http:// ijp.mums.ac.ir
Original Article (Pages: 3615-3626)

Evaluation of Brain Natriuretic Peptide Plasma Levels in Children with Congenital Heart Diseases

Noor Mohammad Noori[1], *Alireza Teimouri[1], Iraj Shahramian[2], Samaneh Akhavan Sales[3]

[1]Children and Adolescent Health Research Center, Zahedan University of Medical Sciences, Zahedan- Iran.
[2]Department of Pediatric, Faculty of Medicine, Zabol University of Medical Sciences, Zabol, Iran.
[3]Department of Pediatric, Faculty of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran.

Abstract

Background

Since the studies about the diagnostic value of Brain Natriuretic Peptide (BNP) in determining ventricular dysfunction in patients with Congenital Heart Diseases (CHD) is low and early detection of heart dysfunction from the mortality and morbidity rates decrease, this study aimed to assess BNP early diagnose of cardiac function in children with CHD.

Materials and Methods

This study was performed on children with CHD (n=100, case group) and healthy children (n=50, control group). Severity of heart failure modified Ross classification system was used for grouping patients in four classes. For all participants, height, weight and head circumference were measured. From all participants 3cc blood samples were taken and after separation, the plasma placed at temperature of -80° C. After collecting all samples they were in testing using an ELISA, BNP kit. For control group, statistical methods used to generate right venrticle (RV) and pulmonary artery (PA) pressure randomly. The data were analyzed using SPSS-15 with 0.05 for the level of significant.

Results

The results of the study showed that among cyanotic patients 68.19% were boys when these proportions were 51.28% and 60% in cyanotic patients and control respectively. Also, RV, HB and O2 saturation (O_2Sat) had different mean significantly accordance with the severity of disease. BNP had correlation with PA ($P<0.05$ and $r=021$) and PA had correlation with pulmonary-to-systemic blood flow ratio (Qp/Qs) ratio ($P<0.05$ and $r=0.45$), resistance (Rp/Rs) ratio ($P<0.05$ and $r=0.59$), RV ($P<0.001$ and $r=0.28$) and O2Sat ($P<0.05$ and $r=0.36$) respectively.

Conclusion

The results of the present study showed that the BNP levels in children with CHD compared with healthy children increased; and the positive correlation was observed between the pulmonary hypertension and BNP level.

Key Words: BNP, Children, CHD, Diagnostic, Iran.

*Please cite this article as: Noori NM, Teimouri A, Shahramian I, Akhavan Sales S. Evaluation of Brain Natriuretic Peptide Plasma Levels in Children with Congenital Heart Diseases. Int J Pediatr 2016; 4(10): 3615-26. DOI:

Corresponding Author:

Alireza Teimouri: M.Phil, Ph.D in Demography, Children and Adolescent Health Research Center, Zahedan University of Medical Sciences, Zahedan, Iran.

Email: Alirezateimouri260@gmail.com

Received date Jul 23, 2016; Accepted date Aug 22, 2016

1- INTRODUCTION

Congenital heart disease (CHD) is a leading cause of death in the first year of life. CHD occurs in 8 of 1000 live birth and the early detection shows a fall in mortality rate (1).

Natriuretic Peptide (NP) refers to a peptide which induces natriuresis. NP has been considered as a diagnostic biomarker for cardiovascular diseases and it contains of B-type natriuretic peptide (BNP), prohormone brain natriuretic peptide (proBNP), and amino-terminal pro-BNP (NT-proBNP). Recently, BNP levels were found to be reliable test for the diagnosis of underlying cardiovascular disease in infants with respiratory distress. ProBNP (108 amino acids) has been shown to be released from ventricular myocardium in heart failure (HF) (2, 3).

In comparison, NT-proBNP is more stable and has a longer half-life about 2 hours in compare to BNP which is 20 minutes. Elevation of plasma BNP has been described with ventricular dysfunction and cardiomyopathy or CHD in children and young adults (4).

BNP is a 32 amino acid polypeptide that secreted from the ventricles of heart in response to excess stretching of myocyte in heart (5). NP has a strong role in a long-term regulation of sodium, water balance, blood volume and arterial pressure in human's body. BNP physiological activities are similar to Atria Natriuretic Peptide (ANP) and included of a reduction in systemic vascular resistance and central venous pressure by urinary excretion of sodium (6).

