B-type natriuretic peptide in paediatric patients with congenital heart disease

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Aims To examine the diagnostic value of B-type natriuretic peptide (BNP) plasma concentration in congenital heart disease.

Methods and results BNP was measured in 288 consecutive patients (mean age 6.0 ± 6.4 years) with left-to-right shunt, left or right heart obstruction, tetralogy of Fallot, functionally univentricular heart, or impaired left ventricular function and compared with age- and gender-specific normal values, and to haemodynamic and echocardiographic data. BNP increased with decreasing left ventricular shortening fraction (r = −0.80; P < 0.001). In patients with left-to-right shunt, BNP was increased (mean SDS +1.64; P < 0.001) and positively correlated (P < 0.001) to shunt volume (r = 0.66), systolic right ventricular pressure (r = 0.69), mean pressure of the pulmonary artery (r = 0.66), and pulmonary resistance (r = 0.59). There was no correlation between BNP and invasive pressure gradient or extent of ventricular hypertrophy in patients with left or right heart obstruction. In patients with tetralogy of Fallot, BNP was not significantly increased. Patients with functionally univentricular heart had elevated BNP plasma levels (mean SDS +1.39; P < 0.001) without decrease after volume unloading by cavopulmonary connection.

Conclusion In children with congenital heart defects, plasma BNP correlates closely to ventricular function. BNP plasma levels do not reflect directly the extent of ventricular pressure or volume work, but mirror the impairment of the loaded ventricles. Normal BNP cannot exclude pathology, but reflects a compensated status of the heart.

Introduction

B-type natriuretic peptide (BNP) is a cardiac hormone with diuretic, natriuretic, and vasodilatory properties secreted mainly by the ventricles in response to volume expansion and pressure load.1,2 Within the myocyte, the active hormone is cleaved from the C-terminus of the precursor protein proBNP.3,4 Measurement of plasma BNP levels or the concentration of the N-terminal fragment of proBNP (NT-proBNP) is increasingly used to aid diagnosis, assess prognosis, and tailor therapy in adults with congestive heart failure.2,3 BNP may be useful in various other conditions such as hypertrophic cardiomyopathy,4 left ventricular remodelling after myocardial infarction,5 arrhythmogenic right ventricular dysplasia,6 or congenital heart disease.7–9 The few data dealing with BNP and NT-proBNP in children suggest that these peptides are useful in paediatric patients too.10–15 However, the groups of investigated paediatric patients with congenital heart disease were small or heterogeneous,10–13 and the results were not compared with age- and gender-specific normal values.14,15 Recently, we have reported normal concentrations of both BNP values were compared with haemodynamic data from cardiac catheterization (e.g. pressure data, invasive pressure

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gradients, pulmonary and systemic flow, and resistance using Fick’s principle) and to echocardiographic data.

The study was approved by the local Ethics Committee.

Subjects

Patients

From 2002 to 2004, we measured BNP in all consecutive patients with congenital heart disease who were admitted for cardiac catheterization. In general, blood sampling was performed at the beginning of catheterization procedure from the vena cava inferior. Propofol was used to obtain conscious sedation during cardiac catheterization. Intubation was performed only in newborns, very small infants (body weight < 4.5 kg), or severe cyanotic patients. In addition, we measured BNP in patients with cardiac disease admitted for minor operations, outpatient visits, or diagnostic work-up including a venous puncture. These patients were in supine position during blood sampling, and venous puncture was typically performed at a cubital vein between 8:30 and 11:00 a.m. after 10 min of rest.

None of the parents refused to include their child into the study. BNP was measured in 691 patients. A total of 346 patients complied with one of the following requirements: left ventricular shortening fraction currently < 30% or in the normal range but a myocardial disease or damage with one of the following causes: reduced left ventricular shortening fraction or coronary fistula to evaluate the coronary arterial anatomy and perfusion by angiography, and in patients with univentricular heart to evaluate the pulmonary resistance and the pulmonary arterial anatomy before bidirectional or total cavopulmonary anastomosis.

