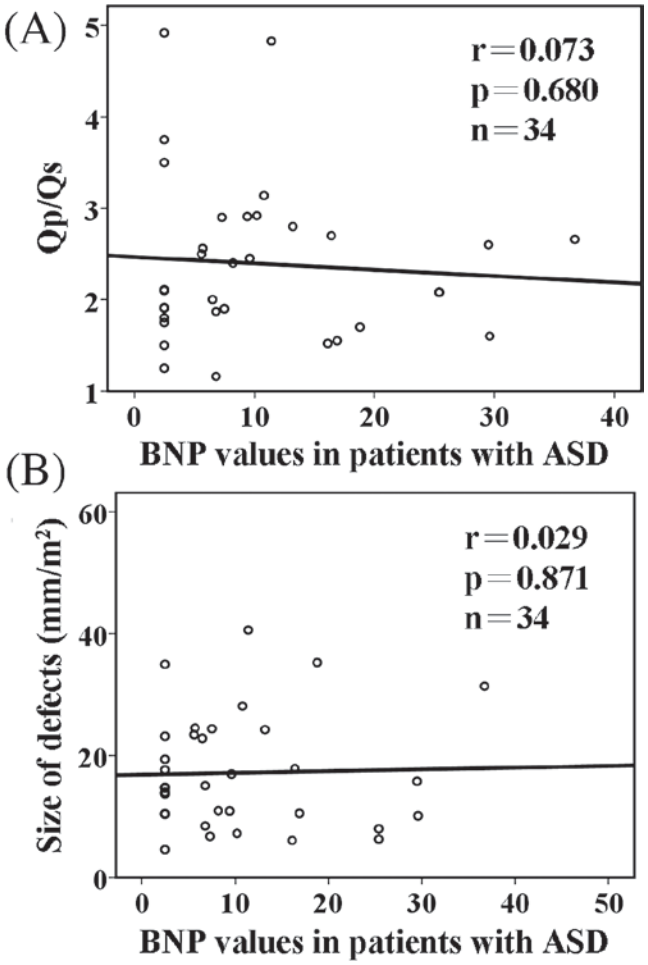

Figure 2. Scatter plot of the correlations between plasma BNP levels in patients with ASD and Qp/Qs ratio (A), and size of interatrial defects (B) with a regression line.

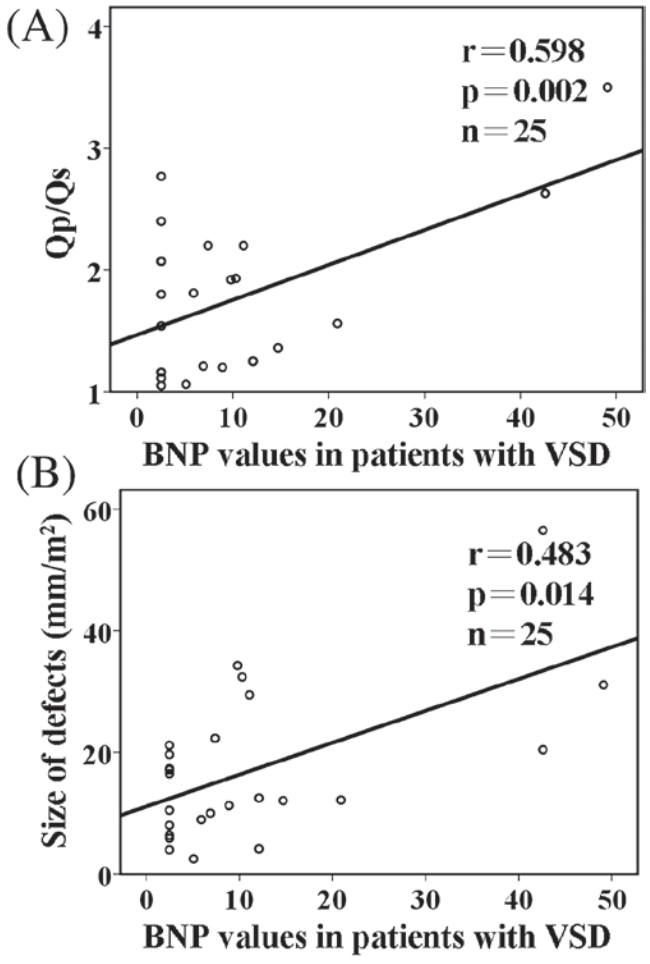

Figure 3. Scatter plot of the correlations between plasma BNP levels in patients with VSD and Qp/Qs ratio (A), and size of interventricular defects (B) with a regression line.

gold standard diagnostic technique for the measurement of intracardiac shunt and pulmonary artery pressure, but it is a radioactive and invasive method.