BNP is a cardiac hormone with diuretic, natriuretic, vasodilatory and anti-fibrotic properties. It has been accepted as a marker in the assessment of left- and right ventricular function and heart failure. BNP is mainly secreted by cardiac myocytes and main stimuli for secretion is volume expansion or pressure load (7). BNP levels had a close association with left ventricular function and does not reflect the ventricular volume overload or pressure overload directly. BNP is a reflection of ventricular volume overload. The normal level of BNP cannot eliminate the role of pathology but can be a reflection of the compensated cardiac status.

A negative correlation has been observed between BNP levels and left ventricular systolic function. Increasing the BNP levels is associated with a decrease in left ventricular fractional shortening. In children with left to right shunt, an increase of BNP correlated with shunt volume, right ventricular systolic pressure, mean pulmonary artery pressure and pulmonary vascular resistance (8).

Severe increasing in the left ventricular volume occurs in neonates due to changing in the fetal blood circulation. It could be considered in regarding of umbilical cord starting, closing ductus venosus, and closing patent ductus arteriosus (PDA) and foramen ovale.

BNP has the highest level at birth, but starting to decrease during the first week of life and will reach to the level that is lower than adults after two weeks (9).

A significant correlation has been reported between hemodynamic parameters of right ventricle and plasma BNP levels in children with right ventricular volume overload. This abnormality is due to the different types of CHD (10). Mean of BNP in children with heart failure is much higher (110 pg/ml) compared to normal children (20-40 pg/ml). There is a moderate correlation between BNP and left ventricular ejection fraction, but there is not a significant correlation between BNP levels and ventricular dimension (11).

A comparison between children with left ventricle volume overload and children with overload volume on right ventricle showed that if when the severity of volume

overload is same in both groups, the ventricular morphology and severity of volume overload can affect on natriuretic peptides levels (12). Since an increase in BNP is associated with severity of heart failure and defined as a useful biomarker for the diagnosis and prognosis of heart failure (8) and the number of studies about the diagnostic value of BNP in determining ventricular dysfunction is less and the early detection of heart dysfunction from the mortality and morbidity rates decrease in patients with CHD, the present study aimed to assess the BNP using in early diagnose of heart function in CHD patients.

2- MATERIALS AND METHODS

2-1. Study Design and Population

This case-control study was performed in two hospitals belong to the Zahedan University of Medical Sciences (ZaUMS) , Iran from Jan 2014 to Dec 2015. The study conducted on 150 participants with the distribution of 100 and 50 for case (congenital heart disease patients) and control respectively. The participants were selected randomly from those treated in the hospitals and from children who referred for the routine check up to the Ali Asghar or Ali-ebne-Abitalib hospitals. The participant's age was ranged from 6 months to 18 years.

2-2. Methods and measuring tests

The severity of heart failure modified Ross classification system was used for grouping patients in four classes. Class I refers to the patients with no limitations or symptoms, class II refers to the mild tachypnea or diaphoresis with feedings in infants, dyspnea at exertion in older children; no growth failure, class III refers to the marked tachypnea or diaphoresis with feedings or exertion and prolonged feeding times with growth failure from CHF and class IV refers to the symptomatic at rest with tachypnea, retractions, grunting, or diaphoresis (13). For all participants height, weight and head circumference were measured by trained pediatric resident. Height for children under 2 years measured in sleeping position with the amount of logs scaled and for the rest in the standing position. Weight was measured using a special Mika scale (made in Japan) for children under 2 years and by Rasa scale (made in Iran) for the rest. Head circumference was measured by standard tape measure. Body mass index (BMI) was calculated using the direction bellow.

BMI= (Weight in Kilograms) / (Height in Meters)^2.

Then 3cc blood sample was taken from the patients and controls by single resident. After separation, the plasma placed at temperature of -80 c and they were in testing using an ELISA BNP Kit.

2-3. Inclusion and exclusion criteria

Congenital heart diseases patients aged from 6 months to 18 years were entered to the study to compare with same age range healthy children. Those who had other diseases such as chronic metabolic diseases, endocrine hypertension and serious infections were excluded from the study.

2-4. Ethical considerations

All the children's parents received written information about the aims of the study. Consent letter gave to parents for taking agreement. The study was in accordance with the ethical standards for human experimentation and approved by the Research Deputy (RD) ethics committee of the ZaUMS, Iran.

2-5. Data analysis

Statistical analysis was performed with SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA). Statistical differences between patient groups and healthy subjects were evaluated by student t-test

and ANOVA. Correlations were evaluated by Pearson's correlation test. Statistical significance was accepted with a P-value less than 0.05.

