Diagnostic value of N-terminal pro-brain natriuretic peptide levels in pediatric patients with ventricular septal defect

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Received 30 March 2012; accepted 17 August 2012
Available online 24 September 2012

Abstract Background and aim: The plasma concentrations of N-terminal pro-brain natriuretic peptide (NT-proBNP) can reflect the cardiac functions in patients with cardiac diseases. Our aim is to assess the value of NT-proBNP in the diagnosis of heart failure and evaluation of cardiac functions in pediatric patients with ventricular septal defect (VSD).

Patients and method: The study comprised 40 children with VSD (mean age 12 ± 5 months) and 20 healthy children as a control group. Detailed echocardiographic examination was performed and the level of NT-proBNP level was measured.

Results: The plasma level of NT-proBNP was significantly higher in patients with VSD than in control subjects (P < 0.05). Also, it was significantly increased in VSD patients with congestive heart failure (CHF) than those without heart failure (P < 0.05). Moreover, NT-proBNP level increased with increasing severity of clinical symptoms. There were positive correlations between NT-proBNP level and left ventricular end diastolic diameter, left ventricular end systolic diameter, estimated systolic pulmonary artery pressure and VSD size and negative correlations with ejection fraction (EF) and fractional shortening (FS) in VSD patients with or without heart failure. The plasma levels of NT-proBNP with cutoff value of 101 fmol/ml (854 pg/ml), predicted CHF with a sensitivity of 90.0%, specificity of 80%, and area under ROC curve was 0.980.

Conclusion: NT-proBNP level is a good marker of disease severity and correlates with echocardiographic measurements and clinical symptoms in pediatric patients with VSD.

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1. Introduction

Congenital heart diseases contribute significantly to the disease-related morbidity and mortality in children especially in the first year of life.1 Ventricular septal defect (VSD) is the most common congenital heart disease (CHD) and the most common cause of congestive heart failure (CHF) in children, especially in infants.2

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Peer review under responsibility of Egyptian Society of Cardiology.
In VSD patients, the presence of a large left to right shunt results in an excessive volume load, and subsequent dilation of the left ventricle that induces left ventricular overload. Increased cardiac volume and afterload are thought to be the main pathophysiological mechanisms leading to CHF. Congestive heart failure is a common clinical syndrome, but clinical symptoms lack specificity, which is particularly true in infants. Clinical scores are used to increase the accuracy in the diagnosis of the disease.

Brain natriuretic peptide (BNP) is a cardiac hormone secreted from the left ventricular mycardium in response to ventricular volume expansion and pressure overload. It is synthesized as a preprohormone, consisting of 108 amino acids; processing releases the biologically active 32-amino acid peptide and an N-terminal pro-brain natriuretic peptide. The plasma concentrations of BNP and NT-proBNP can reflect the cardiac function. NT-proBNP is a more stable structure compared with BNP in whole blood for more than 24 h and is not significantly influenced by exercise and position. These factors confer its potential as an additional tool in the assessment of ventricular systolic dysfunction.

Many publications described BNP as an excellent marker of left ventricular function and a simple and effective tool to detect heart failure (HF) or left ventricular dysfunction. Therefore, the aim of the present study was to determine the concentrations of NT-proBNP in pediatric patients with VSD presenting with or without HF and to correlate the level of NT-proBNP with their clinical and echocardiography data, aiming to assess the diagnostic value of the new marker in these patients.

2. Methods

2.1. Study design

This case-control study was conducted during the period from June 2010 to February 2011. It included forty patients with VSD, selected randomly from the pediatric cardiology outpatient clinic and inpatient ward of Zagazig University Hospitals. Any child with isolated significant VSD, with or without CHF, was included. Exclusion criteria were: VSD with other cardiac anomalies, chest infections, or other diseases affecting ventricular function like hypertension and abnormal renal function. Twenty healthy children without any abnormal echocardiographic findings were taken as a control group. Parents gave an informed consent before starting the study.