With scattered exceptions (single patients with very large left-to-right shunts or markedly reduced ventricular function), all patients were in good clinical condition. Naturally, patients with tetralogy of Fallot and patients with functionally univentricular heart before complete separation of systemic and pulmonary venous return were cyanotic in a variable degree. All patients with bidirectional or complete cavopulmonary anastomosis were taking antithrombotic drugs (acylsalicylic acid 2–5 mg/kg/day, dipyridamole 2–3 mg/kg/day), almost half of the patients with tetralogy of Fallot propranolol (1–2 mg/kg/day) to prevent hypoxic spells, and some patients with large VSD or PDA diuretics (furosemide/spironolactone 1–2 mg/kg/day) and digoxin (3–10 μg/kg/day).

Controls

The 152 infants, children, and adolescents from 2 weeks to 17.6 years of age (mean age 8.7 ± 5.0 years, median age 9.1 years; age >2 weeks to <10 years: n = 43 males/42 females; age ≥10 years: n = 31 males/36 females) were admitted for minor operations (e.g. hernia repair, tonsillectomy) or diagnostic work-up (e.g. for short stature, headache, neonatal screening). Physical examination and laboratory testing (e.g. electrolytes, kidney function, blood count) did not give any indication for acute illness (fever, infections, water and electrolyte imbalance, neoplastic disease, infections, water and electrolyte imbalance).

Table 1 Clinical characteristics of the study population

<table>
<thead>
<tr>
<th>Patients</th>
<th>Number</th>
<th>Male/female</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>288</td>
<td>156/132</td>
<td>6.0 ± 5.4</td>
</tr>
<tr>
<td>Left-to-right shunt</td>
<td>74</td>
<td>31/43</td>
<td>5.2 ± 5.2</td>
</tr>
<tr>
<td>ASD</td>
<td>11</td>
<td>3/8</td>
<td>9.1 ± 7.3</td>
</tr>
<tr>
<td>VSD</td>
<td>35</td>
<td>18/17</td>
<td>4.7 ± 5.2</td>
</tr>
<tr>
<td>PDA</td>
<td>26</td>
<td>9/17</td>
<td>4.2 ± 2.9</td>
</tr>
<tr>
<td>Coronary fistulas</td>
<td>2</td>
<td>1/1</td>
<td>2.3, 13.9*</td>
</tr>
<tr>
<td>Isolated outflow obstruction</td>
<td>70</td>
<td>45/25</td>
<td>7.0 ± 6.6</td>
</tr>
<tr>
<td>Pulmonary valve stenosis</td>
<td>22</td>
<td>12/10</td>
<td>8.8 ± 6.6</td>
</tr>
<tr>
<td>Aortic valve stenosis</td>
<td>30</td>
<td>22/8</td>
<td>8.8 ± 6.6</td>
</tr>
<tr>
<td>Ischemic coarctation</td>
<td>18</td>
<td>11/7</td>
<td>9.9 ± 6.9</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>33</td>
<td>22/11</td>
<td>0.5 ± 0.4</td>
</tr>
<tr>
<td>Functionally univentricular heart</td>
<td>81</td>
<td>44/37</td>
<td>6.9 ± 6.5</td>
</tr>
<tr>
<td>Before separating surgery</td>
<td>26</td>
<td>15/11</td>
<td>1.1 ± 1.1</td>
</tr>
<tr>
<td>Bidirectional cavopulmonary anastomosis</td>
<td>21</td>
<td>14/7</td>
<td>3.7 ± 2.3</td>
</tr>
<tr>
<td>Complete cavopulmonary anastomosis</td>
<td>34</td>
<td>15/19</td>
<td>13.1 ± 5.2</td>
</tr>
<tr>
<td>Impaired left ventricular function</td>
<td>30</td>
<td>14/16</td>
<td>10.8 ± 8.2</td>
</tr>
</tbody>
</table>

Age data are mean ± standard deviation. *Individual age (years).

ASD, atrial septal defect; VSD, ventricular septal defect; PDA, persistent ductus arteriosus
liver disease, renal disease) and the subjects had no history of heart disease or another serious disease. Blood sampling was typically done between 8:30 and 11:00 h in the supine position after 10 min of rest. They were not on drug treatment, they were not receiving intravenous infusions, and their diet was appropriate for their age.