3- RESULTS

This case-control study was consisted of 100 children with CHD and 50 healthy. The sex distribution was shown in **Table.1**. It was observed that among cyanotic patients 68.19% were boys; when these proportions were 51.2% and 60% in acyanotic and control respectively. Results showed that the sex ratio for cyanotic, acyanotic and controls were 2.14, 1.05 and 1.5 respectively in the given order.

Demographic factors and laboratory measures were compared in groups. The results of independent t- test showed that BNP had different means higher in controls (P=006), RV pressure had higher mean in case (P<0.001), PA had higher mean in case (P<0.001), hemoglobin had higher mean in case (P<0.001) and oxygen saturation had higher mean in case (P<0.001) (**Table.2**).

Table.3 showed the demographic factors and measures of laboratory. These factors were compared in cyanotic, acyantoc and control groups. The results of ANOVA test showed that, BNP (P=0.0128), RV pressure (P<0.001), PA pressure (P<0.001), HB (P<0.001) and oxygen saturation (P<0.001) had different means.

A post hoc Tukey test showed all significant paired groups in each variable.

For BNP, pair of acyanotic and controls, for RV pressure all pairs, for PH pressure pair of cyanotic and acyanotic and for oxygen saturation pair of acyanotic and control were significant.

Age and laboratory data were compared in terms of Ross Heart Failure classifications in patients groups. The results of ANOVA test showed that RV (P<0.001), HB (P=0.004) and oxygen saturation (P=0.030) had differences means significantly. For PA pressure, BNP and age the comparison, resulted non-significant difference (**Table.4**).

Table.5 showed a post hoc Tukey for BNP, RV pressure, PA pressure and age in Ross Classifications in which demonstrated for RV pressure, pairs of (I,II), (I, III) and (I, IV), for HB, pairs of (I,III) and (II,III) and for oxygen saturation, pair of (I,III) were the causes of significant. Pearson correlation statistic was used and the results are shown in the **Table.6**.

Results showed that BNP has correlation significantly with PA (r=0.21, P=0.04). PA showed a strong relationship with the Qp/Qs ratio (r=0.45, P<0.001), Rp/Rs (r=0.59, P<0.001), RV(r=0.29, P<0.001) and O2Sat (r=0.36, P<0.001). The ratio of Rp/Rs didn't show any significant correlation with all other laboratory data (**Table.6**).

Table-1: Gender distribution in case and control groups of the study

Gender	Groups			Total
	Cyanotic	Acyanotic	Control	
Girl	7	38	20	65
Boy	15	40	30	85
Total	22	78	50	150

Table-2: The mean and standard deviation of BNP and growths variables in case and control groups

Variables	Group	N	Mean	SD	t- test	P - value
Height(cm)	Case	100	94.180	26.889	0.402	0.689
	Control	50	92.320	26.435		
Weight(kg)	Case	100	14.130	9.503	-1.24	0.217
	Control	50	16.594	14.673		
BNP (pg/ml)	Case	98	123.324	259.200	-2.83	0.006
	Control	50	268.416	311.755		
RV pressure (mmHg)	Case	100	67.223	35.087	11.213	0.000
	Control	50	27.140	4.836		
PA pressure (mmHg)	Case	100	40.592	29.659	8.124	0.000
	Control	50	16.320	2.551		
HB(gr/dl)	Case	100	12.934	3.276	2.226	0.000
	Control	50	12.096	1.312		
O_2Sat (%)	Case	100	86.037	15.596	-3.788	0.000
	Control	50	92.040	1.989		
Age (months)	Case	99	55.934	52.910	0.305	0.761
	Control	49	53.082	54.854		

Table-3: Difference of BNP and Growths variables in Cyanoti, Acyanotic children compared with controls

Variables	(I) diseases	(J) diseases	Mean Difference (I-J)	95% CI		P value
				LB	UB	
Height (cm)	Cyanotic	Acyanotic	7.333	-7.695	22.360	NS
		Control	7.506	-8.427	23.439	
	Acyanotic	Control	0.174	-11.312	11.659	
Weight (kg)	Cyanotic	Acyanotic	1.836	-4.633	8.304	NS
		Control	-1.051	-7.909	5.808	
	Acyanotic	Control	-2.886	-7.830	2.058	
BNP (pg/ml)	Cyanotic	Acyanotic	11.099	-148.782	170.980	0.0128
		Control	-136.484	-305.440	32.472	
	Acyanotic	Control	-147.583	-267.836	-27.330	
RV pressure (mmHg)	Cyanotic	Acyanotic	44.826	31.104	58.548	0.000
		Control	74.599	60.050	89.148	
	Acyanotic	Control	29.773	19.285	40.261	
PA pressure (mmHg)	Cyanotic	Acyanotic	-17.539	-30.823	-4.254	0.000
		Control	10.767	-3.318	24.852	
	Acyanotic	Control	28.306	18.152	38.459	
Hb (gr/dl)	Cyanotic	Acyanotic	5.377	4.207	6.546	0.000
		Control	4.978	3.738	6.218	
	Acyanotic	Control	-0.399	-1.292	0.495	
O_2Sat (%)	Cyanotic	Acyanotic	-26.079	-31.211	-20.946	0.000
		Control	-26.083	-31.525	-20.642	
	Acyanotic	Control	-0.005	-3.928	3.918	

