The Correlation Between Pulmonary Hypertension and “Pro-Brain Natriuretic Peptide” Serum Level and the Quantity of Left to Right Shunt (Qp/Qs Ratio) in Children With Congenital Heart Disease

Mahmood Samadi, Ahmad Jameii Khosroshahi*, Ali Aghyar Macooie, Elnaz Eskandartash, Shahriar Anvari

Abstract
Objective: Pulmonary arterial hypertension (PAH) is a common complication in congenital heart diseases. To evaluate the quantity of the shunt and the systolic pulmonary pressure the serum level of B-type natriuretic peptide (BNP) was investigated.

Materials and Methods: In this analytical-descriptive study, 30 infants and children with respiratory distress, recurrent pneumonias, failure to thrive and had a murmur in their physical examinations and a cardiomegaly on the chest x-ray was selected. Patients have one of ventricular septal defect (VSD), atrial septal defect (ASD) or pulmonary duct artery (PDA) in echocardiography. The BNP serum level measured and compared to the quantity of the left to right shunt and systolic pulmonary pressure detected through evaluation of tricuspid regurgitation (TR) by echocardiography. Velocity time integral (VTI) measured by doppler echocardiography at the pulmonary and aortic valves for VSD and ASD, mitral and tricuspid valves for PDA, the Qp/Qs ratio was detected to determine if there was any significant relationship between the former and the two latter.

Results: There was a significant relationship between level of pro-BNP and the quantity of the shunt in the patients with VSD, ASD and PDA (P=0.01). A positive correlation between BNP serum level and Qp/Qs ratio in all the patients. There was significant relationship between pro-BNP level and the systolic pulmonary pressure (P<0.001). The cut-off point of pro-BNP demonstrating a Qp/Qs ratio more than 1.5 was measured at the level of 36.95 pg/mL, with a sensitivity and specificity of 100% and 83.3%, respectively.

Conclusion: In patients whom PAH pressure cannot be measured for any reason, measure BNP serum can be useful.

Keywords: Pulmonary arterial hypertension, B-type natriuretic peptide, Congenital heart disease, Left to right shunt

Introduction
Pulmonary arterial hypertension (PAH) is an early and late complication of congenital heart disease (CHD) with left to right shunt. Left to right shunt cause pulmonary over flow, arterial, remodeling and progressive pulmonary vascular resistance. Early detect of left to right shunt prevent development of PAH and Eisenmenger syndrome. Persistent of the pulmonary vasculature to increased blood flow and pressure may result in vascular remodeling and dysfunction. This leads to reversal of the shunt and development of Eisenmenger syndrome (1).

The prevalence of PAH-CHD has fallen in developed countries over recent years and the number of patients surviving into adulthood has increased significantly (1, 2). The increase of PAH in patients with CHD is associated with increased mortality and high morbidity, reflected in a substantial increase in health service utilizations (3,4).

Thirty percent to 35% of CHD with left to right shunt such as atrial septal defect (ASD) and return ventricular septal defect (VSD) and pulmonary duct artery (PDA). According to quality and severity of shunt and the present or absent of PAH place on medical treatment or heart surgery (5-7). B-type natriuretic peptide (BNP) is produced due to ventricular role overload and heart function and is a sensitive and specific indicator for cardiac function (8, 9). BNP serum level is increased in systolic and diastolic dysfunctions as is increased in left to right shunts such as VSD, ASD and PDA (10-14).

The quantity of the shunt no determined always, perfectly by echocardiography and catheterizations are invasive and not always feasible. In the current study, it was evaluated whether the serum level of BNP would be useful to measure the quantity of the shunt and the systolic pulmonary pressure (15-19).
Our aim was to provide a guide for starting the treatment strategy, either medical or surgery, and also prevent the mortality and morbidity such as recurrent pulmonary infections, severe heart failure, failure to thrive and most of all, unnecessary diagnostic and surgical measures.

Materials and Methods
In this descriptive-analytic study, 30 patients including infants, children and adolescents who had gone through echocardiography due to heart murmur, respiratory distress, failure to thrive, recurrent pneumonias and cardiomegaly on the chest x-ray, and who were diagnosed to have VSD, ASD and PDA were entered into our study. The exclusion criteria included those who had heart failure due to cardiomyopathy, primary pulmonary hypertension, systemic hypertension and muscular dystrophies with left to right shunt. Velocity time integral (VTI) measured by Doppler echocardiography at the pulmonary and aortic valves for VSD and ASD, and mitral and tricuspid valves for PDA, the Qp/Qs ratio was detected by the following formula:

\[ Qs = \frac{Qp}{Qs} = \frac{LVOT \times \pi \times LVOT}{2} \]

Based on this formula, the patients were divided into three degrees of severity: 1) Mild (Qp/Qs<1.5), 2) Moderate (1.5>Qp/Qs<2), and 3) Severe (Qp/Qs>2).