**Statistics**

Statistical analyses were performed with SPSS 12.0 for Windows. Statistical differences between patient groups and healthy subjects were evaluated using Student’s t-test. In patients with functionally univentricular heart, statistical differences between patients with complete, partial, or without separation of systemic and pulmonary venous return were evaluated using one-way analysis of variance. Correlations were performed by Pearson’s correlation method. Statistical significance was accepted with a P-value below 0.05. The significance level was adjusted by use of Dunnett’s test to compare patient groups with controls (see Figure 1). Bonferroni adjustment was used to account for the inflation of the overall Type I error rate in case of multiple testing in patients with functionally univentricular heart.

Sample size calculations indicated that groups comprising 16 patients were sufficient to detect a difference in plasma BNP concentration of 1 SDS with 80% power at the 5% significance level.

The total coefficient of variation was between 4.0 and 12.4%.

**Results**

Plasma BNP concentration increased significantly (r = −0.80; P < 0.001) with decreasing left ventricular shortening fraction (Figure 2).

In patients with left-to-right shunt, plasma BNP was increased (mean SDS +1.63 ± 2.41; P < 0.001) (Figure 1). Plasma BNP was positively correlated to shunt volume (r = 0.66; P < 0.001), to systolic right ventricular pressure (r = 0.69; P < 0.001), to mean pressure of the pulmonary artery (0.66; P < 0.001), and to increasing pulmonary resistance (r = 0.59; P < 0.001) (Figure 3).

Plasma BNP levels in patients with aortic valve stenosis was slightly increased with significance (mean SDS +1.23 ± 1.92; P = 0.003) (Figure 1). In patients with pulmonary valve stenosis (mean SDS +0.58 ± 1.65) or isthmic coarctation (mean SDS +1.01 ± 2.00), there was no significant difference to healthy subjects (P > 0.1) (Figure 1). There was no correlation between BNP and invasive pressure gradient (Figure 4).

In patients with tetralogy of Fallot, plasma BNP was not significantly increased (mean SDS +0.57 ± 1.84; P = 0.43) (Figure 1).

Patients with functionally univentricular heart had higher plasma BNP levels than normal subjects (mean SDS +1.39 ± 1.95; P < 0.001). There was no difference between plasma BNP in patients before separation of systemic and pulmonary venous return (mean SDS +1.28 ± 1.62), after bidirectional Glenn operation (mean SDS +1.04 ± 2.04), or after complete cavopulmonary connection (mean SDS +1.70 ± 2.12) (Figure 1).

**Discussion**

There is an increasing interest in BNP and its N-terminal propeptide not only in patients with congestive heart failure, but also in patients with congenital heart disease. According to the rapid and accurate measurement, the Triage test system allows a widespread clinical use of BNP determination and recent studies reported usefulness of BNP and NT-proBNP in predominantly adult patients with variable congenital heart disease. However, it has to be taken into account that normal values of BNP plasma concentration are totally different in paediatric and adult patients. Healthy newborns, for example, have very high plasma concentration of BNP and NT-proBNP in predominantly adult patients with variable congenital heart disease. In contrast, in infants and children, BNP plasma levels are much lower than in adults, with significant differences in girls and boys after puberty. Accordingly, in adults, a 10-year increase in age is associated with a 1.4-fold increase in plasma BNP. Therefore, the results of studies on BNP in patients with congenital heart disease have to be compared with age- and gender-specific normal values. The need for adequate normal values is underlined by reports indicating a more discreet increase of natriuretic peptides in patients

Figure 1 Correlation of BNP plasma concentration to left ventricular shortening fraction in 35 patients with dilated cardiomyopathy (solid dots), left ventricular non-compaction (open dots), myocarditis (triangles), Bland-White–Garland syndrome (rhombs), or congenital heart defect before (open squares; 1, patient with isthmic coarctation and hypoplasia of the left coronary artery; 2, patient with congenital mitral regurgitation) and after surgery (solid squares; 3, patient with Shone complex 1 year after aortic and mitral valve replacement; 4 and 5, patients with tetralogy of Fallot 3 and 5 years after corrective surgery; 6, patient 4 years after closure of a muscular VSD and resection of an isthmic coarctation; 7, patient 0.6 year after closure of a large perimembranous VSD). Individual z-scores (standard deviation score) and normal range (SDS ±2 to ±2, dotted lines) are shown.

