

N-Terminal pro-Brain Natriuretic Peptide in decompensated ventricular septal defect

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Abstract

Introduction: B-type natriuretic peptide (BNP) is a cardiac neurohormone secreted predominantly from the ventricles in response to increased ventricular pressure and volume overloads. There is little information available concerning plasma concentrations of BNP in children with ventricular septal defect (VSD), the most common congenital heart disease. The aim of the present study is to determine the plasma concentrations of NT-ProBNP in VSD patients presenting with cardiac decompensation and to correlate the level of NT-pro BNP with their clinical and echocardiography data.

Material and methods: NT-proBNP was measured in forty five ventricular septal defects patients presenting with cardiac decompensation of various Ross Scores and the results were compared to thirty age and sex matched control group. The NT-proBNP level correlated with clinical and echocardiography data.

Results: The mean value of NT-proBNP was significantly higher in patients with mild/moderate symptoms [Ross Class 2 and 3] (mean: 52.8 ± 12.5 pg/ml), and patients with severe symptoms [Ross Class 4] (mean: 92.2 ± 6.9 pg/ml) compared to the control group, (mean 14.7 ± 3.6 pg/ml), p value < 0.0001 . There was a positive correlation between Plasma NT-PROBNP level and left atrial dimension, left ventricular end diastolic dimension, pulmonary artery pressure, fractional shortening and weight affection with $p < 0.01$.

Conclusions: NT-proBNP is elevated in VSDs with cardiac decompensation, it is correlated to clinical score and echocardiography parameters. It reflects pressure and volume loads to the pulmonary artery and right ventricle and may help to identify children with VSD and pulmonary hypertension that demands early intervention.

Key words: ventricular septal defect, NT-proBNP, cardiac decompensation.

Introduction

B-type natriuretic peptide (BNP) is an endogenous peptide hormone mainly secreted by the cardiac ventricles in response to increased wall stress [1, 2].

It is synthesized as preprohormone, consisting of 108 amino acids; processing releases the biologically active 32-amino acid peptide and an amino-terminal fragment (NT-PROBNP) [3, 4]. NT-proBNP is a sensitive and specific marker of ventricular dysfunction [5-7].

As NT-proBNP is more stable structure compared with BNP in whole blood for more than 24 h at 20°C 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 [8-10].

NT-proBNP plays an important role in the regulation of extracellular fluid volume and blood pressure. It induces natriuresis, diuresis, and arterial, venous vasodilatation and specifically acts to counter the effects of the renin-angiotensin-aldosterone system. It allows the heart to participate in the regulation of vascular tone and extracellular volume status [11].

There is little information available concerning plasma concentrations of BNP in children with ventricular septal defect (VSD), the most common congenital heart disease.

The aim of the present study is to determine the plasma concentrations of NT-proBNP in ventricular septal defects patients presenting with cardiac decompensation and to correlate the level of NT-pro BNP with their clinical and echocardiography data.

Material and methods

Patients

Forty five patients were enrolled in the study (27 female and 18 male) (group I), their age ranged from 3 months to 36 months (mean 19.5 months), they had VSD as a primary cardiac lesion who were

admitted in the Pediatric, Cardiology in-patient Departments of the Faculty of Medicine, Cairo University and National Heart Institute for cardiac decompensation management. A modified scoring system described first by Ross [12] for infants with left-to-right shunt and modified by Reithmann *et al.* [13] and L  er *et al.* [14] was used for clinical evaluation of the patients. Two physicians independently graded the following variables: diaphoresis, tachypnea, breathing with abdominal retractions, respiratory rate, heart rate, and hepatomegaly. The scores were then added and the mean of the two scores was taken. These symptoms of CHF were graded on a scale of 0, 1, or 2 points according to the severity. The sum of all points was added up to form the clinical score (range: 0-12 points). A higher score corresponds to more severe symptoms of heart failure. Patients with a score of ≥ 1 point were included in the study (Table I). A verbal consent was taken from the parents of the children.

Of the 45 VSD patients in the group I, It was found that 4 patients were in Ross class 1 asymptomatic patient (group IA), 20 patients were in Ross class 2 and 3 with mild to moderate symptoms (group IB) and 21 patients were in Ross class 4 with severe symptoms (group IC).

Patients were thoroughly evaluated through history taking, examination, ECG, X-ray chest and echocardiography. No patients showed significant ventricular outflow obstruction with pressure gradient ≥ 10 mm Hg, or significant aortic regurgitation \geq grade 3.

