http:// ijp.mums.ac.ir
Original Article (Pages: 7769-7780)

Evaluation of Serum NT-Pro Brain Natriuretic Peptide Levels in Neonates with Respiratory Distress

Noor Mohammad Noori[1], Amer Yazdanparast[2], Maryam Nakhaee Moghaddam[3], *Alireza Teimouri[4]

[1]Professor of Pediatric Cardiology, Research center for children and adolescent's health, Resistant Tuberculosis institute,Zahedan University of Medical Sciences and Health Services, Zahedan, Iran.
[2]Assistant Perofessor of Pediatric Cardiology, Department of Pediatrics, Faculty of Medicine, Bushehr University of Medical Sciences, Bushehr, Iran.
[3]Assistant Professor of Pediatric Endocrinology, Resistant Tuberculosis institute, Research Center for Children and Adolescent's Health, Zahedan University of Medical Sciences, Zahedan, Iran.
[4]Assistant Professor of Demography, Children and Adolescent Health Research Center, Resistant Tuberculosis institute, Zahedan University of Medical Sciences, Zahedan, Iran.

Abstract

Background
Respiratory Distress (RD) is a life-threatening respiratory failure. This study aimed to evaluate the diagnostic value of N-terminal prohormone of brain natriuretic peptide (NT-pro-BNP) in distinguishing respiratory and heart diseases in neonates.

Materials and Methods
Hundred fifty neonates aged 2-3 days randomly collected from those who hospitalized in the related ward of the Ali Ebne Abitaleb Hospital, Zahedan, Iran. After sampling 2ml blood from venipuncture by trained nurse in the related ward separated serums performed in a laboratory. Then, 250 µl of the patients' serum was isolated to assess NT- pro-BNP level using ELISA kit (USA). Data were analyzed using SPSS software version 20.0 with considering of $P< 0.05$.

Results
Mean of NT-pro-BNP in respiratory, Acyanotic, cyanotic and controls were 386.22±208.82, 384.83±183.74, 372.23±143.04, and 161.70-± 121.2, respectively. Weight, height and head circumference had different mean ranks for respiratory, Acyanotic, cyanotic and healthy groups, respectively ($P<0.05$).

Conclusion
According to the results, despite of some reports, NT-proBNP is good biomarker to determine differentiate between cardiac and respiratory during neonate.

Key Words: Congenital heart disease, Neonates, NT- pro-BNP, Respiratory.

*Please cite this article as: Noori NM, Yazdanparast A, Nakhaee Moghaddam M, Teimouri A. Evaluation of Serum NT-Pro Brain Natriuretic Peptide Levels in Neonates with Respiratory Distress. Int J Pediatr 2018; 6(6): 7769-80. DOI: **10.22038/ijp.2018.30163.2654**

Corresponding Author:

Dr. Alireza Teimouri, Assistant Professor of Demography, Children and Adolescent Health Research Center, Resistant Tuberculosis institute Zahedan, University of Medical Sciences, Zahedan, Iran

E-mail: Alirezateimouri260@gmail.com

Received date: Jan.15, 2018; Accepted date: Mar. 12, 2018

1- INTRODUCTION

Respiratory Distress (RD) is a life-threatening due to lung injury in neonates. Pathologically, RD is included of several features such as alveolar capillary leakage, protein rich pulmonary edema, diffused alveolar image, leading to the clinical manifestations of poor lung compliance, severe hypoxemia and bilateral infiltrates on the chest radiograph (1). The prevalence of acute lung injury has been reported of 16.1% in ventilated patients who are admitted for more than 4 hours. The severe sepsis is the most common cause of RD (2). Other causes may are included of mechanical ventilation, pneumonia, circulatory shock, aspiration, pulmonary contusion, major surgery, massive blood transfusions and drug reaction (3). The death rate of RD varies from 25–40% in centers using up-to-date ventilator strategies and up to 58% in all centers (4).