Figure 2 Plasma concentration of BNP in controls and in patients with isthmic coarctation (IST), aortic valve stenosis (AST), pulmonary valve stenosis (PST), tetralogy of Fallot (TOF), left-to-right shunt defects (LRS), univentricular heart before separation of pulmonary and systemic venous return (SV), after superior bidirectional cavopulmonary connection (Glenn), and after total cavopulmonary connection (TCPC). Individual z-scores (standard deviation score) and normal range (SDS ±2 to ±2, dotted lines) are shown. Additionally, median (horizontal line), interquartile range (box), mean (bold horizontal line), and significant differences (*) to normal individuals are shown.
with congenital heart disease compared with adults with acquired left ventricular dysfunction.8–10

In our patients, there was a very strong negative correlation between left ventricular systolic function and BNP plasma concentration. This finding is in line with the very few reports in the literature dealing with BNP and NT-proBNP values in children. We found increasing plasma BNP concentration with decreasing left ventricular shortening fraction, and Mir et al.13 described a significant relationship between NT-proBNP and left ventricular ejection fraction. Law et al.10 found significantly higher BNP plasma concentrations in children with reduced shortening or ejection fraction.

In children with left-to-right shunt, we found an increase of plasma BNP correlated to shunt volume, systolic right ventricular pressure, mean pressure in the pulmonary artery, and pulmonary resistance. These data are very consistent to the current conception of BNP released by the ventricular myocytes in response to volume and pressure load. The results are in line with one other report on natriuretic peptides in children with ventricular septal defect.15 Although their data were not compared with BNP concentrations in healthy children, the authors found BNP plasma levels positively correlated to shunt size, mean pulmonary artery pressure, ratio of pulmonary to systemic pressure, and pulmonary resistance.15 In addition, elevated NT-proBNP plasma levels have been described in small groups of children with cardiac defects causing a left-to-right shunt.12,13

Although we found a slightly increased BNP concentration in our patients with aortic valve stenosis, most of the BNP plasma levels were in the normal range. In addition, BNP plasma levels did not correlate to the invasive pressure gradient. In contrast, in adult patients with aortic stenosis, elevated plasma levels of BNP and NT-proBNP have been reported with a correlation to severity,20–23 particularly to transvalvular pressure gradient.23–25 The differences between paediatric and adult patients with aortic stenosis may be explained by the greater possibility for compensation of left ventricular function in younger than in elderly patients. Some details of our data support this suspicion. The two neonates with critical aortic stenosis characterized by a reduced left ventricular function had very high BNP levels of 1300 pg/mL, however, because of high BNP plasma levels even in healthy newborns, the elevation with regard to normative data was cut down (SDS +2.44 and +2.86). One of the two patients with the proportionally highest BNP level (SDS +5.76) was a 2-month old girl with slightly reduced left ventricular shortening fraction and increased left ventricular diameter. In addition, in children with preserved left ventricular function, normal BNP levels were found, despite an invasive pressure gradient of up to 105 mmHg, a left ventricular systolic pressure of up to 220 mmHg, and a markedly increased left ventricular hypertrophy.26 Cowley et al.14 reported a correlation of plasma BNP with the degree of left ventricular outflow obstruction. However, looking at their data in detail, the results are less conflicting to our findings: 18/21 patients had very similar plasma BNP levels with gradients between 10–90 mmHg. The positive correlation was based on 3/21 patients with high plasma BNP levels of 379–1060 pg/mL. However, the data were not compared with age specific normal values. The age of the three decisive patients was 3 days, 4 days,
and 2 months and high BNP concentrations are normal in healthy newborns, in particular, in the first week of life.  

In patients with isolated right-heart obstruction because of a pulmonary valve stenosis, we could not find any increase of plasma BNP concentration, even in patients with invasive pressure gradients of more than 100 mmHg. Moreover, patients with tetralogy of Fallot featuring systemic pressure in the right ventricle and increased right ventricular mass again had normal BNP levels. In contrast, a positive correlation between right ventricular pressure and plasma BNP has been described in patients with tetralogy of Fallot after surgical correction.  