2.2. Clinical assessment

All children were subjected to full history taking and thorough clinical examination which included complete cardiac examination. The severity of HF was assessed according to Modified Ross’s Clinical score for diagnosis of HF. This score classified patients into: No CHF = 0–2 points, Ross A (mild CHF) = 3–6 points, Ross B (moderate CHF) = 7–9 points, and Ross C (severe CHF) = 10–12 points.

2.3. Echocardiographic examination

All patients underwent echocardiographic examination using GE Vivid-7 multipurpose system with different probe sizes. Each patient was examined according to the recommendations of the American Society of Echocardiography. Echocardiographic examination included M-mode, 2D, and Doppler echocardiography. The left atrial diameter (LAD) was estimated from the parasternal long axis view. The left ventricular end systolic diameter (LVESD), left ventricular end diastolic diameter (LVEDD), ejection fraction (EF) and fractional shortening (FS) were measured using M-mode echocardiography in the left parasternal view. Estimated systolic pulmonary artery pressure (ESPAP) was calculated through Doppler tracing of the peak velocity of the tricuspid regurgitation jet by using the Bernoulli equation.

\[ ESPAS = 4(V^2) + RAP \]

where

\[ V = \text{Peak velocity of the tricuspid regurgitation jet.} \]

An arbitrary 10 mmHg is added to the gradient as the RAP.

According to relation between VSD size and Aortic annulus, VSD was classified into:-

(I) Small: VSD size is usually ≤1/4 the size of the Aortic Valve annulus.

(II) Moderate: VSD size is usually 1/3–2/3 the size of the Aortic Valve annulus.

(III) Large: The VSD size is >2/3 the size of the Aortic Valve annulus.

2.4. Measurement of plasma level of NT-proBNP

This was done using radioimmunoassay (Roche, diagnostic system). The blood samples were collected in chilled ethylene diamine tetra acetic acid, placed immediately on ice, and centrifuged for 20 min. The plasma was stored at −80 °C before being assayed.

2.5. Statistical analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS) 10.0. The quantitative data showing a normal distribution are presented as mean ± standard deviation. For comparison between two groups mean, t-test was used. For comparison between three groups’ means, one way ANOVA (analysis of variance) was used. Non parametric values represented as median and range and the median of the two groups was tested by Mann–Whitney-U test, also the comparison between three groups’ median was analyzed by Kruskall–Wallis test. Qualitative data are represented by frequency and relative percentage and chi-square test was used for testing association of qualitative data. Receiver operating curve (ROC) characteristic was used to determine cut off value of NT-proBNP in heart failure development. Correlations were performed using the Pearson bivariate correlation. P value of < 0.05 was considered statistically significant.

3. Results

The study included 40 patients with VSD. They classified into 2 groups regarding the presence of CHF. Group I included twenty VSD patients without CHF (16 males and 4 females) and their ages ranged from 2.5 to 32 months (median: 14.5 months). Group II included twenty VSD patients with
CHF (12 males and 8 females) and their ages range from 5.5 to 15.5 months (median: 10 months). There were 20 normal control subjects, of whom 10 (50%) were males and 10 (50%) were females, their ages ranged from 5 to 20 months. There were no significant differences between the three studied groups in respect of age and gender ($P = 0.36$, $P = 0.13$ respectively).

In all patients, the perimembranous type of VSD was the commonest type. Regarding the severity of HF in group II; 8 patients had score IA, 6 had score IB, and 6 had score IC (Table 1).

# Table 1  Demographic and clinical data of studied groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I ($n = 20$)</th>
<th>Group II ($n = 20$)</th>
<th>Control Group ($n = 20$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months) median (range)</td>
<td>14.5 (2.5–32)</td>
<td>10 (5.5–15)</td>
<td>13 (5–20)</td>
<td>0.36</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>16:4</td>
<td>8:12</td>
<td>10:10</td>
<td>0.13</td>
</tr>
<tr>
<td>VSD Type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perimembranous</td>
<td>14(70.0%)</td>
<td>14(70.0%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Muscular</td>
<td>2(10.0%)</td>
<td>4(20.0%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Outlet</td>
<td>2(10.0%)</td>
<td>2(10.0%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Inlet</td>
<td>2(10.0%)</td>
<td>0.0</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>VSD size (mm) mean ± SD</td>
<td>7.81 ± 2.46</td>
<td>8.71 ± 2.37</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Ross score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score IA</td>
<td>NA</td>
<td>8 (40.0%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Score IB</td>
<td>NA</td>
<td>6 (30.0%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Score IC</td>
<td>NA</td>
<td>6 (30.0%)</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

NA, not available.