Congenital heart disease (CHD) is a kind of lesions or anomalies in one or more structures of the heart that occurs between 3 to 8 weeks of gestation age and has a wide spectrum of severity in neonates (5). The diagnosis is established by the first week of age in half of patients and by 1 month of age in rest of patients (6). It also is one of the most common causes of respiratory distress in newborns when its prevalence reported 4 to 50 in 1,000 live births (7, 8). Peptides such as brain natriuretic peptide (BNP) and N-terminal prohormone of brain natriuretic peptide (NT-pro-BNP) are biomarkers that used to diagnose the congestive heart failure. These peptides may apply in screening of asymptomatic high-risk patients and are reliable tests for diagnosis of functional and structural disorders of CHD (9). They are released into the blood from myocyte cells in response to various kinds of stress on the heart and exert various physiological functions such as diuretic action, vasodilation and myocardial remodeling. In fact, several types of BNP molecules are present in the blood. N-terminal pro-BNP is an N-terminal protein, originating from NT- pro-BNP and is released from the myocardial cellular. NT-pro-BNP is excreted in its original form from the kidney (10). Measurement of the concentration of the NT- pro-BNP is increasingly used to aid diagnosis, to assess prognosis, and tailor therapy in adults with congestive heart failure. A few data dealing with NT- pro-BNP suggest that this peptide is useful in pediatric patients. However, the groups of investigated pediatric patients with CHD were small or heterogeneous, and the results were not compared with age, gender and specific normal values (11).

NT- pro-BNP level is elevated in children with heart disease causing ventricular pressure and volume loading. In addition, it has a close correlation to shunt volume in left-to-right cardiac lesions, increasing with decreasing left ventricular ejection fraction, and positively correlating with increasing right ventricular systolic pressures and it is a good marker for persistent left ventricular dysfunction in children with dilated cardiomyopathy. Among infants with respiratory diseases, plasma NT- pro-BNP measurement can differentiate between acute heart failure and lung disease (12).

The level of NT- pro-BNP is a sensitive marker for predicting patent ductus arteriosus (PDA) in preterm infants in the second day. Successful closure of PDA is also correspondent with the decline in plasma NT- pro-BNP (13). In pediatric NT- pro-BNP is strongly correlated with predicted changes in clinical variables and hemodynamic and it can be added as additional information towards predicting these clinical measurements (14). According to the background, the importance of differentiating the causes of respiratory and heart diseases and a few studies on the diagnostic value of NT- pro-

BNP in respiratory distress, we decided to assess the NT- pro-BNP power in differentiating respiratory diseases from CHD in neonates in compered with controls.

2- MATERIALS AND METHODS

2-1. Patients

This case-control study conducted on 150 neonates aged 2-3 days in three groups of participants with respiratory disease, heart diseases, and controls to differentiate the respiratory diseases from heart diseases using NT pro- BNP. The study performed in pediatric cardiac center in collaboration of center for specific diseases in Ali Ebne Abi taleb hospital, Zahedan city, Sistan and Baluchestan province (South East of Iran) during the year of 2017. These neonates collected from those who admitted to the Neonatal Intensive Care Unit (NICU) wards of the hospital. Controls selected from those neonates that their mothers came to the hospital for routine checkup at the third day randomly.

2-2. Exclusion Criteria

Respiratory distress appears with the symptoms such as rapid and difficulty breathing, moaning, retraction of intercostal muscles between ribs and the suprasternal with the nostrils on inspiration and eventually cyanosis in neonates (15). Exclusion criteria were lack of parental consent or agreement, metabolic diseases, anatomical disorders, hematologic disorders, renal diseases, neonates with hyperbilirubinemia and infectious diseases.

2-3. Ethical Approve

Ethical notes were considered in all the stages of study such as sampling, collecting controls from hospital base and case collection from the neonate ward. The parents of neonates informed from the aims of the study and after taking signature from them on the constant form, their neonates entered to the study. This study approved by medical research ethics committee of Zahedan University of Medical Sciences (ID-number: 7228).

2-4. Methods

Cardiac patient's collection was based on the following approach: hospitalized patients with respiratory distress were examined by cardiologist for probable CHD symptoms. If observed any heart problems they assigned to the cardiac patients but else assigned to the group of respiratory diseases. This course continued until the number of patients for each group received to 50 neonates. Cardiac patients classified in two groups as cyanotic and a cyanotic accordance with the type of diseases. All participants examined by Para-clinical tests such as chest X-ray, biochemical test, Arterial Blood Gas (ABG). These examinations performed by same pediatric cardiologist. In all cases, information related to gestational age, gender, birth weight, height and head circumference recorded.

