



Plasma N-terminal Pro Brain Natriuretic Peptide as a Prognostic Biomarker in Children with Pulmonary Hypertension

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Authors' contributions

This work was carried out in collaboration between all authors. Author FAR designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript.

Authors DEA and AZ managed the analyses of the study. Author HES managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aim: To evaluate plasma level of N-terminal pro brain natriuretic peptide (NT pro-BNP) as a prognostic biomarker in children with pulmonary hypertension (PH) due to congenital heart disease (CHD).

Study Design: Prospective case controlled study.

Place and Duration of the Study: Pediatric cardiology department, Tanta University hospital, Egypt during the period from February 2016 to February 2017.

Methodology: Thirty children with PH due to CHD were enrolled as patients group. Thirty healthy children of matched age and sex were taken as control group. All children were evaluated by echocardiography and plasma level of NT pro-BNP at admission. We followed up patients for 6 months after discharge for adverse effects, mortality or readmission.

Results: Plasma level of NT pro-BNP was significantly elevated in patient group than control group (P=0.001). Both systolic and diastolic functions of left ventricle and right ventricle were impaired in

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patient group compared to control group. Moreover, both left ventricular and right ventricular dimensions were increased in patient group than control group. Plasma NT pro-BNP was significantly elevated in patient with unfavorable prognosis compared to patients with favorable prognosis ($P < 0.001$). Plasma NT pro-BNP level was positively correlated with heart rate, estimated systolic pulmonary artery pressure and left ventricular end systolic dimension. While, it was significantly inversely correlated with left ventricular fraction shortening, left ventricular E'/A' ratio, right ventricular outlet fraction shortening and right ventricular E'/A' ratio. Receiving operating characteristics curve showed that sensitivity of NT pro BNP as a prognostic biomarker in PH patients was 100% and specificity was 92% at cutoff value of more than 103 pg/ml.

Conclusion: NT pro-BNP may serve as a reliable biomarker for predicting adverse outcome in children with PH due to CHD.

Keywords: NT pro BNP; PH; children; prognosis.

1. INTRODUCTION

Pulmonary hypertension (PH) is a life threatening condition with high morbidity and mortality in pediatrics with large varieties of underlying etiologies. It is defined as an increase in pulmonary artery pressure over 25 mmHg when measured at rest [1]. The disease is usually monitored through serial measurements of pulmonary artery systolic pressure by echocardiography. The gold standard for diagnosis and prognosis of PH is right heart catheterization, but being invasive maneuver limits its use [2]. So, the presence of alternative non invasive simple biomarker for monitoring PH and predicting adverse outcome will be invaluable.

Natriuretic peptide is a hormone that has diuretic, natriuretic and vasodilator effects. In humans BNP is produced mainly by ventricular myocytes in response to ventricular wall stretching or pressure overload [3]. Pro BNP is cleaved into two components, active component called BNP and inactive one called NT pro-BNP [4]. NT pro BNP has many advantages over BNP, a longer plasma half life, lower biological variation and being biologically inactive. The widely used clinical application of NT pro-BNP is for the emergent diagnosis of heart failure in patients presenting with acute dyspnea [5]. However, Both BNP and NT pro-BNP are recommended by guidelines for risk stratification in PH due to different causes [6]. Most studies were performed in primary PH [7-8], but to the best of our knowledge, there is the lack of studies carried out on children suffering from PH due to congenital heart disease (CHD), that was investigated only in one study [9] and measured the association between NT pro-BNP levels from one side and both pulmonary pressure and quantity of left to right shunt from the other side. The objective of the present work was to

evaluate plasma level of NT pro-BNP as a prognostic biomarker in children with pulmonary hypertension due to cardiac disease and to correlate its level with clinical and echocardiographic variables in these patients.