Age (months)	Cyanotic	Acyanotic	12.489	-17.697	42.675	NS
		Control	12.440	-19.620	44.500	
	Acyanotic	Control	-0.049	-23.287	23.190	

NS: Not significant; SD: Standard deviation.

Table-4: The mean and SD of BNP, RV pressure, PA pressure and age in Ross Heart Failure classifications

Variables	ROSS classification	N	Mean	SD	P-value
Age (months)	I	23	57.65	43.38	0.196
	II	50	46.09	50.77	
	III	20	71.30	64.69	
	IV	6	80.17	52.91	
	Total	99	55.93	52.91	
BNP(pg/ml)	I	23	79.62	209.40	0.685
	II	51	148.02	285.99	
	III	20	104.37	229.82	
	IV	6	178.55	276.71	
	Total	100	125.39	257.03	
RV pressure (mmHg)	I	23	42.54	22.41	0.000
	II	51	70.16	35.33	
	III	20	82.55	33.78	
	IV	6	85.83	33.23	
	Total	100	67.22	35.09	
PA pressure (mmHg)	I	23	34.09	20.61	0.059
	II	51	42.27	28.52	
	III	20	35.30	33.74	
	IV	6	68.83	42.40	
	Total	100	40.59	29.66	
HB (gr/dl)	I	23	11.94	1.95	0.004
	II	51	12.39	2.97	
	III	20	14.92	4.28	
	IV	6	14.80	3.18	
	Total	100	12.93	3.28	
O_2Sat (%)	I	23	91.03	7.91	0.030
	II	51	87.57	12.54	
	III	20	78.55	24.75	
	IV	6	78.83	14.70	
	Total	100	86.04	15.60	

SD: Standard deviation.

Tabel-5: Difference of BNP, RV pressure, PA pressure and age in Ross Classifications based on Tukey follow-up test

Dependent Variable	(I) Ross Classification	(J) Ross Classification	Mean Difference (I-J)	P- value
RV pressure (mmHg)	I	II	-27.62	0.01
		III	-40.01	0.00
		IV	-43.30	0.02
	II	III	-12.39	0.47
		IV	-15.68	0.68
	III	IV	-3.28	1.00
HB (gr/dl)	I	II	-0.45	0.94
		III	-2.98	0.01
		IV	-2.86	0.19
	II	III	-2.53	0.01
		IV	-2.41	0.28
	III	IV	0.11	1.00
O_2Sat (%)	I	II	3.46	0.80
		III	12.48	0.04
		IV	12.20	0.30
	II	III	9.02	0.11
		IV	8.74	0.54
	III	IV	-0.28	1.00

Table-6: Thr correlations and inferential statistics of BNP, PA pressure, RV pressure, age and HB variables, ratios of Qp/Qs and Rp/Rs and O_2Saturation

Variables	statistics	PA	Qp/Qs	Rp/Rs	RV	HB	O_2Sat	Age
BNP(pg/ml)	Pearson Correlation	0.21	0.12	0.11	0.07	0.02	0.11	0.05
	P- value	**0.04**	0.23	0.26	0.51	0.82	0.30	0.65
PA pressure (mmHg)	Pearson Correlation		0.45	0.59	0.28	-0.17	0.36	-0.12
	P- value		**0.00**	**0.00**	**0.00**	0.10	**0.00**	0.25
Qp/Qs	Pearson Correlation			0.14	-0.31	-0.55	0.53	-0.25
	P- value			0.17	**0.00**	**0.00**	**0.00**	0.02
Rp/Rs	Pearson Correlation				0.17	-0.18	0.12	-0.12
	P- value				0.09	0.08	0.22	0.26
RV pressure (mmHg)	Pearson Correlation					0.53	-0.34	0.11
	P- value					**0.00**	**0.00**	0.29
HB (gr/dl)	Pearson Correlation						-0.46	0.37
	P- value						**0.00**	**0.00**
O_2Sat (%)	Pearson Correlation							0.06
	P- value							0.55

4- DISCUSSION

The results of the present study showed that BNP, RV pressure, PA pressure, HB and O_2 saturation had different means in cyanotic, acyanotic and control. BNP, O_2 saturation, RV pressure, PA pressure and HB had different means in case and controls.