Weight measured by Mika Mark recumbent weighing scale made in Japan with an error factor of 10 gr. Participants' height measured with a wooden scaled table in supine position. Head circumference measured with a flexible non-stretchable measuring tape. Blood samples for the measurement of NT-pro-BNP concentration collected when blood sampling indicated for the clinical management of a newborn. Therefore, vein puncture not performed exclusively for the purpose of this study. Blood samples collected to measure NT-pro-BNP concentration. Therefore, venipuncture not performed exclusively for the purpose of this study. After taking 2 ml blood samples from both case and controls in the neonate ward by high-trained nurse, the samples centrifuged at 5 ° C with a round of 3000 g for 10 minutes. The separated serum kept in -20 ° C until NT pro Brian Natriuretic peptide measured. Finally, with

consideration to the cold chain, it transferred to the biochemistry laboratory. Then, 250 µl of the patients' serum was isolated to assess NT- pro -BNP by using ELISA kit (USA).

2-5. Statistical Analysis

Data were analyzed using SPSS software version 20.0 (SPSS, Chicago, IL, USA). Categorical variables summarized as frequency and percentages, and continuous data were presented as mean ± SD and median. Normality test consider for using parametric or non-parametric statistical test. Kruskal-Wallis and Mann-Whitney tests were used for the analysis with Pearson correlation. Significant level considered when the p-value was less than 0.05.

3- RESULTS

The study aimed to evaluate the diagnostic value of N-terminal prohormone of brain natriuretic peptide (NT-pro-BNP) in distinguishing respiratory and heart diseases in neonates. First of all, the test of normality used to check the variables distribution. It was resulted that all the main variables had free distribution (**Table.1**).

The distributions of participants in different groups were 50, 26, 24 and 50 in respiratory distress, cyanotic, Acyanotic patients and controls, respectively. Of 150 participants 64 (42.7%) were girl. Boys' distribution was 72.0%, 41%, 69.2% and 44% in respiratory distress, cyanotic, Acyanotic patients and controls, respectively (**Figure.1**).

The **Table.2** shown that different groups of neonates had different NT- pro -BNP ($p<0.001$), different weight ($p<0.001$), different height ($p<0.001$), different head circumference ($p<0.001$), different neonatal age ($p=0.002$), and different gestation age ($p<0.001$). **Table.3** shown the results of Mann-Whitney U test to clear the difference of the groups (respiratory-CHD, respiratory-controls and CHD-controls). In the case of NT- pro – BNP, the significant difference was due to the pairs of (respiratory and controls, $p<0.001$), and (CHD and controls, $p<0.001$). Neonates' weight was different in all pairs of groups. Neonates' height, head circumference, neonatal age and gestation age were different in all pairs of groups except CHD-controls.

The **Tables 4, 5** shown the results of significant differences of all the variables between 4 groups of participants by Kruskal Wallis test. NT-pro-BNP had mean ranks of 91.66, 92.83, 95.56 and 40.59 for respiratory, Acyanotic, cyanotic and controls ($p<0.001$). This difference was due to the pairs of respiratory - controls, Acyanotic - controls and cyanotic -controls. Weight ($p<0.001$), height ($p<0.001$), and Head Circumference ($p<0.001$) had different mean ranks in groups of participants.

These differences were due to all pairs except Acyanotic - cyanotic, Acyanotic - controls and cyanotic - controls in weight, pairs of respiratory - controls, respiratory - Acyanotic and respiratory - cyanotic in height, and pairs of respiratory - controls, respiratory –Acyanotic, and respiratory - cyanotic in head circumference. Age ($p=0.006$), and gestation age ($p<0.001$) of neonates had significant different values between groups. In both variables, respiratory groups made these differences.

Table-1: The Kolmogorov-Smirnov test of normality for the main variables.

Variables	Mean (standard deviation)	Kolmogorov-Smirnov value	P-value
Neonate age (day)	2.5000 (0.501)	0.341	<0.001
Gestational Age(week)	35.6800(3.541)	0.224	<0.001
Weight (gr)	2480.2000(691.914)	0.108	<0.001
Height (cm)	46.8167(7.200)	0.216	<0.001
Head Circumference (cm)	33.6807(5.146)	0.246	<0.001
NT- pro -BNP (pg)	380.2838(141.217)	0.118	<0.001