After taking 0.5 mL blood and collected in tubes containing K-EDTA, the samples were sent to the laboratory for measuring BNP levels. The outpatients were presented directly to the laboratory where the blood samples was taken. Then the serum separated by centrifuging at the speed of 3500 cycles/second, and were kept at -20 degrees centigrade before measuring the BNP level.

The BNP serum level was measured by BNP triage kits capable of detecting 20-1300 pg/mL of the substance through "fluorescence immunoassay." Finally the BNP level was compared with the quantity of left to right shunt (Qp/Qs) and the systolic pulmonary pressure and the correlation was evaluated among the three items.

Before starting the study, all the steps were described completely for the parents and the patients entered into the study after their parents consent. No extra charge was considered for the patients throughout the study. In addition, no damage happened for them and even the related samples were taken at the same time with others. The patients were allowed to leave the study any time they wanted. It must be pointed out that all the files were kept confidential.

Statistical Analysis
The data were evaluated using descriptive statistical methods (mean ± standard error [SE]), incidence, percentage, and mean differential test in independent groups for quantitative variables and chi-square test for qualitative variables. Also we used box-and-whisker plots for demonstrating the distribution of the data in the subgroups. The statistical analysis of the data were done using SPSS 17. The P value <0.05 was considered, statistically significant.

Results
Results of study demonstrated from the 30 evaluated patients, 43.3% (13) were male and 56.7% (17) female. The average age of all the patients was 3.96 ± 0.43 (Max = 9, Min = 0.5). The average age, was 4.42 ± 0.63 (Max = 9, Min = 0.5) and 3.6 ± 0.59 (Max = 9, Min = 0.53), for male and female patients, respectively. There was no significance different between average age and patient numbers between groups (Table 1).

Results of study indicated that there was significant relationship between the BNP level and the left to right shunt in patients with ASD, VSD and PDA (P=0.01). Increasing level of shunt in ASD, VSD and PDA was accompanied with increasing levels of Qp/Qs ratio, systolic PAP and Pro-BNP, which were statistically significant (Table 2, P<0.0001).

| Table 1. Results of the Demographic Variables on the Left-to-Right Shunt Patients |
|----------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                   | ASD             | VSD             | PDA             | P Value         |
| No. of Patients (&)              | 10 (33.3%)      | 10 (33.3%)      | 10 (33.3%)      | -               |
| Age                              | 5 ± 0.64        | 3.9 ± 0.98      | 2.9 ± 0.46      | 0.16            |
| Sex                              | Male            | Female          | Male            | Female          |                      |
|                                  | 4 (40)          | 6 (60)          | 5 (50)          | 5 (50)          | 0.87                |
| Weight                           | 17.4 ± 1.41     | 13.9 ± 2.26     | 11.8 ± 1.01     | 0.07            |

Abbreviations: VSD, ventricular septal defect; ASD, atrial septal defect; PDA, pulmonary duct artery.
Table 2. Results of the Shunt in Patients With Left-to-Right Shunt Based on serum Pro-BNP and the Qp/Qs

<table>
<thead>
<tr>
<th>Left-to-Right Shunt Type</th>
<th>No. of patients</th>
<th>Pro-BNP</th>
<th>Qp/Qs</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASD</td>
<td>10 (33.3)</td>
<td>&lt;0.001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VSD</td>
<td>10 (33.3)</td>
<td>&lt;0.0001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDA</td>
<td>10 (33.3)</td>
<td>&lt;0.0001*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: BNP, B-type natriuretic peptide; P = P value mild shunt; P = P value moderate shunt; P = P value sever shunt.

Table 3. Results of the Shunt and the Final Diagnosis Based on Serum Pro-BNP, PAP Systolic and the Qp/Qs

<table>
<thead>
<tr>
<th>Qp/Qs</th>
<th>No. of patients</th>
<th>Pro-BNP</th>
<th>P value</th>
<th>Systolic PAP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.5</td>
<td>6 (20)</td>
<td>&lt;0.0001*</td>
<td></td>
<td></td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>1.5-2</td>
<td>16 (53.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>8 (26.7)</td>
<td>&lt;0.0001*</td>
<td></td>
<td></td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

Abbreviation: PAP, pulmonary artery purser; P = P value mild shunt; P = P value moderate shunt; P = P value sever shunt.