In the analyzing patients, accordance with ROSS classification RV, HB and O_2 saturation were dissimilar in patients. In HB the difference was due to the pairs consisted of the third level with the first and the second level. Cyanotics group of patients showed different values with controls an acyanotics; and finally for O_2 saturation, the significant difference resulted by ANOVA test caused due to the first and the third pair. BNP had a significant correlation with PA pressure only.

Hsu et al. conducted a study on patients with ventricular septal defect (VSD) to find BNP levels and the amounts of shunt (QP/QS). They reported a significant correlation and they in addition found that surgical repairing of palliative treatment on ventricular defects with outflow obstruction decreased pressure load caused the low secretion level of BNP (14). Our study conducted on patients with CHD before surgical operation. Therefore, the results of these two studies were not comparable.

Bibhuti in a study on patients with left to right shunt showed that the level of BNP had direct correlation with severity of shunt, with right ventricular systolic pressure, with mean of pulmonary artery pressure and with an increase in pulmonary vascular resistance (9).

In our study resulted that the level of BNP and pulmonary artery pressure in CHD patients was significantly correlated. Needs to pointed that 3 (3%) of our patients had Eisenmenger syndrome (right to left shunt), so that in these three patients, the level of BNP were less than 8pg/ml. Our results were consistent with the results of the Bibhuti study. In comparison of these two study, increasing stress in free wall of right ventricular and the severity of pulmonary vascular resistance are the main reasons in decreasing BNP level in patients with Eisenmenger.

Noori et al. performed a study on patients with dilated cardiomyopathy and showed that BNP had significant relationship with the majority of echocardiographic parameters as well as with the severity of illness based on the Ross classification; but in the present study a significant relationship observed between BNP and PA pressure in CHD patients. An increase in PA pressure in CHD patients is due to left to right shunts that is created by defects in arteria (ASD) ventricle (VSD) and great arteries (PDA). These defects can make an increase in volume overload and pressure overload that caused an increase in wall stress that the final outcome can be a high secretion of BNP from myocytes in CHD patients (5).

Miyamoto showed that most of the clinical biomarkers like BNP have significant prognostic value in adult patients with CHD that is a confirmation for the BNP for being a great and valuable prognostic marker. Compatible with our study, confirmed that BNP is a good biomarker in child patients with CHD. Miyamoto also presented that BNP can be a strong predictor in cardiovascular mortality among adult patients with CHD (15).

An increase in left-to-right shunt (Qp/Qs) due to ASD, VSD and PDA make an increase in the NT-proBNP in CHD patients. Accordingly, the levels of BNP and NT-proBNP plasma are useful tools to evaluate CHF in CHD patients. In our patients, the pulmonary-to-systemic blood flow ratio (Qp/Qs) (Qp/Qs) had a significant correlation with PA pressure. PA pressures had a clear correlation with

BNP. Obviously is resulted that our findings related to this specific matter indirectly consisted with Sugimoto findings (16). Fan resulted that the serum NT-ProBNP in CHD children increased in three subgroups of ASD, VSD and PDA defects before surgery. Along with this result they concluded an elevation in the intervention or after surgery; the results of the present study was consisted with the case related before surgery (17).

Koura resulted that QP/QS and PA pressure were significantly higher in elevated NT-pro BNP patients compared to patients with normal NT-Pro BNP and recommended NT-ProBNP using as a routine biomarker in patients with heart failure and pulmonary hypertension. In our study with CHD patients, the level of BNP plasma increased with PA pressure. In compare with Koura study, our study was varied in biomarkers (BNP vs. NT-Pro BNP) (18).

Shiva explored that cyanotic heart patients had lower mean of age than acyanotic because of early symptoms before surgery. Both type of patients with CHD had BMI and LVEF lower than controls, but not significant. Cyanotic patients had lower O_2 saturation than acyanotic and control (19). In our study O_2 saturation were lower for cyanotic patients compared with acyanotics and controls. In comparison of these two studies resulted that the lower level of O_2 saturation in cyanotic patients was due to the low blood flow to the lung because of severe pulmonary stenosis such as Tetralogy of Fallot (TF).