2. MATERIALS AND METHODS

This is a prospective case control study that was performed on 30 children with PH due to CHD, their age ranged from 1-60 months with mean of (16.06±19.03), they were 16 males and 14 females. Thirty healthy children of matched age and sex were taken as control group, their ages ranged from 1-60 months with mean of (17.14±19.54), they were 16 males and 14 females. Patients were selected from those admitted to pediatric cardiology unit, Tanta university hospital during the period from February 2016 to February 2017. The study was approved by the local ethical committee of our faculty of medicine. Written informed consent was signed by all parents of the included children.

Inclusion criteria: Children and infants with CHD complicated with PH.

Exclusion criteria: Children with primary PH, respiratory cause of PH, core-pulmonale, renal disease, central nervous system disease, sepsis, shock, or anemia.

All children included in the study were subjected to the following:

- I- Complete history taking and clinical examination.
- II- Plain X ray of the chest and heart.
- III- Electrocardiography (ECG): was done by 12 leads ECG using 3 channels α 1000 apparatus.

- IV- Echocardiographic examination: was performed using Vivid 7 machine (GE medical system, Horten, Norway) with 3.5 and 4S multi-frequency transducers. We used different modalities as M mode, 2D examination, pulsed and continuous wave Doppler, color flow mapping, and tissue Doppler for assessment of estimated systolic pulmonary artery pressure (ESPAP), systolic and diastolic functions for both left ventricular (LV) and right ventricle (RV). Systolic function was evaluated by measuring the fraction shortening (FS). $FS\% = (LVEDD - LVESD / LVEDD) \times 100 \%$. diastolic function was also measured through estimation of peak mitral and tricuspid flow of E' wave, A' wave and the ratio between them (E'/A' ratio) using tissue Doppler echocardiography, where the normal value ranged between 1-2. Pulmonary hypertension was diagnosed when ESPAP exceeds 25 mmHg.
- V- Estimation of plasma N-terminal pro-brain natriuretic peptide (NT-pro BNP): using ELISA kit, supplied by Sunred biocompany, Shanghai, China, catalogue number 201-12-1240. Two ml of venous blood was collected in tubes containing EDTA from each included subject then the sample was centrifuged for 20 minutes at a speed of 2000-3000 cycle/minute and the supernatant was removed. The plasma was stored at -20 C till the time of analysis of NT pro BNP. The kits use double antibody sandwich enzyme linked immunosorbent assay (ELIZA) technique to assay the level of NT pro-BNP in samples.

The patients were followed up for 6 months for mortality, readmission or complications. The primary outcome was to evaluate the plasma levels of NT pro BNP in children with PH due to CHD and to evaluate the prognostic value of NT pro BNP to predict unfavorable outcome in these children. The secondary outcome was to correlate NT pro-BNP level with clinical and echocardiographic variables.

2.1 Statistical Analysis

Statistical analysis was performed using SPSS V. 20. (SPSS Inc. Chicago, IL, USA). All results were presented in the form of mean \pm standard deviation (SD). Normal distribution of the data was checked by Shapiro-Wilk test. Independent t test was used for comparison between means of

the two groups. Chi-square test was used to compare non parametric values between the two groups. Linear correlation was done using Pearson correlation coefficient to assess the strength of association between variables. Receiver operating characteristics (ROC) curve was performed to evaluate the predictive value of NT-pro BNP in PH due to cardiac disease. P value was considered significant if it was <0.05 .

3. RESULTS

Children with PH was 16 males and 14 females with mean age of (16.06 ± 19.03) months and mean weight of (10.3 ± 6.1) while control group was 16 males and 14 females with mean age of (17.14 ± 19.54) months and mean weight of (13.7 ± 6.3) with no statistical difference regarding age and sex but weight was significantly lower in patient group than control group. Respiratory rate (RR) and heart rate (HR) were significantly higher in patient group than control group with $(P=0.006, 0.001)$ respectively. Diagnosis of patients group was shown in Table 1. Plasma levels of NT-pro BNP was significantly higher in patient group (92.17 ± 54.34) than control group (27.59 ± 18.16) with $P=0.001$ (Table 1).