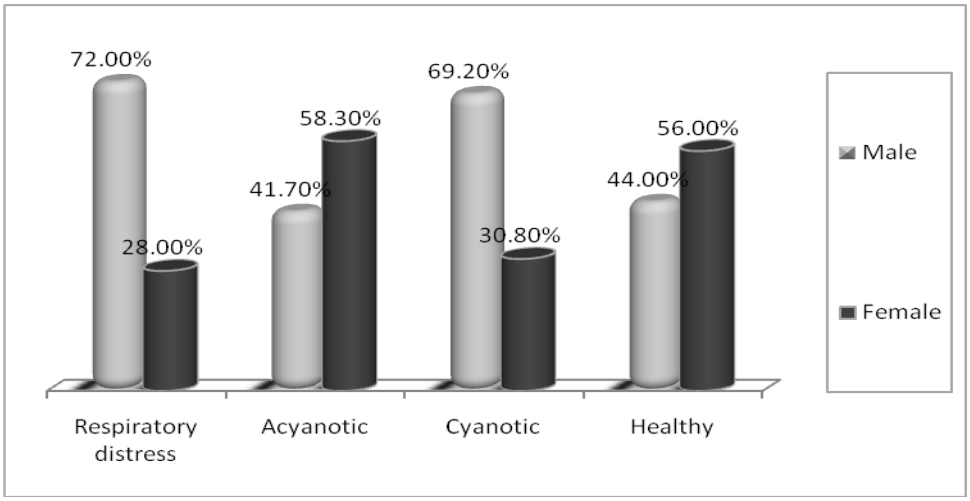

Fig.1: The sex distribution of participants in different groups.

Table-2: The Kruskal Wallis test results for the main variables amongst 3 groups of participants.

Variables	Groups of participants	Mean Rank	Chi-Square	P-value
NT- pro -BNP (pg)	Respiratory	91.66	48.529	<0.001
	CHD	94.25		
	Control	40.59		
Weight (gr)	Respiratory	34.19	71.714	<0.001
	CHD	87.85		
	Control	104.46		
Height (cm)	Respiratory	48.83	28.818	<0.001
	CHD	87.64		
	Control	90.03		
Head Circumference (cm)	Respiratory	43.45	43.052	<0.001
	CHD	86.66		
	Control	96.39		
Neonate age (day)	Respiratory	60.5	12.079	0.002
	CHD	84.5		
	Control	81.5		
Gestation age (week)	Respiratory	29.93	85.171	<0.001
	CHD	96.83		
	Control	99.74		

Table-3: The Mann-Whitney U test results for the main variables amongst 3 groups of participants

Variables	Groups of participants	Mean Rank	Sum of Ranks	Mann-Whitney U	P-value
NT- pro -BNP (pg)	Respiratory	67.06	3353.00	422.000	<0.001
	Control	33.94	1697.00		
	Respiratory	50.10	2505.00	123.000	0.89
	CHD	50.90	2545.00		
	CHD	68.85	3442.50	332.500	<0.001
	Control	32.15	1607.50		
Weight (gr)	Respiratory	27.91	1395.50	120.500	<0.001
	Control	73.09	3654.50		
	Respiratory	31.78	1589.00	114	<0.001
	CHD	69.22	3461.00		
	CHD	44.13	2206.50	931.5	0.028
	Control	56.87	2843.50		
Height (cm)	Respiratory	37.41	1870.50	595.5	<0.001
	Control	63.59	3179.50		
	Respiratory	36.92	1846.00	571	<0.001
	CHD	64.08	3204.00		
	CHD	49.06	2453.00	1178	0.613
	Control	51.94	2597.00		
Head Circumference (cm)	Respiratory	33.33	1666.50	391.5	<0.001
	Control	67.67	3383.50		
	Respiratory	35.62	1781.00	506	<0.001
	CHD	65.38	3269.00		
	CHD	46.78	2339.00	1064	0.189
	Control	54.22	2711.00		
Neonate age (day)	Respiratory	43.50	2175.00	900	0.005
	Control	57.50	2875.00		
	Respiratory	42.50	2125.00	850	0.001
	CHD	58.50	2925.00		
	CHD	51.50	2575.00	1200	0.6858
	Control	49.50	2475.00		
Gestation age (week)	Respiratory	27.38	1369.00	94	<0.001
	Control	73.62	3681.00		
	Respiratory	28.05	1402.50	127.5	<0.001
	CHD	72.95	3647.50		
	CHD	49.38	2469.00	1194	0.685
	Control	51.62	2581.00		

CHD: Congenital heart disease.