Reynolds et al. reported that the primary levels of BNP were higher than $550_{pg/ml}$ and predicted that the primary pulmonary hypertension of new born (PPHN) was with sensitivity of 83% and specificity of 100% in term infants. The higher levels of BNP showed a worse clinical status. Reynolds also showed a direct correlation between the level of BNP and Pulmonary artery pressure similar to our findings, but that was not matched with our results because of the different age groups (20). Yuk performed a study on infants, children and adults patients with heart failure. The main study report was a positive correlation between BNP and NT-PRO BNP and heart failure (21). In addition, has been resulted that the heart defects with obstructive outflow tract were associated with corrected surgery or palliative therapy (14). In the present study, accordance to ROSS classification, with increasing severity of heart failure, the BNP plasma level increased, but not significant.

According to a recent study, it was found that the levels of BNP has a relationship with the severity of obstruction of the left ventricular outflow tract (aortic stenosis) in children and 24 hours after successful balloon valvuloplasty, the BNP level will be decreased. This research is matched with ours before the balloon valvuloplasty because BNP levels increases with increasing of severity disease (22).

Price and Mangar conducted studies on children with left ventricular dysfunction and they resulted that the patients had a ejection fraction less than 50% three months after their diagnosis. They reported that a BNP level of 300 ng/ml or higher has a predictive value for events such as cardiovascular death, hospitalization for heart disease and listing on the heart transplant (23, 24). Plasma BNP levels of 20pg/ml or higher can determined children with average pulmonary artery pressure of 20 mmHg or higher with the sensitivity of 82% and specificity of 89 percents (25).

In our study we did not evaluate the sensitivity and specificity of average pulmonary artery pressure, but a significant correlation observed between hemodynamic parameters of right ventricle and plasma BNP levels due to right ventricular volume overload in children with different types of CHD such as TF after the complete repaired of pulmonary

regurgitation and stenosis, pulmonary atresia, atrial septal defect or anomaly pulmonary venous return. BNP measure could be a good biomarker for following right ventricular pressure overload and volume overload in these patients (9). Our study findings showed that in patients with cyanotic and acyanotic with right ventricular obstruction outflow tract, the level of BNP increased due to the severity of the obstruction.

Scott conducted a study and showed that the level of BNP in children with symptomatic heart failure was higher compared to normal children. The mean level of BNP did not change with gender, diagnosis and subgroups within the systemic ventricle. A moderate correlation was observed between BNP levels and left ventricular ejection fraction; but not observed a clear correlation between the BNP and left ventricular dimensions (11). These results are agreed with our findings, because with increasing the severity of heart failure the BNP levels also have increased.

In a study by Holmgren et al. the most important findings were higher level of plasma BNP and Atrial natriuretic peptide (ANP) concentration in children with left ventricular volume overload compared with the right ventricle volume overload. This fact that Qp/Qs judge on the equality of the severity of volume overload in both groups could be diagnosed that the ventricular morphology and higher severity of volume overload affects on BNP level. Approved that the level the BNP and ANP plasma concentrations were higher in patients with a volume overloaded LV especially in children compared with a volume or pressure overloaded RV. As judged by QP, in spite of this fact that the right ventricle (RV) and left ventricle (LV) have similar degree of cardiac load, it demonstrated that QS, pressure gradient measurements, LV and RV pressure may differently react to a hemodynamic load without myocardial dysfunction (12). It is acceptable that an observed increase in NPs levels are not due to the myocardial mass, but it is a result of an increasing in wall stress. Another interested outcome in this study was that the level of NPs in patients with Left Ventricular Outflow Tract obstruction was closer to the observed data compared with controls. That is why the systolic stress wall making low levels of ANP and BNP compared to the diastolic stress wall. The fact that NPs levels in right ventricle pressure is equal with RV volume, shows that right ventricular not only damaged by the diastolic wall stress, but also damaged with stress walls of systolic (26).

The result of the Daniel Holmgren study was partly similar with our results. The levels of BNP reflect the severity of illness in patients with volume overload of the right and left ventricles, and the level of 35-40 pg/ml for BNP is useful as an indicator for surgery in patients with ventricular septal defect (VSD) (27, 28). Cowley explored that the BNP level is an indicator of pulmonary artery pressure and high level of shunt (Qp/Qs).