For a biomarker to be valuable in clinical practice, it should be rapidly and accurately measurable at a reasonable cost, add diagnostic or prognostic information to available methods, and help to guide patient management. BNP can fulfill most of these criteria in patients with heart failure and ventricular overload (de Lemos et al. 2003). The triage test system allows a widespread clinical use of BNP determination and recent studies reported the usefulness of BNP in adult patients with various cardiovascular diseases (Mizuno et al. 2000; Cheng et al. 2001; Bolger et al. 2002; Grabowski et al 2005). Plasma BNP can be measured quickly at the bedside using a device that employs as little as 0.25 mL of venous blood, which enables BNP measurement even in neonates. Holmstrom et al. and Choi et al. indicated that serial BNP measurements may provide clinically useful information to help determine the severity of shunting and to guide the management of preterm infants with patent ductus arteriosus (Holmstrom et al. 2000; Choi et al. 2005). Suda et al. reported that plasma BNP reflects pressure and volume loading of the pulmonary artery and the right ventricle and suggested that BNP determinations may help to identify children with VSD complicated by PH (Suda et al. 2003). Therefore, the purpose of this study was to investigate the relationship between BNP and hemodynamics from cardiac catheterization in pediatric patients with ASD or VSD. In addition, we wanted to determine whether rapid bedside detection of the plasma BNP value could be used to predict the severity of shunt and PH, which would indicate whether there was a need for further intervention. In this study, we found that an increase in BNP positively correlated to shunt volume measured by cardiac catheterization in ASD and VSD patients. The accuracy of BNP for predicting the size of defect and magnitude of intracardiac shunt of ASD or VSD was acceptable. Ozhan et al. investigated the relationship between the levels of BNP and shunt severity in patients with ASD or VSD and found a significant positive correlation between the plasma level of BNP and the magnitude of the shunts (Ozhan et al. 2007). Their findings were concordant with our results, though the Qp/Qs ratio was derived from pulsed-wave Doppler evaluation in their study. This finding can be

explained by the fact that an increase in shunting will cause more significant ventricular volume overload and an increase in BNP production. Theoretically, BNP levels will increase in proportion to the degree of the increase in right-ventricular pressure overload. However, the BNP levels did not correlate significantly with systolic right-ventricular pressure, mean pulmonary artery pressure and pulmonary resistance in this study. A possible explanation is the amount of BNP elevation would be less than that seen with processes leading to ventricular volume overload, thus limiting the statistical significance.

De Lemos et al. reported that there were some limitations of BNP testing including the finding that small increases in BNP are not specific since many diseases such as cor pulmonale, left or right ventricular dysfunction and left ventricular hypertrophy are also associated with small increases in BNP (de Lemos et al. 2003). In this study, we focused on pediatric patients with simple, isolated congenital heart diseases to avoid the above concern. Similarly, BNP may also be elevated in patients with renal insufficiency. We did not measure routinely renal function in this study, but no patients with a history of renal failure were enrolled. As children grow, BNP level increases with a positive and powerful linear correlation to age that reflects increasing cardiac load (Koch & Singer 2003). Koch et al. reported normal plasma BNP concentrations are lower in children than in adults, with mean plasma BNP values of 8.3 and 8.5 pg/mL, respectively, in boys and girls younger than 10 years and mean plasma BNP values of 12.1 and 5.1 pg/mL, respectively, in girls and boys aged 10 years or older. They proposed that plasma BNP concentrations should be expressed as standard deviation scores calculated according to age- and gender-specific normal values by formulas (Koch et al. 2006). Although BNP *z*-score can be derived from formulas, we used a BNP value > 15 pg/mL as a predictor of significant shunting in this study. We focused on a pediatric population to minimize the influence of age factor, and we found there was a similar correlation between shunting severity and BNP value or BNP *z*-score in this study. The BNP *z*-score is not suitable for clinical practice because it requires a more complex calculation.

Conclusions

There was a trend toward a positive correlation between plasma BNP and severity of shunt in pediatric patients with ASD or VSD, but plasma BNP could not be used to predict PH in this study. We speculate that a plasma BNP value > 15 pg/mL would identify pediatric patients with ASD or VSD who need further cardiac catheterization evaluation and the addition of BNP data may be beneficial in cases where it is unclear if defect closure, but a lower value of BNP may not be accurate enough to rule out interventional studies. To reach definitive conclusions about the clinical utility of BNP as a biomarker of shunt severity in pediatric patients with ASD or VSD, large multiinstitutional studies will be required.

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Declaration of interest

This study was supported by the Taichung Veterans General Hospital, Taiwan (TCVGH976505B). The manuscript has not any potential conflict of interest, real or perceived and has not any study sponsor. The first draft of the manuscript was written by Dr Jan, but not by an honorarium, grant, or other form of payment was given to anyone to produce the manuscript. The corresponding author has the right to grant on behalf of all authors and does grant on behalf of all authors. All authors have read and approved the final manuscript, and hereby transfer and assign all copyright ownership of the paper to the "BIOMARKERS," in the event that such work is published.

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