# Table 2  Comparison of echocardiographic parameters among the studied groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I ($n = 20$) Mean ± SD</th>
<th>Group II ($n = 20$) Mean ± SD</th>
<th>Control Group ($n = 20$) Mean ± SD</th>
<th>$F$</th>
<th>$p_1$</th>
<th>$p_2$</th>
<th>$p_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD(mm)</td>
<td>28.7 ± 3.92</td>
<td>30.9 ± 2.6</td>
<td>22.4 ± 3.08</td>
<td>36.56</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LVESD(mm)</td>
<td>18.1 ± 3.4</td>
<td>20.2 ± 2.5</td>
<td>16.00 ± 2.98</td>
<td>9.8</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>EF%</td>
<td>71.6 ± 7.27</td>
<td>61.5 ± 6.66</td>
<td>69.6 ± 4.61</td>
<td>14.46</td>
<td>&lt;0.05</td>
<td>&gt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FS%</td>
<td>35.1 ± 5.7</td>
<td>30.3 ± 5.7</td>
<td>39.2 ± 8.5</td>
<td>8.35</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ESPAP(mmHg)</td>
<td>45.3 ± 13.36</td>
<td>53.5 ± 13.1</td>
<td>23.0 ± 5.80</td>
<td>22.10</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

$p_1 = \text{Group I vs. Group II}, p_2 = \text{Group I vs. control group}, p_3 = \text{Group II vs. control group}.

LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; EF, ejection fraction; FS, fractional shortening; ESPAP, estimated systolic pulmonary artery pressure.

# Table 3  Comparison of NT-proBNP level among the studied groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I ($n = 20$) median (range)</th>
<th>Group II ($n = 20$) median (range)</th>
<th>Control Group ($n = 20$) median (range)</th>
<th>Kruskal–Wallis $P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-proBNP (fmol/ml)</td>
<td>55 (10–120)</td>
<td>830 (100–950)</td>
<td>32.5 (10–105)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

$p_1 = \text{Group I vs. Group II}, p_2 = \text{Group I vs. control group}, p_3 = \text{Group II vs. control group}.

The plasma levels of NT-proBNP were significantly higher in VSD patients with or without HF than in controls (830 vs. 32.5 fmol/ml, $P < 0.05$ and 55 vs. 32.5 fmol/ml, $P < 0.05$, respectively). Also, it was significantly higher in VSD patients with HF than in those without HF (830 vs. 55 fmol/ml, $P < 0.05$).
In the present study, the plasma NT-proBNP levels were given in fmol/ml; in order to convert the results of NT-proBNP from fmol/ml to pg/ml, results should be multiplied by factor 8.457 (Fig. 1).

Moreover, the plasma level of NT-proBNP increased with increasing severity of the clinical symptom as it was significantly higher in Ross score C than Ross score B (950 vs. 830 fmol/ml, \( P < 0.001 \)) while there was an insignificant difference between Ross score B and Ross score A (830 vs. 675 fmol/ml, \( P \) value > 0.05) (Table 4).

In Group I and II, there were positive correlations between NT-proBNP level and LVEDD, LVESD, ESPAP and VSD size, and there were negative correlations between NT-proBNP level and LVEF and LVFS (Table 5).

The plasma levels of NT-proBNP with cutoff value of 101 fmol/ml (854 pg/ml), predicted CHF with a sensitivity of 90.0%, specificity of 80%, and area under ROC curve was 0.980 (Fig. 2).