It is approved a meaningful association of BNP concentration with right atrial pressure, with right ventricular end-diastolic pressure and with pulmonary artery pressure. Our results are similar with Daniel Holmgren findings. Cowley confirmed a stronger association between BNP levels and left ventricular outflow obstruction. In this study a strong correlation approved between BNP concentration and left ventricular outflow tract obstruction. BNP concentrations and aortic valve stenosis were assessed in adults and shown a correlation with left ventricular mass and poor communication with aortic valve in moderate gradient. Cowley study compatible with our study partly, because we resulted that BNP

levels increased with pulmonary artery pressure increased (29).

4-1. Limitations of the study

Our study was limited by small sample size especially in controls, because of dissatisfaction for blood sampling.

5- CONCLUSION

The results of the present study showed that brain natriuretic peptide, pulmonary artery pressure, right ventricle pressure, hemoglobin and O_2 saturation had not similar levels in cyanotic, acyanotic and control as well in case and control. In our patients group right ventricle pressure, hemoglobin and O_2 saturation had dissimilar levels in various degree of ROSS classification.

A positive correlation was observed between the pulmonary hypertension and BNP level. It would be recommended to consider the brain natriuretic peptide as a biomarker to evaluate the volume overload and pressure overload in congenital heart defects patients.

6- CONFLICT OF INTEREST: None.

7- AKNOWLEDGMENTS

The authors would like to show their deep gratitude to the parents for their honest participations.

8- REFERENCES

1. Shahramian I, Noori NM, Hashemi M, Sharafi E, Baghbanian A. A study of serum levels of leptin, ghrelin and tumour necrosis factor-alpha in child patients with cyanotic and acyanotic, congenital heart disease. JPMA 2013; 63:1332-37.

2. Noori NM, Savadkoohi S, Teimouri A, Alizadeh F. Evaluation of Serum Levels of N-terminal Pro Brain Natriuretic Peptide and Atrial Natriuretic Peptide in Neonates with Respiratory Distress. International Journal of Pediatrics 2016; 4(6):1847-56.

3. Sahingozlu T, Karadas U, Eliacik K, Bakiler AR, Karadas NO, Kanik MA, et al. Brain natriuretic peptide: the reason of respiratory distress is heart disease or lung disease? The American journal of emergency medicine 2015; 33(5):697-700.

4. Medar SS, Hsu DT, Ushay HM, Lamour JM, Cohen HW, Killinger JS. Serial Measurement of Amino-Terminal Pro-B-Type Natriuretic Peptide Predicts Adverse Cardiovascular Outcome in Children With Primary Myocardial Dysfunction and Acute Decompensated Heart Failure. Pediatric Critical Care Medicine 2015; 16(6):529-34.

5. Noori NM, Mahjoubifard M, Shahramian I, Teimouri A, Jahangirifard A. Comparison between Procalcitonin, Brain Natriuretic Peptide, and Uric Acid in Children with Cardiomyopathy and Controls. Biomed Res Int 2015;2015:510450.doi: 10.1155/2015/510450. Epub 2015 Oct 1.

6. Braunwald E. Biomarkers in heart failure. New England Journal of Medicine 2008; 358(20):2148-59.

7. Haberger S, Hauser M, Braun SL, Schuster T, Ewert P, Nagdyman N, et al. Prognostic Value of Plasma B-Type Natriuretic Peptide in the Long-Term Follow-up of Patients With Transposition of the Great Arteries With Morphologic Right Systemic Ventricle After Atrial Switch Operation. Circulation Journal 2015; 79(12):2677-81.

8. Koch A, Zink S, Singer H. B-type natriuretic peptide in paediatric patients with congenital heart disease. European heart journal 2006; 27(7):861-6.

9. Bibhuti B. DasPlasma B-Type Natriuretic Peptides in Children with Cardiovascular Diseases Pediatric Cardiology 2010; 31(8): 1135-45.

10. Mir TS, Falkenberg J, Friedrich B, Gottschalk U, Lê TP, Laer S, et al. Levels of brain natriuretic peptide in children with right ventricular overload due to congenital cardiac disease. Cardiology in the Young 2005; 15(4):396-401.

11. Auerbach SR, Richmond ME, Lamour JM, Blume ED, Addonizio LJ, Shaddy RE, et al. BNP Levels Predict Outcome in Pediatric Heart Failure Patients Post Hoc Analysis of the Pediatric Carvedilol Trial. Circulation: Heart Failure 2010; 3(5): 606-11.