All children had normal renal function as assessed by serum concentration of creatinine, normal serum electrolytes, normal blood sugar and normal liver function. Demographic and clinical characteristics of the 45 VSD patients with cardiac decompensation shown in (Table II).

Echocardiography evaluation

Transthoracic complete M-mode, two-dimensional and Doppler (pulsed-wave, continuous-wave and color) echocardiography was performed obtained in the Parasternal long-axis view, left ventricular (LV) end-systolic, end-diastolic and left atrial dimension were measured to all enrolled patients at rest using Sonos 5500 ultrasound system (HP Hewlett Packard), with a 5 MHz transducer for children.

Ejection fraction and fractional shortening of the left ventricle were estimated according to the guidelines of the American Society of Echocardiography [15]. The global systolic function was considered abnormal if the ejection fraction was less than 55% and the fractional shortening was below 30% [16].

Table I. Ross's Clinical Score for cardiac decompensation

Score (points)	0	1	2
History			
Diaphoresis	Head only	Head and body during exercise	Head and body at rest
Tachypnea	Rare	Several times	Frequent
Physical examination			
Breathing	Normal	Retraction	Dyspnea
RR (respiration/min)			
0-1 y	< 50	50-60	> 60
1-6 y	< 35	35-45	> 45
7-10 y	< 25	25-35	> 35
11-14 y	< 18	18-28	> 28
HR (beats/min)			
0-1 y	< 160	160-170	> 170
1-6 y	< 105	105-115	> 115
7-10 y	< 90	90-100	> 100
11-14 y	< 80	80-90	> 90
Hepatomegaly (liver edge from right costal margin)	< 2 cm	2-3 cm	> 3 cm

Ross IA = 1-3 points

Ross IB = 4-8 points

Ross IC = 9-12 points

Ventricular septal defect location and size were identified in different windows parasternal and subcostal views, shunt volume (restrictive or unrestrictive VSD) indirectly detected by measuring the dimension of left atrium and left ventricular end diastolic dimension [17].

Pulmonary artery pressure was measured in VSD patients in absence of right and left ventricular outflow obstruction, using a Doppler recording of peak velocity across ventricular septum, peak velocity pressure gradient between right and left ventricles is calculated using the Bernoulli equation:

$$RVSP = SBP - 4 (VSD)^2$$

while RVSP – right ventricular systolic pressure, SBP – systemic blood pressure, that modified according different age of the patients.

Patients had pulmonary hypertension if estimated RVSP more than 25 mm Hg [18].

Control group

30 (17 female and 13 boys) (group II) patients, their age ranged from 6 months to 36 months (mean 22 months) as a control non cardiac group. These children were enrolled from outpatients clinics (no cardiac symptoms or signs) or who were admitted for non cardiac reasons, any patient with electrolyte disturbances or impaired renal or liver function were excluded.

BNP measurements

Blood for peptide levels was taken from enrolled studied subjects via peripheral venous puncture in the supine position and collected in tubes containing EDTA. Plasma was separated and stored at (-20°C). NT-proBNP was measured by electrochemiluminescence immunoassay with the Elecsys system 101/2010 (Roche, Mannheim, Germany), Elecsys proBNP contains polyclonal antibodies that recognize epitopes located in the Nterminal part (1-76) of proBNP (1-108). The assay range is 5-35,000 pg/ml and higher value were obtained by dilution. No cross-reactivity was reported with BNP.

Statistical analysis

Numerical data was expressed as a mean \pm standard deviation. Comparison of means for changes in variables was performed using the paired Student's *t*-test, while the non-paired Student's *t*-test was used for numeric comparison between two different groups. ANOVA (analysis of variance) was used to compare between more than two numeric groups.

Correlations were performed using the Pearson bivariate correlation. Non-numeric data was compared using χ^2 are test, when two groups were compared. ANCOVA (analysis of co-variance) was used when more than 2 groups were compared.

A *p* value of < 0.05 was considered significant in our statistical analysis. All calculations were performed using an IBM-compatible personal computer using the SPSS, STATISTICA and EXCEL programs for analysis.

Results

Our patient and control groups were both matched regarding the age and sex. As regards the weight of our population, we found that there is a lower body weight the more severe the heart failure was, group 1A had a mean weight 10 \pm 1.5 kg, group 1B had a mean weight of 8 \pm 1 kg, while group 1C had a mean weight of 7 \pm 1 kg. This is compared to the weight of the control group II which was 12 \pm 2 kg.

