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Plasma Natriuretic Peptides As Predictors of Hemodynamically in Children with Congenital Heart Disease.

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Abstract

Background: *The objects of the study was to investigate the role and importance of N-Terminal Pro-B-Type natriuretic peptide (NT-Pro-BNP) as a biochemical marker in patients with congenital heart disease and to determine if there is any relationship between anthropometric measurements and natriuretic peptide.*

Method: *Forty-five children with CHD (17 cyanotic and 28 acyanotic) and thirty children with normal echocardiography were enrolled in the study. Patients were divided into two groups as cyanotic or acyanotic. Anthropometric measurements including body weight, height, BMI and Z-score(weight) and Z-score(height) and thorough physical examination were recorded on admission. Serum NT-Pro-BNP was also measured*

Results: *Majority of patients in cyanotic and acyanotic groups had tetralogy of fallot and ventricular septal defect, respectively. The mean age was significantly lower in cyanotic patients compared with acyanotic and controls. N-Terminal-Pro-B-Type natriuretic peptide levels were significantly elevated in cyanotic and acyanotic patients compared with controls. N-Terminal-Pro-BNP was negatively correlated with left ventricular ejection fraction among the echocardiographic parameters (p=0.014, r=-0.364). In acyanotic patients, NT-Pro-BNP was positively correlated with shunt ratio (p=0.029, r=0,428) and Systolic pulmonary arterial pressure (p=0.005, r= 0.519) while it was negatively correlated with Z-score (weight) (p=0.044, r=-0.390).*

Conclusion *N-Terminal-pro-BNP is one of essential serum markers for cardiac disease and it could be used to predict the severity and prognosis of CHD as a response to ventricular volume expansion and pressure overload.*

Keywords: *Congenital heart disease, brain natriuretic peptide, anthropometric measurements*.

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Introduction

Congenital heart disease (CHD) is a common cause of childhood morbidity and mortality, occurring in 6–8/1000 live births, with up to 50% of these children requiring open-heart surgery to correct their defect (1,2). Plasma brain-natriuretic peptide (BNP) and its biologically inactive fragment N-terminal pro-BNP (NT-pro-BNP) are essential serum markers of cardiac disease and have been reported to be useful in the diagnosis of pulmonary hypertension (PH) and ventricular dysfunction including isolated diastolic dysfunction and in the assessment of prognosis in heart failure (3,4). These cardiac neurohormones are mainly being secreted from the left and right ventricles as a response to ventricular volume expansion and pressure overload and thus resulted in increased wall tension (5,6). There are many studies showing that in adults, NT-proBNP is an important biomarker for monitoring the severity of cardiac disease and its therapeutic response. However, in children, data remain limited due to smaller numbers and inhomogeneous groups of patients. Early detection of pulmonary PH and ventricular dysfunction in patients with CHD is essential as it leads to substantial morbidity and mortality. Therefore we aimed to determine whether noninvasive biochemical marker can predict the severity of PH and ventricular dysfunction in 45 children with CHD without clinical manifestations of heart failure. We also aimed to determine if natriuretic peptide is related to anthropometric measurements.

Materials and Methods

Patients

Forty five children with CHD (17 cyanotic and 28 acyanotic) and thirty age-gender-Z-scores and BMI matched well-nourished children with normal echocardiography who had applied to University Hospital for routine check-up and had no clinical signs of any illness including cardiovascular heart disease were enrolled in the present study. The study was conducted between 2007 and 2009 at the Department of Pediatrics and Department of Cardiology, Dicle University. The parents of all subjects gave informed consent prior to study entry and the study was conducted in accordance with the Declaration of Helsinki. Patients were excluded from the study if findings showed clinical or laboratory evidence of any infectious or heart failure at the time of blood collection.