Table-4: The Kruskal Wallis test results for the main variables amongst 4 groups of participants

Variables	Groups of participants	Mean (SD)	Mean Rank	Chi-square	P-value
NT- pro -BNP (pg)	Respiratory	386.22(208.82)	91.66	48.578	<0.001
	Acyanotic	384.83(183.74)	92.83		
	Cyanotic	372.23(143.04)	95.56		
	Control	161.7(121.2)	40.59		
Weight (gr)	Respiratory	1775.6(515.9)	34.19	71.88	<0.001
	Acyanotic	2654.17(624.31)	85.25		
	Cyanotic	2805.77(500.86)	90.25		
	Control	2932(304.52)	104.46		
Height (cm)	Respiratory	43.7(5.27)	48.83	31.301	<0.001
	Acyanotic	46.52(5.91)	77.65		
	Cyanotic	48.73(3.24)	96.87		
	Control	49.08(9.54)	90.03		
Head Circumference (cm)	Respiratory	30.7(4.73)	43.45	44.291	<0.001
	Acyanotic	33.92(3.59)	79.63		
	Cyanotic	34.71(3.41)	93.15		
	Control	36.01(5.57)	96.39		
Neonate age (day)	Respiratory	2.3(0.46)	60.5	12.325	0.006
	Acyanotic	2.58(0.50)	81.75		
	Cyanotic	2.65()	87.04		
	Control	2.58(0.50)	81.5		
Gestation age (week)	Respiratory	31.82(2.90)	29.93	85.179	<0.001
	Acyanotic	37.38(2.46)	96.25		
	Cyanotic	37.65(1.52)	97.37		
	Control	37.7(1.68)	99.74		

SD: Standard Deviation.

Table-5: The Mann-Whitney U test results for the main variables amongst 4 groups of participants.

Variables	Groups of participants	Mean Rank	Sum of Ranks	Mann-Whitney U	P-value
NT- pro -BNP (pg)	Respiratory	67.06	3353.00	422.00	<0.001
	Control	33.94	1697.00		
	Respiratory	37.59	1879.50	595.50	0.959
	Acyanotic	37.31	895.50		
	Respiratory	38.01	1900.50	625.50	0.788
	Cyanotic	39.44	1025.50		
	Acyanotic	26.23	629.50	294.50	0.734
	Cyanotic	24.83	645.50		
	Acyanotic	54.29	1303.00	197.00	<0.001
	Control	29.44	1472.00		
	Cyanotic	58.29	1515.50	135.50	<0.001
	Control	28.21	1410.50		

Weight (gr)	Respiratory	27.91	1395.50	120.50	<0.001
	Control	73.09	3654.50		
	Respiratory	29.32	1466.00	191.00	<0.001
	Acyanotic	54.54	1309.00		
	Respiratory	27.96	1398.00	123.00	<0.001
	Cyanotic	58.77	1528.00		
	Acyanotic	24.60	590.50	290.50	0.675
	Cyanotic	26.33	684.50		
	Acyanotic	31.10	746.50	446.50	0.075
	Control	40.57	2028.50		
	Cyanotic	32.15	836.00	485.00	0.069
	Control	41.80	2090.00		
Height (cm)	Respiratory	37.41	1870.50	595.50	<0.001
	Control	63.59	3179.50		
	Respiratory	32.58	1629.00	354.00	0.004
	Acyanotic	47.75	1146.00		
	Respiratory	29.84	1492.00	217.00	0.000
	Cyanotic	55.15	1434.00		
	Acyanotic	22.19	532.50	232.50	0.116
	Cyanotic	28.56	742.50		
	Acyanotic	32.71	785.00	485.00	0.177
	Control	39.80	1990.00		
	Cyanotic	40.15	1044.00	607.00	0.630
	Control	37.64	1882.00		
Head Circumference (cm)	Respiratory	33.33	1666.50	391.50	<0.001
	Control	67.67	3383.50		
	Respiratory	31.31	1565.50	290.50	<0.001
	Acyanotic	50.40	1209.50		
	Respiratory	29.81	1490.50	215.50	<0.001
	Cyanotic	55.21	1435.50		
	Acyanotic	22.75	546.00	246.00	0.185
	Cyanotic	28.04	729.00		
	Acyanotic	31.48	755.50	455.50	0.087
	Control	40.39	2019.50		
	Cyanotic	36.90	959.50	608.50	0.642
	Control	39.33	1966.50		
Neonate age (day)	Respiratory	43.50	2175.00	9000.00	0.005
	Control	57.50	2875.00		
	Respiratory	34.10	1705.00	430.00	0.020
	Acyanotic	44.58	1070.00		
	Respiratory	33.90	1695.00	420.00	0.003
	Cyanotic	47.35	1231.00		
	Acyanotic	24.58	590.00	290.00	0.611
	Cyanotic	26.35	685.00		