Although there was no significant difference in weight between group IA and group II (*p* = 0.06), there was a significant weight difference (*p* = 0.0001) between groups IB, IC and group II. This gives an indication of the severity of heart failure in groups 1B and 1C. There is also a significant difference between group IB and 1C (*p* = 0.0027), and between groups IA versus group IB and 1C (*p* = 0.003). Thus, the more severe the heart failure the less the weight gain.

Table II. Demographic and clinical characteristics of the patient population

Parameter	Characteristics
Age	3 months to 36 months (mean 19.5 months)
Sex	27 girls and 18 boys
Type of VSD:	
• Perimembranous	35 (77.7%)
• Outlet	8 (17.7%)
• Others	2 (4.4%)
Size:	
• Unrestrictive	41 (91.1%)
• Restrictive	4 (8.8%)
Ross stage:	
• I	4 (8.8%)
• II and III	21 (46.6%)
• IV	20 (44.4%)
Pulmonary artery pressure:	
• PHT	30 (66.6%)
• No PHT	15 (33.3%)
Medical treatment:	
• Diuretics	45 (100%)
• ACE inhibitors	41 (91.1%)
• Inotropic support	33 (73.3%)
Associated defects:	
• ASD or PFO	10 (22.2%)
• PDA	5 (11.1%)

Echocardiographic data

The Table III shows the different echocardiographic findings in our patient population.

What can be seen, is that the bigger the size of the VSD, the higher the Ross Score, the more severe the heart failure, and thus the larger the left atrial (LA) and left ventricular end-diastolic dimensions (LVED), the higher the pulmonary artery pressure (PAP) and the lower the fractional shortening (FS).

Plasma NT-PROBNP levels in control group

Plasma NT-PROBNP levels in 30 control children ranged between 6 and 22 pg/ml (mean: 14.7 ±3.6 pg/ml) (Figure 1).

Plasma NT-PROBNP levels in VSD patients with cardiac decompensation

Of 45 VSD patients in the group I, it was found that 4 patients were in Ross class 1 asymptomatic patient (group IA) who had a plasma NT-proBNP levels ranging between 33 and 36 pg/ml (mean: 34.5 ±1.29 pg/ml), 20 patients were in Ross class 2 and 3; with mild to moderate symptoms (group IB),

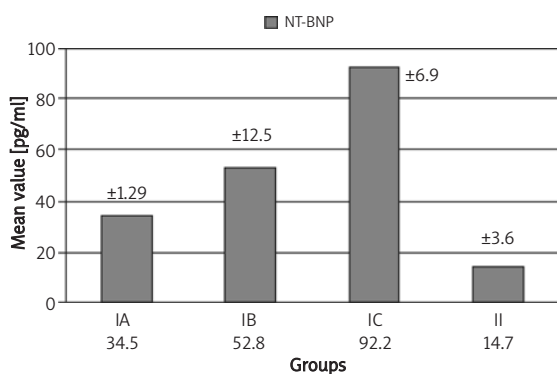


Figure 1. Plasma NT-proBNP levels in control and VSD patients with cardiac decompensation

there plasma NT-proBNP levels ranged between 33 and 78 pg/ml (mean: 52.8 ±12.5 pg/ml). Twenty one patients were in Ross class 4 with severe symptoms (group IC) patients they had a plasma NT-proBNP levels ranged between 78 and 100 pg/ml (mean: 92.2 ±6.9 pg/ml) (Figure 1).

We found that mean value of NT-proBNP was significantly higher in patients (group IB: mean: 52.8 ±12.5 pg/ml, and group IC: mean: 92.2 ±6.9 pg/ml) than the control group: mean: 14.7 ±3.6 pg/ml (p value < 0.0001).

Correlation between plasma NT-PROBNP levels and echocardiography data and clinical score in VSD patients with cardiac decompensation

There is positive correlation between plasma NT-PROBNP levels and increase LA dimension ($r = 0.568$, $p < 0.01$) (Figure 2). There is also a positive correlation between plasma NT-PROBNP levels and increase LVEDD dimension ($r = 0.520$, $p < 0.01$) (Figure 3). There is a positive correlation between plasma NT-proBNP levels and pulmonary artery pressure ($r = 0.727$, $p < 0.001$) (Figure 4). There is positive correlation between plasma NT-proBNP levels and low FS% ($r = -0.890$, $p < 0.01$) (Figure 5). There is also a positive correlation between plasma NT-PROBNP levels and under weight/age ($r = -0.743$, $p < 0.01$).