Echocardiography

Congenital heart disease was diagnosed by echocardiography (ECHO). Two-dimensional and Doppler echocardiographic examinations were performed by a standart technique using Vingmed System Five machine with a 5-MHz probe. M-mode measurements were taken according to the recommendations of the American Society of Echocardiography (ASE) (7). Standard echocardiographic images were obtained in the parasternal long- and short-axis views, apical 2- and 4-chamber views. Echocardiographic modalities applied included M-mode, two-dimensional (2D) and Doppler studies. Systolic pulmonary arterial pressure (SPAP) was calculated using the modified Bernoulli equation from the tricuspid regurgitation velocity, plus the right atrial pressure. Doppler estimated pulmonary to systemic blood flow ratio (Qp/Qs) was done by conventional (velocity time integral method) method. Left ventricular ejection fraction (LVEF) was calculated using the modified simpson method. Patients were divided into two groups as cyanotic (17) or acyanotic (28) based on the following findings (Table 1). Those having tetralogy of fallot (TOF), transposition of the great vessels (TGV), and tricuspid atresia (TA) were classified as cyanotic and those having ventricular septal defect (VSD), atrial septal defect (ASD), patent ductus arteriosus (PDA), and corrected transposition of the great arteries (c-TGA) classified as acyanotic.

Anthropometric Evaluation

Anthropometric factors such as age, sex, weight, height, body mass index and Z-score were recorded. Body weight was measured with light clothing, in kilograms. Height was measured without shoes in centimeter. Examinations of the children and antropometric measurements were made by the same physician and all anthropometric measurements were recorded as the mean of three measurements. The values were compared with the median age-related World Health Organization (WHO) (8) standards and expressed as Z-scores compared with the standard deviation (SD) of the reference value. Body mass index was calculated as weight in kilograms divided by height in meters squared. Maximum abdominal girth (in cm) was taken as the waist circumference. Waist circumference was considered as a measure of body fat distribution.

Biochemical Analysis

Blood serum samples were taken from patients and control after overnight fasting. Biochemical measurements including serum Alanin amino transferase (ALT) and Aspartate amino transferase (AST) levels, urea and creatinine were determined by autoanalyzer (Abbott Aeroset, Japan).

Measurement of NT-proBNP levels

Peripheral venous blood samples were collected into tubes containing ethylenediamine-tetra-acetic acid (EDTA) for each subject at rest. The samples were centrifuged within 20 minutes at +4◦C. The plasma was stored at –80◦C until analysis. Serum NT-Pro-BNP was measured by a double antibody sandwich technique using electrochemiluminescence immunoassay kit (Elecsys NT-proBNP, Roche Diagnostics, Mannheim, Germany). The results were reported as picogram per milliliter (pg/mL). The clinicians involved in the study were blinded to the NT-pro-BNP values obtained.

Statistical analyses

SPSS 15.0 software package program was employed for the statistical evaluation. The parameter values were all expressed as the mean ± S.D. ANOVA test was used to obtain significant difference among the groups, followed by using post hoc test of Benferroni to obtain pair-wise comparisons. Correlation analyses were carried out using Pearson correlation coefficient. The results were considered significant if the value of p was less than 0.05.

Results

The diagnoses of congenital heart disease for both the cyanotic and acyanotic groups are shown in Table 1. Majority of patients in cyanotic and acyanotic groups had TOF and VSD, respectively. The characteristic features and laboratory findings of the patient and control groups are given in Table 2.

Table 1: Diagnosis of Congenital Heart Disease for Both the Cyanotic and Acyanotic Groups.