	Acyanotic	37.58	902.00	598.00	0.978
	Control	37.46	1873.00		
	Cyanotic	40.35	1049.00	602.00	0.535
	Control	37.54	1877.00		
Gestation age (week)	Respiratory	27.38	1369.00	94.00	<0.001
	Control	73.62	3681.00		
	Respiratory	27.10	1355.00	80.00	<0.001
	Acyanotic	59.17	1420.00		
	Respiratory	26.45	1322.50	47.50	<0.001
	Cyanotic	61.67	1603.50		
	Acyanotic	25.60	614.50	309.50	0.595
	Cyanotic	25.40	660.50		
	Acyanotic	36.48	875.50	575.50	0.767
	Control	37.99	1899.50		
	Cyanotic	37.29	969.50	618.50	0.717
	Control	39.13	1956.50		

4- DISCUSSION

Hundred fifty participants were enrolled in the present study with distribution of 50, 24, 26 and 50 for respiratory, Acyanotic, cyanotic patients and controls respectively. Mean gestational age for respiratory neonates was 31.66±0.52 weeks while it was 37.257±0.351 weeks for CHD. Cardiac patients had the highest level of NT- pro -BNP and followed by respiratory patients. Amongst the three groups, controls had the lowest level of NT-pro-BNP and its concentration had the highest level in Acyanotic. The levels of NT- pro -BNP increase immediately after birth and decrease in the first week (16) and have been found to be correlated with the magnitude of a left-to-right shunt (17). Increasing evidences support the use of NT- pro -BNP levels as biomarkers in screening, diagnosis, management, and follow-up of children with cardiac disease (18-20). Markovic-Sovtic et al. (21) conducted a study using of NT- pro -BNP to assess respiratory distress in term neonates from umbilical cord blood sampling. They resulted that the concentration of NT- pro -BNP was higher in heart compared with respiratory but non- significant. Although we did our study on neonates who ranged 2-3 days but received to the same results that cardiac patient had higher level of NT- pro -BNP compared to respiratory diseases and controls significantly. In the present study the level of NT- pro -BNP had a significant difference in different pairs of groups such as cardiac- respiratory, cardiac-controls and respiratory -controls. Similarly, Markovic-Sovtic et al. (21) concluded that neonates with respiratory diseases had higher NT- pro -BNP level compared to their healthy counterparts significantly. Lechner et al. (13) showed that NT- pro -BNP from umbilical cord blood in neonates with CHD were significantly elevated at labor compared with healthy similar with our findings. Nir et al. (22) in their study received to a conclusion that NT- pro -BNP was an important biomarker for CHD in children. The levels of NT- pro -BNP were the highest in the first days of life and decreased by age and suggested that this biomarker can be used as a tool to differentiate heart disease from healthy in infants. Using NT- pro -BNP promotes the clinical practice in pediatric congenital heart diseases. Aydemir et al. (23) conducted a study and revealed that

Plasma levels of NT- pro -BNP will be increased with severity of TTN. The measurement of plasma NT- pro -BNP can be used to predict long-term tachypnea and long term needs of mechanical ventilation in newborns with respiratory distress. Accordance with our results, the level of NT- pro -BNP had a rise for Acyanotic compared to others which was similar with Farombi-Oghuvbu et al.'s report (24).

Perez-Piaya et al. (25) performed a study on patients aged from first day of life to 15-year-old to recognize the levels of NT-pro -BNP in CHD children after surgery. From Perez-Piaya's study resulted that the level of NT- pro -BNP was higher in CHD patients with hypertension compared to volume overload and cyanotic diseases in preoperative and during 24 hours after surgery. Our finding is similar with Perez-Piaya's et al., study in consideration of a different in the patients' age and regardless of surgery. Due-Andersen conducted a study on NT- pro -BNP during hypoxemia in normal population and concluded that hypoxemia stimulates NT-pro-BNP release. The hypoxemia-induced rise in NT-pro-BNP is fair and supports the use of NT-pro-BNP as a rule-out marker of heart failure in the emergency department. Joseph et al. (26) carried out a study on NT- pro -BNP as a marker of bronchopulmonary dysplasia in premature infants and resulted that NT- pro -BNP levels were high in healthy premature compared with terms, and a significant increase in those who developed bronchopulmonary dysplasia (BPD).