Discussion

Biochemical markers have become important diagnostic tools in heart disease. The BNP is secreted from the heart in response to volume or pressure overload, consistent with cardiac failure [19]. NT-proBNP has been found to be comparable to BNP as a marker for cardiac disease [20].

This study showed elevation in NT-proBNP level in VSD patient with Ross class I (group IA), consistent with other studies of BNP values in congenital heart disease that indicate that even asymptomatic patients will have mild elevations of BNP levels compared with a normal population

Table III. Echocardiographic findings in our patient population

Group	IA (n = 4)	IB (n = 20)	IC (n = 21)	II (n = 30)	p value
VSD site	Peri-memberanous (n = 4)	Peri-memberanous (n = 18) Outlet (n = 2)	Peri-memberanous (n = 15) Outlet (n = 5) Others (n = 1)		
VSD size [mm]	3 ±0.5	5 ±1.6	8 ±2		0.0001
LA dimension [cm]	1.62 ±0.05	1.87 ±0.04	2 ±0.08	1.7 ±0.23	0.0001
LVED dimension [cm]	2.6 ±0.3	2.95 ±0.2	2.95 ±0.2	2.5 ±0.3	0.0001
Mean PAP [mm Hg]	24 ±0.8	32 ±1.4	36 ±2.1	23 ±1.5	0.0001
FS (%)	29.2 ±0.5	28.2 ±0.6	25.9 ±1.1	32.5 ±1.2	0.0001

of children. These findings have relevance when using NT-proBNP levels to discriminate between pulmonary and cardiac causes for tachypnea and dyspnea [21].

Also our study found in the decompensated VSD patients a higher plasma NT-proBNP concentrations than control children (with p value < 0.0001) and that NT-proBNP concentrations correlated with the severity of clinical symptoms, higher value with Ross score 4 (with p value < 0.0001).

That could be explained as excessive elevation of NT-proBNP levels results from a surge in NTproBNP production in reaction to the acute muscle dysfunction and increased wall tension. It also may result from myocyte injury and death, resulting in the release of excessive amounts of the prohormone of BNP. The transient nature of the NT-proBNP surge also supports the theory that the extremely high levels are associated with acute cardiac injury [22].

Furthermore, our study showed, a positive correlation between low fraction shortening, increased left atrial dimension, increased left

ventricular end diastolic dimension in children with decompensated VSD and NT-proBNP plasma concentrations (with p value < 0.01). A possible explanation for our finding is that the amount of shunting may cause more significant volume overload of the left atrium and left ventricle, causing an increase in BNP production, that was supported with other studies [23].

Our study showed also a higher pulmonary artery pressure was positively correlated with NT-proBNP plasma concentrations (with p value < 0.01). Pulmonary hypertension produces pressure overload to the right ventricle and subsequent deterioration of the right heart function, 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 BNP [24]. Also Increased BNP in parallel with the degree of pulmonary hypertension in these patients may play an important role in protecting the pulmonary bed from their pulmonary vasodilatory effect [25]. That was supported with other studies [26].