Cyanotic Group	**N**	**Acyanotic Group**	**N**
Tetralogy of Fallot	12	Ventricular septal defect	19
Transposition of the great arteries	1	Atrial septal defect	4
Tricuspid atresia	2	Patent ductus arteriosus	1
Transposition of the great arteries and Ventricular septal defect	1	Atrial septal defect and Ventricular septal defect	1
Transposition of the great arteries and Patent ductus arteriosus	1	Atrial septal defect and Ventricular septal defect and Patent ductus arteriosus	1
		Corrected transposition of the great arteries	2
Total	**17**		**28**

The mean age was significantly lower in cyanotic patients compared with acyanotic and controls. No statistically significant differences were found between the groups in terms of gender distribution ($p > 0.05$). Z-scores (weight) and BMI were significantly lower in cyanotic patients compared with acyanotic and controls while Z-score (height) was significantly lower in two patient groups compared with controls.

Table 2: The Characteristic Features and Laboratory Findings of the Patient and Control Groups.

Parameters	**Control** (n=30)	**Cyanotic** (n=17)	**Acyanotic** (n=28)	*P* (ANOVA)
Age (months)	26.1±15.4	16.8±13.7	30.1±20.3	0.045$^{€}$
Sex (F/M)	13/17	9/8	12/16	0.77
BMI	16.8±0.8	15.3±1.4	16.9±1.7	0.0001$^{£€}$
Z core(weight)	0.55±0.27	-2.2±1.2	0.46±0.53	<0.0001$^{\mathbf{£€}}$
Z Score(height)	0.17±0.12	-2.9±1.4	-0.29±0.57	<0.0001$^{\mathbf{£\$€}}$
ALT	18±5	19±7	32±45	0.2
AST	31±	30±6	33±18	0.8
Üre	22±3	23±4	22±4	0.43
Creatin	0.67±0.09	0.65±0.06	0.65±0.07	0.45
NT-ProBNP	64±12	841±465	450±604	<0.0001$^{\mathbf{£\$€}}$
SPAP	15.13±4	27.11±6.3	39.2±8	<0.0001$^{\mathbf{£\$€}}$
LVEF(%)	69±3	62±4	68±4	<0.0001$^{£€}$

P (Bonferroni) < 0.05 for pair-waise comperasion of groups. £: cyanotic with controls, $: acyanotic with controls; €: cyanotic with acyanotic.

Abbreviations; AST: Alanin amino transferaz (ALT), ALT: Aspartat amino transferaz, NT-ProBNP: N-terminal pro-brain natriuretic peptide, LVEF: left ventricular ejection fraction, SPAP: Systolic pulmonary arterial pressure

When groups are compared in terms of echocardiographic parameters, left ventricular ejection fraction (LVEF) was significantly lower in cyanotic patients.. N-terminal-Pro-BNP levels were significantly elevated in both patient groups compared with controls, still higher in the cyanotic group compared with acyanotic. When groups are compared in terms of biochemical values such as ALT, AST, urea and creatinine, they were in normal ranges in all groups. Pearson's correlation analysis indicated that NT-Pro-BNP was not significantly correlated with age, SPAP and anthropometric parameters in patients with CHD.

Table 3: Comparison of NT-ProBNP and a Pulmonary Artery Pressure and Shunt Ratio in Acyanotic Patients

Parameters	p	r
SPAP	0.005	0.519
Shunt ratio	0.029	0.428
Z score(weight)	0.044	-0.390

SPAP : Systolic pulmonary artery pressure

However, It was found that NT-Pro-BNP was negatively correlated with LVEF among the echocardiographic parameters (p=0.014, r=-0.364). In acyanotic patients, it was found that NT-Pro-BNP was positively correlated with shunt ratio (p=0.029, r=0,428) and SPAP (p=0.005, r= 0.519) while it was negatively correlated with Z-score (weight) (p=0.044, r=-0.390).

Discussion

The recognition of heart disease in children can be challenging, because children often have a restricted of presenting signs and symptoms. The diagnosis of heart disease can be especially difficult where institutions children applied do not specialize in pediatric health care and do not have ready access to pediatric echocardiography as well. Pediatric patients would benefit from plasma NT-pro-BNP level in the recognition of heart disease even in the absence of significant clinical evidence of heart failure. The serum level of BNP, which is a neurohormone that plays a key role in volume hemostasis, is a sensitive sign of ventricular dysfunction in symptomatic and asymptomatic patients and is closely related to the severity of dysfunction (9-11).