From the present study resulted that the level of NT- pro -BNP was higher in the cardiac and respiratory patients compared to controls in which seems to be due to hypoxia. The results of the two late studies support our findings that NT pro-BNP is a biomarker to differentiate between respiratory and heart diseases in neonates. Sahingozlu et al. (27) showed that in infants with respiratory distress, plasma NT- pro -BNP measurements can make a difference between heart disease and lung disease. In another study that conducted by Hammerer-Lercher et al. (28) has been shown no significant difference in NT- pro -BNP levels between controls group and lung disease group. The NT- pro -BNP levels of patients with heart disease were significantly higher than lung disease group and controls group in the same study. Similar to this study, the NT-pro-BNP levels of children aged older than 14 years were compared and found significantly high in heart failure group. Zhu and Nie (29) showed that NT-pro-BNP level is a useful biomarker for neonatal myocardial injury after asphyxia and can help us to understand the disease' severity and managing the treatment. They reported that the existence of PDA and Respiratory distress syndrome (RDS) will increase the cardiac loads that cause an increase in the level of NT-pro-BNP.

Accordance with mentioned studies, it may be concluded that NT-pro-BNP levels could not be a marker to differentiate RD and CHD patients. It would be due to PDA and RDS in which both can make an increase in volume overload in PDA in preterm neonates and hypoxia in RDS in same infants. In our center patients with RD were under echocardiography and those with PDA excluded from the study.

4-1. Limitations of the study

The study limitations were lack of Proper Corporation by the parents of the neonates specially controls. And low number of the patients with CHD.

5- CONCLUSION

The results of the present study revealed that NT-pro-BNP had higher concentration in CHD neonates compared to respiratory diseases and controls, respectively; and in CHD neonates, Acyanotic had higher levels. Although, some of studies reported that NT-pro-BNP

cannot be used as a tool for differentiation between cardiac and respiratory as a cause of respiratory distress during neonate, but results of the present study was confirmed that this biomarker can be used as a differentiated tool for this specific matter.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGMENT

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

8- REFERENCES

1. Shahramian I, Noori NM, Sharafi E, Ramezani AA, Hesaraki M. Brain Natriuretic Peptide: A Predictor for Severity Respiratory Distress Syndrome in Newborns. Journal of Comprehensive Pediatrics. 2013; 4(4):189-93.

2. Brun-Buisson C, Minelli C, Bertolini G, Brazzi L, Pimentel J, Lewandowski K, Bion J, Romand JA, Villar J, Thorsteinsson A, Damas P. Epidemiology and outcome of acute lung injury in European intensive care units. Intensive care medicine. 2004;30(1):51-61.

3. Vlaar AP, Binnekade JM, Prins D, van Stein D, Hofstra JJ, Schultz MJ, Juffermans NP. Risk factors and outcome of transfusion-related acute lung injury in the critically ill: a nested case–control study. Critical care medicine. 2010; 38(3):771-8.

4. Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. New England Journal of Medicine. 2000; 342(18):1301-8.

5. 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. J Pak Med Assoc. 2013; 63(11):1332-37.

6. Noori NM, Sadeghi S, Shahramian I, Keshavarz K. Urine β 2-Microglobolin in the Patients with Congenital Heart Disease. International cardiovascular research journal. 2013; 7(2):62.

7. Noori NM, Teimouri A, Shahramian I, Akhavan Sales S. Evaluation of brain natriuretic peptide plasma levels in children with congenital heart diseases. International Journal of Pediatrics. 2016; 4(10):3615-26.

8. Noori NM, Mehralizadeh S, Khaje A. Assessment of right ventricular function in children with congenital heart disease. Doppler tissue imaging. Saudi Medical Journal. 2008; 29(8):1168-72.

9. 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 research international. 2015; 2015.