### Discussion

Brain natriuretic peptide is a cardiac hormone secreted from the ventricular myocardium as a response to ventricular volume expansion and pressure overload.\(^5\) BNP has a diuretic, natriuretic and vasodilator activities.\(^14\) There is an increasing interest in determining BNP and its N-terminal pro-peptide levels not only in patients with CHF but also in patients with CHD.\(^15\) Recent studies have reported the usefulness of the NT-proBNP levels in predominantly adult patients with various CHD.\(^16,17\) A few studies have been performed in children with CHD.\(^18\) So, we conducted this study to assess the value of plasma NT-proBNP in the diagnosis of CHF and evaluation of cardiac function in pediatric patients with VSD.

In our study, the Plasma levels of NT-proBNP were significantly higher in patients with VSD with or without CHF than in control. Also, the plasma level of NT-proBNP was significantly increased in VSD patients with CHF than in those without CHF. Suda et al.,\(^19\) Kunii et al.,\(^20\) and Koch et al.\(^21\) found increasing NT-proBNP level with volume overload in infants and children with left to right shunt and this result agreed with our study.

Moreover, we detected significant correlation between NT-proBNP concentrations and the severity of clinical symptoms. This finding was in agreement with that of Wu et al.\(^2\) study, in which the concentration of plasma NT-proBNP was positively correlated with the clinical CHF score in 51 patients with VSD and with varying degree of CHF. This elevation of NT-proBNP level results from a surge in NT-proBNP production in reaction to the acute muscle dysfunction and increased wall tension.\(^22\)

In our study, the plasma levels of NT-proBNP were correlated with LVEDD, so it could reflect the degree of volume overload. This volume overload may be one of the factors leading to increased NT-proBNP levels. Also, the plasma levels of NT-proBNP were correlated with LVESD. Ootaki et al.\(^23\) found more increasing NT-proBNP with increasing dimension of left ventricle during systole and diastole in children with CHD.

Our data revealed increasing NT-proBNP concentrations with decreasing left ventricular FS and EF in VSD patients.
without or with HF. Our results were in agreement with the study of Mir et al. They aimed to determine plasma levels in healthy children and children with CHF. They included 31 children with CHF caused by dilated cardiomyopathy, hypoplastic left heart syndrome, postoperative tetralogy of Fallot, mitral regurgitation, VSD, and ventricular atrioventricular septal defects. They found a negative correlation between NT-proBNP and left ventricular EF. Ajuluchukwu et al. conducted a study to determine NT-proBNP levels in Nigerian healthy adults and hospitalized CHF patients. Causes of CHF were hypertensive heart disease, primary dilated cardiomyopathy and myocardial infarction. NT-proBNP demonstrated a significant, negative relationship to both ejection fraction \( r = -0.49, P < 0.05 \); and fractional shortening \( r = -0.51; P < 0.05 \).

In our study, ESPAP was positively correlated with NT-proBNP concentrations. Suda et al. and Toyono et al. reported that NT-proBNP reflected pressure and volume loading of the pulmonary artery and the right ventricle and suggested that NT-proBNP determinations may help to identify children with VSD complicated by pulmonary hypertension. Pulmonary hypertension produces pressure overload to the right ventricle thereby resulting in the enlargement of the right ventricle and significant pulmonary and tricuspid regurgitation. These considerable pressure and volume overloads on the right ventricle might lead to the elevation in NT-proBNP level.

Also, our data revealed positive correlation between VSD size and NT-proBNP concentrations. Cowley et al. and Mainwaring et al. demonstrated a positive correlation between NT-proBNP level and shunt severity in patients with left-to-right shunt lesions.

Finally, our results identified NT-proBNP level with a cutoff value of 101 fmol/ml (854 pg/ml), predicted CHF with a sensitivity of 90.0%, specificity of 80%, and area under ROC curve was 0.980. It means that NT-proBNP is a more specific and sensitive biomarker for identifying the CHF.

5. Conclusion

Plasma NT-proBNP is a valuable marker for the diagnosis of heart failure and assessment of the severity of volume overload in children with VSD. These findings open a new additional diagnostic tool that could result in a more precise diagnosis and management of CHF in children. Further studies that correlate NT-proBNP levels with effects of different therapeutic interventions could be of great importance.

References