At the first glance, this seems to be inconsistent with our findings of normal plasma BNP in patients with tetralogy of Fallot before surgical repair. However, corrective surgery of tetralogy of Fallot includes resection of the infundibulum obstruction and often incision of the right ventricle. Possibly, the changes in the myocardial architecture of the right ventricle reduce the ability to compensate and determine the different reaction to pressure load.  

Experimental data indicate that hypertrophy itself may activate BNP expression in mice. In man, a correlation between BNP levels and left ventricular mass in hypertensive patients has been reported. Probably because physiological hypertrophy is not associated with increased wall stress. Although increased BNP levels were described in patients with right ventricular pressure load, BNP levels were not correlated to right ventricular pressure, but inversely to the right ventricular ejection fraction. In one study on a large but very heterogeneous group of paediatric patients with different congenital heart diseases, no correlation was found between plasma BNP and right ventricular systolic pressure or right ventricular outflow tract obstruction.  

These data together with our findings of normal BNP levels in children with left or right ventricular hypertrophy and good ventricular function support the hypothesis that an increase in ventricular mass does not cause directly an increase of BNP plasma level.  

Our patients with functional univentricular heart had on average higher plasma BNP levels than normal subjects. Unexpectedly, reduction of volume load according stepwise separation of systemic and pulmonary venous return did not decrease plasma BNP levels. In accordance, Hjortdal et al. found significantly higher, almost doubled BNP levels in 12 patients after total cavopulmonary connection and slightly, not significantly increased BNP plasma levels in eight patients after Glenn anastomosis compared with controls. Therefore, other factors than volume load have to cause the BNP increase in these patients.  

In fact, there are a lot of data indicating a much more complex role for BNP than only to be the myocardial answer of pressure or volume load. For example, BNP exerts potent actions on cell growth and proliferation of fibroblasts, vascular smooth muscle cells, and cardiac myocytes. Moreover, in the rat heart, experimental ischaemia leads to an increase of BNP messenger RNA in the ventricular myocardium and exogenously administered BNP limited infarct size in a concentration dependant matter and in humans, elevated concentrations of plasma BNP are detected following unstable angina. All these reports suggest that BNP is a pleiotropic peptide with additional effects beyond its natriuretic and cardiac unloading properties.  

BNP is a firmly established marker of ventricular dysfunction, but taking BNP as direct marker of volume and pressure load seems to be an oversimplification. Our data on different effects of pressure and volume on BNP plasma level in children with distinct congenital heart defects suggest that there are additional factors modulating the release of BNP apart from myocyte stretch alone. The role of BNP in patients with congenital heart disease is obviously much more complex.  

Some limitations to this study have to be considered. Although focusing on patients with circumscribed haemodynamic problems, standardization is limited in paediatric patients with congenital heart disease. For example, there were some differences between the patients regarding arterial saturation or oral medication. However, from our own experience, we have no evidence that cyanosis or any of the given drugs influence BNP plasma levels. Next, we have investigated a rather large number of consecutive paediatric patients, but we do not have longitudinal data. Particularly in patients with functionally univentricular heart, data on the same subjects before and after separation of the systemic and pulmonary venous blood would be much more favourable than cross-sectional data.  

In summary, BNP correlates well with systolic ventricular function and with increasing pulmonary pressure and pulmonary resistance in patients with left-to-right shunt. However, the data on patients with severe left and right heart obstruction demonstrated that not every kind of increasing ventricular pressure cause directly an increase of plasma BNP. In addition, the reduction of volume load in patients with functional univentricular hearts could not decrease the elevated BNP levels. There was not a simple, straight correlation between plasma BNP and pressure or volume load regardless of the underlying cardiac defect. Therefore, we have to conclude, that in children with congenital heart defects, plasma BNP levels do not reflect directly the extent of ventricular pressure or volume load, but reflect more likely the degree of impairment of the ventricles because of the increased volume and pressure work. A normal BNP value cannot preclude any pathology, but reflects a compensated status of the heart.  

In future, BNP may change the current strategies for clinical management of congenital heart disease. However, data on adult patients cannot be directly transferred to children and the clinical impact of measuring BNP plasma levels has to be evaluated separately for each entity, before we can use this marker in clinical routine.  

Conflict of interest: none declared.

References