Brain natriuretic peptide levels measured in cases without cardiovascular disease or cardiac dysfunction show different ranges and hence it has not been well established. Although a few studies imply that circulating natriuretic peptide levels may be influenced by age and gender (12-15) the extent of these influences and their potential importance in the elucidation of BNP is sill unclear. Similar contradicting arguments exist in patients with cardiovascular diseases (16). In our study, the mean age was significantly lower in cyanotic patients compared with acyanotic and controls. This might be ascribed to earlier realization of cyanosis in children by parents and consequently earlier admission to the hospital. In the present study, NT-pro-BNP levels were lower in controls and markedly elevated in pediatric patients with CHD. NT-pro-BNP levels were also found significantly higher in cyanotic group than acyanotic and control groups. This may be attributed to the fact that both left and right ventricular functions are affected by pressure overload in cyanotic patients since most of them had TOF. The present study indicated that plasma NT-pro-BNP level in children with CHD is influenced by LVEF but not by age, gender and anthropometric

measurements. Although some reports indicated that BNP was negatively correlated with BMI (17,18), a correlation was not found between these parameters in this study. Despite the absence of the correlation, BMI levels were significantly lower in cyanotic patients who had the highest NT-Pro-BNP levels. Besides, to our knowledge the direct correlation of BNP with body weight was not reported in the literature in CHD patients with exception of few reports on the correlation of BNP with obesity in heart failure patients (19) and on the correlation of BNP with malnutrition inflammatory score (MIS) in chronic hemodialysis patients with overt cardiovascular disease (20). We found that NT-Pro-BNP was negatively correlated with Z-scores (weight), particularly in acyanotic patients. This raises thoughts that nutrition deficiency may worsen the clinical status of these patients. Studies by Kjaer et al (21) and Wei et al (22) presented a negative correlation between LVEF and mean BNP levels. A similar correlation was also found in our study. Decrease in LVEF increases the tension in the ventricular wall and thus results in increase in the mean BNP levels with a parallel increase in wall tension. Systolic pulmonary artery pressure was significantly higher in acyanotic patients compared with cyanotic and controls. We demonstrated that the concentration of brain natriuretic peptide was higher in the plasma from children with pulmonary hypertension (PH) than that in controls. Besides it was found that BNP was positively correlated with shunt ratio and SPAP in these patients. This was associated with the volume overload in left and/or right ventricular. Elevated NT-Pro-BNP levels in cyanotic patients may be ascribed to the right ventricular pressure overload.

Clinical implications.
Echocardiography is considered as a reliable, relatively well validated tool for the noninvasive assessment of pulmonary artery pressure in daily clinical practice (23). Right heart catheterization is impractical as a general screening tool as it requires hospitalization and experience and is not free of complications (24,25). The findings of our study imply that a combined noninvasive strategy including echocardiography and measurements of NT-pro-BNP levels may be effective to identify high-risk patients for further investigation with cardiac catheterization and timing of operation, thus reducing the need for unnecessary invasive procedures. By using these widely accessible and easily obtained parameters, physicians from nontertiary centers can refer patients for further assessment and diagnostic evaluation in tertiary referral centers.

Limitations
This is a single-center, cross-sectional study covering a small number of patients. Moreover, the main limitation of this study is the lack of application of catheterization in these patients.

In conclusion, NT-pro-BNP is one of essential serum markers for cardiac disease and it could be used to predict the severity and prognosis of CHD as a response to ventricular volume expansion and pressure overload. In addition, it may be used as predictors of elevated pulmonary artery pressure in these patients. However, further studies are required in order to establish these new markers in the routine clinical practice in monitoring and follow-up of these patients.

Disclosures
No conflicts to disclose

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