10. Sugimoto M, Manabe H, Nakau K, Furuya A, Okushima K, Fujiyasu H, et al. The role of N-terminal pro-B-type natriuretic peptide in the diagnosis of congestive heart failure in children. Circulation Journal. 2010; 74(5):998-1005.

11. 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.

12. EL-Khuffash A, Molloy E. The use of N-terminal-pro-BNP in preterm infants. International Journal of pediatrics. 2009; 2009.

13. Lechner E, Weissensteiner M, Wagner O, Schreier-Lechner E, Rehak P, Prandstetter C, et al. Aminoterminal pro-B-type natriuretic peptide: heart or lung disease in the neonate?. Pediatric Critical Care Medicine. 2013; 14(4):396-402.

14. Shinichi Takatsuki, Brandie D. Wagner andDavid Dunbar Ivy.B-type Natriuretic Peptide and Amino-terminal Pro-B-type Natriuretic Peptide in Pediatric Patients with Pulmonary Arterial Hypertension.Congenital Heart Disease.2012; 7(3): 259–67.

15. 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.

16. Nir A, Lindinger A, Rauh M, Bar-Oz B, Laer S, Schwachtgen L, Koch A, Falkenberg J, Mir TS. NT-pro-B-type natriuretic peptide in infants and children: reference values based on combined data from four studies. Pediatric cardiology. 2009; 30(1): 3.

17. Cantinotti M, Law Y, Vittorini S, Crocetti M, Marco M, Murzi B, Clerico A. The potential and limitations of plasma BNP measurement in the diagnosis, prognosis, and management of children with heart failure due to congenital cardiac disease: an update. Heart failure reviews. 2014; 19(6):727-42.

18. Rusconi PG, Ludwig DA, Ratnasamy C, Mas R, Harmon WG, Colan SD, et al. Serial measurements of serum NT-proBNP as markers of left ventricular systolic function and remodeling in children with heart failure. American heart journal. 2010; 160(4):776-83.

19. Xue Y, Chan J, Sakariya S, Maisel A. Biomarker-guided treatment of congestive heart failure. Congest Heart Fail. 2010;16 Suppl 1:S62-7.

19. Cantinotti M, Walters HL, Crocetti M, Marotta M, Murzi B, Clerico A. BNP in children with congenital cardiac disease: is there now sufficient evidence for its routine use? Cardiology in the Young. 2015; 25(3):424-37.

20. Markovic-Sovtic G, Kosutic J, Jankovic B, Bojanin D, Sovtic A, Radojicic Z, et al. N-terminal pro-brain natriuretic peptide in the assessment of respiratory distress in term neonates. Pediatrics International. 2014; 56(3):373-7.

21. Nir A, Nasser N. Clinical value of NT-ProBNP and BNP in pediatric cardiology. Journal of cardiac failure. 2005; 11(5):S76-80.

22. Aydemir O, Aydemir C, Sarikabadayi YU, Altug N, Erdeve O, Uras N, et al. The role of plasma N-terminal pro-B-type natriuretic peptide in predicting the severity of transient tachypnea of the newborn. Early human development. 2012; 88(5):315-9.

23. Farombi-Oghuvbu I, Matthews T, Mayne PD, Guerin H, Corcoran JD. N-terminal pro-B-type natriuretic peptide: a measure of significant patent ductus arteriosus. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2008; 93(4):F257-60.

24. Pérez-Piaya M, Abarca E, Soler V, Coca A, Cruz M, Villagrá F Levels of N-terminal-pro-brain natriuretic peptide in congenital heart disease surgery and its value as a predictive biomarker. Interactive CardioVascular and Thoracic Surgery 2011: 12; 461-66.

25. Joseph L, Nir A, Hammerman C, Goldberg S, Shalom EB, Picard E. N-terminal pro-B-type natriuretic peptide as a marker of bronchopulmonary dysplasia in premature infants. American journal of perinatology. 2010; 27(05):381-6.

26. 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.

27. Hammerer-Lercher A, Geiger R, Mair J, Url C, Tulzer G, Lechner E, et al. Utility of N-terminal pro-B-type natriuretic peptide to differentiate cardiac diseases from noncardiac diseases in young pediatric patients. Clinical chemistry. 2006; 52(7):1415-19.

28. Zhu R, Nie Z. A clinical study of the N-terminal pro-brain natriuretic peptide in myocardial injury after neonatal asphyxia. Pediatrics and Neonatology. 2016; 57(2):133-9.