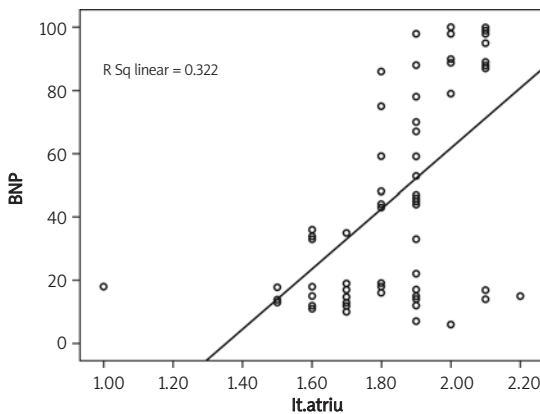


Figure 2. Correlation between the left atrial dimension and the plasma NT-proBNP

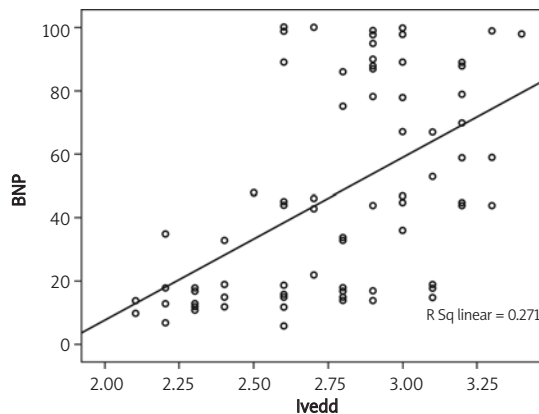


Figure 3. Correlation between plasma NT-proBNP and the left ventricular end-diastolic dimensions

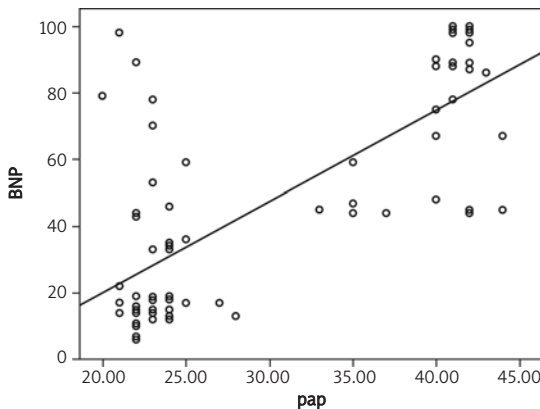


Figure 4. Correlation between plasma NT-proBNP and pulmonary artery pressure

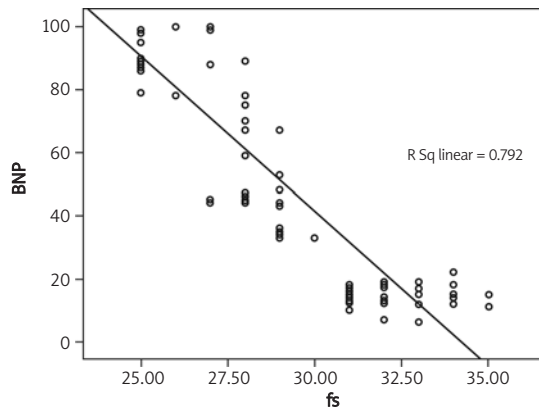


Figure 5. Correlation between fractional shortening and plasma NT-proBNP

The study showed plasma NT-proBNP significantly correlated with the patients' growth failure as expressed by bodyweight; the higher the plasma NT-proBNP and the lower the bodyweight (with p value < 0.01). It could be explained as VSD patient with high left to right shunt was associated with repeated chest infection and deficient intake and failure to weight gain [25].

In the clinical management of patients with VSD, it is important to quantify the shunt size of VSD and identify the patients with VSD and pulmonary hypertension that demands early intervention. Although echocardiography is a standard diagnostic modality and can be clinically useful for these purposes, it relies on sonographers and echocardiographers individual skills. In contrast, the measurement of NT-BNP can be a time efficient, simple and objective screening tool in following up these patients and non invasive compared to cardiac catheterization.

Because of their impact on heart failure diagnosis and management, NT-BNP will make the transition from research to routine application, as did cardiac troponins. HF is an important clinical problem with significant morbidity, mortality, and socioeconomic impact. Early identification is important to initiate appropriate treatment, which can delay disease progression. For primary care physicians, NT-BNP measurement is useful to decide which patient with suspected heart failure warrants further investigation, particularly when assessment of left ventricular function is not readily available, but NT-BNP cannot replace imaging techniques in heart failure diagnosis because the underlying cause of heart failure has to be clarified and these methods provide different information.

However our study was limited as no patient showed apparent Eisenmenger's physiology. In patients with Eisenmenger's physiology, the right ventricle may redirect the blood into left ventricle via VSD, keeping a systemic cardiac output. In this situation, an increased wall stress and a decreased volume load to the right ventricle may counteract the production of NT-BNP. Non of our patients did cardiac catheterization. Also, the small number of patients in group 1A, the asymptomatic group, was a limitation for the statistical analysis of this group.

In conclusion, NT-BNP is elevated in children with VSD and cardiac decompensation, the more severe the decompensation the higher the level of BNP. It reflects pressure and volume loads to the pulmonary artery and right ventricle and may help to identify children with VSD and pulmonary hypertension that demands early intervention.

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