12. Holmgren D, Westerlind A, Lundberg PA, Wåhlander H. Increased plasma levels of

natriuretic peptide type B and A in children with congenital heart defects with left compared with right ventricular volume overload or pressure overload. Clinical physiology and functional imaging 2005; 25(5): 263-9.

13. Ross RD. The Ross classification for heart failure in children after 25 years: a review and an age-stratified revision. Pediatric cardiology 2012; 33(8):1295-300.

14. Hsu JH, Keller RL, Chikovani O, Cheng H, Hollander SA, Karl TR, et al. B-type natriuretic peptide levels predict outcome after neonatal cardiac surgery, J Thorac Cardiovasc Surg 2007; 134(4):939-45.

15. Miyamoto K, Takeuchi D, Inai K, Shinohara T, Nakanishi T. Prognostic value of multiple biomarkers for cardiovascular mortality in adult congenital heart disease: comparisons of single-/two-ventricle physiology, and systemic morphologically right/left ventricles. Heart and vessels 2016:1-4.

16. Sugimoto M, Kuwata S, Kurishima C, Kim JH, Iwamoto Y, Senzaki H. Cardiac biomarkers in children with congenital heart disease. World Journal of Pediatrics 2015; 11(4):309-15.

17. Fan S, Huang H, Zhang D, Li Q, Xu H, Xu Y, Qiao J. The dynamic change of serum cTnT and NT-ProBNP during the intervention therapy for congenital heart disease and the value for prognosis prediction. Int J Clin Exp Med 2016; 9(3):5842-47.

18. Koura HM, Abdalla NM, Ibrahim MH, Hashish MM, Zaki SM. NT-proBNP in Children With Left to Right Shunt and Dilated Cardiomyopathy. Iran J Pediatr 2016. (InPress): e4485.

19. Shiva S, Samadi M, Mohammadpour Shateri M, Habibzadeh A. Growth Parameters and Insulin Like Growth Factor-1: Comparison between Cyanotic and Acyanotic Congenital Heart Disease and Normal Children. Life Sci J 2013; 10: 577-80.

20. Reynolds EW, Ellington JG, Vranicar M, Bada HS. Brain-type natriuretic peptide in the diagnosis and management of persistent pulmonary hypertension of the newborn, Pediatrics 2004; 114(5):1297-1304.

21. Yuk M. Law, Bradley B. Keller, Brian M. Feingold, Gerard J. Boyle. Usefulness of plasma B-type natriuretic peptide to identify ventricular dysfunction in pediatric and adult patients with congenital heart disease, American Journal of Cardiology 2005; 95(4): 474-78.

22. McKie PM, Burnett JC Jr. B-type natriuretic peptide as a biomarker beyond heart failure: speculations and opportunities, Mayo Clin Proc 2005; 80(8):1029-36.

23. Price JF, Thomas AK, Grenier M, Eidem BW, O'Brian Smith E, Denfield SW, et al. B-type natriuretic peptide predicts adverse cardiovascular events in pediatric outpatients with chronic left ventricular systolic dysfunction, Circulation 2006; 114(10): 1063-69.

24. Mangat J, Carter C, Riley G, Foo Y, Burch M. The clinical utility of brain natriuretic peptide in paediatric left ventricular failure. Eur J Heart Fail 2009; 11(1):48-52.

25. Ozhan H, Albayrak S, Uzun H, Ordu S, Kaya A, Yazici M. Correlation of plasma B-type natriuretic peptide with shunt severity in patients with atrial or ventricular septal defect. Pediatr Cardiol 2007; 28(4): 272-5.

26. Holmgren D, Westerlind A, Lundberg PA, Wåhlander H. Increased plasma levels of natriuretic peptide type B and A in children with congenital heart defects with left compared with right ventricular volume overload or pressure overload. Clinical physiology and functional imaging 2005; 25(5):263-9.

27. Paul MA, Backer CL, Binns HJ, Mavroudis C, Webb CL, Yogev R, et al. B-type natriuretic peptide and heart failure in patients with ventricular septal defect: a pilot study, Pediatr Cardiol 2009; 30(8):1094-97.

28. Kunii Y, Kamada M, Ohtsuki S, Araki T, Kataoka K, Kageyama M, et al. Plasma brain natriuretic peptide and the evaluation of volume overload in infants and children with congenital heart disease, Acta Med Okayama 2003; 57(4):191-7.

29. Cowley CG, Bradley JD, Shaddy RE. B-type natriuretic peptide levels in congenital heart disease. Pediatr Cardiol 2004; 25(4):336.