Table 4. The Relationship Between Systolic PAP, Left-To-Right Shunt

<table>
<thead>
<tr>
<th>Qp/Qs</th>
<th>No. of patients</th>
<th>Pro-BNP</th>
<th>P value</th>
<th>PAP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.5</td>
<td>6 (20)</td>
<td>0.06*</td>
<td></td>
<td>0.18*</td>
<td></td>
</tr>
<tr>
<td>1.5-2</td>
<td>16 (53.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>8 (26.7)</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Abbreviations: VSD, ventricular septal defect; ASD, atrial septal defect; PDA, pulmonary duct artery; PAP, pulmonary artery purser; P = P value mild shunt; P = P value moderate shunt; P = P value sever shunt.

Discussion

Improvements in the diagnosis of CHD and its surgical and medical management have led to a development of PAH, and particularly Eisenmenger syndrome, in these patients is associated with increased morbidity and mortality. There is increasing evidence of the benefits of PAH-specific therapy in PAH-CHD significant increase in the number of patients surviving into adulthood (1,2,5).

Open-heart surgery has a significant risk for cardiac dysfunction. In children, no precise surgery method exists currently to decrease preoperative risks of cardiac surgery. The preoperative evaluation of the blood markers in patients would be a quantitative, cost-effective, time-efficient method to decrease preoperative risks of cardiac surgery. Since the quantity of the shunt is not always determined perfectly by echocardiography and additionally catheterizations are invasive and not always feasible, we evaluate the serum level of BNP to measure the quantity of the shunt and the systolic pulmonary pressure.

BNP in response to cardiac volume load will secreted into the circulation and causing diuresis, natriuresis and vasodilation, in addition, its secretion causes renin-aldosterone system and sympathetic activity inhibition (21). BNP levels will be elevated in serum of congestive heart failure patients (22). Recently, in adults cardiac dysfunction, BNP was known as sensitive biochemical marker (23). In both systolic and diastolic dysfunction BNP was play an important role as a sensitive marker (24), and its levels indicate the response to therapy (24-26). It is believed that the increase of BNP following impairment of left ventricular systolic or diastolic function causes to left ventricular wall stretch. In addition, BNP levels elevation may also resulted directly from cardiac ischemia (27).

It was demonstrated that in the patients with three different types CHD, the levels of NT-proBNP was very high (28). It was demonstrated that BNP levels in adult patients which was scheduled for open-heart surgery, was elevated significantly (29). In adult patients with cyanotic CHD,
contrarily to reduce of body water and low atrial pressure the levels of BNP have been elevated (28). It has been indicated there was direct relationship between hypoxia and BNP secretion stimulation (30). It is appear that the BNP levels is an indicator of the severity of symptoms of heart failure and the cardiac dysfunction (31,32). Researchers was demonstrated in cardiac mortality of patients with chronic CHF, levels of BNP is more predictive and additionally could provide prognostic information in disease determination (33). It was demonstrated that the BNP levels in the blood of patients with CHF was increase significantly in comparison to control patients and they were stated that the 80 pg/mL blood concentration of BNP, will be accurately predicate of the CHF (95%) (34).

Our results indicated that the increasing level of shunt in ASD, VSD and PDA directly lead to increase levels of Qp/Qs ratio, systolic PAP and pro-BNP. In addition, there was a significant correlation between pro-BNP and BNP level and increasing Qp/Qs ratio lead to pro-BNP and systolic PAP increase significantly. Finally results of study indicated in patients with a Qp/Qs > 1.5, the cut-off point for BNP level was 36.95 pg/mL, with specificity and sensitivity of 83.3% and 100%. Therefore BNP ≥ 36.95 pg/mL is helpful for determining patients who need interventions.

**Conclusion**

The systolic pulmonary pressure was correlated, echocardiographically, to the pro-BNP serum level and the quantity of Qp/Qs ratio. Therefore, in patients with the PA pressure which not measurable for any reason, evaluation of serum BNP could be useful. Therefore early detection of quality and sensitivity of shunt and PAH and appropriate on time intervention reduced, pulmonary resistant in this group.

**Ethical Issues**

This study was performed after approving by the ethics committee of Tabriz University of Medical Sciences based on Declaration of Helsinki. Also, written informed consent was obtained from the patients.

**Conflict of Interests**

The authors declare that there is no potential conflicting interest for this study.

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**References**