Table 2 showed the echocardiographic findings in patient and control group. Left ventricular systolic function measured by LV FS was significantly lower in patient group ($P=0.01$). Moreover, left ventricular diastolic function measured by transmitral flow of E'/A' ratio was significantly lower in patient group than control group ($P=0.01$). Similarly, RVOT FS and RV E'/A' ratios were significantly lower in patient group than control group ($P=0.01$). LV ESD, LV EDD and RV diameters were significantly increased in patient group than control group.

During 6 months of follow up, seven out of 30 patients (23.3%) with PH had unfavorable prognosis in the form of death and readmission. Plasma levels of NT pro-BNP was significantly higher in patients with unfavorable prognosis (174.8 ± 31.8) than those with favorable prognosis (67 ± 28.1) with $P < 0.001$ (Table 3).

Plasma level of NT pro-BNP was significantly positively correlated with HR, MPAP, LVESD, LVEDD and RV diameter. While, it is significantly inversely correlated with LV FS, LV E'/A' ratio, RVOT FS and RV E'/A' ratio. NT pro-BNP was correlated neither to age nor to RR (Table 4).

Comparing NT pro BNP levels in PH patients with favorable prognosis to PH patients with unfavorable prognosis, ROC curve showed that sensitivity of NT pro BNP as a prognostic biomarker for predicting adverse outcome in PH patients was 100%, with a specificity of 92% at cutoff value of more than 103 pg/ml with positive predictive value of 77.8% and negative predictive value of 100%. The area under the curve (AUC) was 0.989 (Fig. 1).

4. DISCUSSION

Pulmonary hypertension (PH) due to congenital heart disease (CHD) is common in pediatric population and is one of the indications of surgical correction of most CHD. Right heart catheterization still the gold standard for diagnosis and prognosis of PH in these children but its invasive nature limits its use in small

Table 1. Demographic and clinical characteristics of the study groups

Variable	Group 1 (Patient group)	Group 2 (Control group)	Test of variables	P value
Age (months)	16.06 ± 19.03 Range (1-60)	17.14 ± 19.54 Range (1-60)	t= 3.25	0.078
Weight (kg)	10.3 ± 6.1 Range (2.5-13)	13.7 ± 6.3 Range (2.9-12.3)	t= 0.253	0.038
Sex (male: female)	16:14	16:14	X ² = 0.0	1.0
Diagnosis:	- 4 ASD (13.3%) - 7 ASD+PDA (23.3%) - 1 ASD+VSD (3.3%) - 1 ASD+MR (3.3%) - 9 VSD (30%) - 1 VSD+PDA (3.3%) - 2 AVC (6.7%) - 4 PDA (13.3%) - 1 MR (3.3%)			
RR (cycle/minute)	33.27±8.44	27.96±5.32	t=2.923	0.006*
HR (beat/minute)	120.47±14	94.03±10.23	t=69.724	0.001*
NT pro BNP (pg/ml)	92.17±54.43	27.59±18.16	t=18.1	0.001*

ASD: Atrial septal defect, PDA: Patent ductus arteriosus, VSD: Ventricular septal defect, MR: Mitral regurgite, AVC: Atrioventricular canal, RR: Respiratory rate, HR: Heart rate, NT pro BNP: N-terminal pro brain natriuretic peptide

Table 2. Echocardiographic findings in studied groups

Variables	Group 1 (patient group)	Group 2 (control group)	P value
LV FS	35.63±4.30	43.70±16.09	0.01*
LV E'/A' ratio	1.4±1.11	1.6±1.39	0.01*
RVOT FS	31.37±5.46	36.97±3.76	0.01*
RV E'/A' ratio	1.19±0.22	1.36±0.11	0.01*
LV ESD (mm)	20.97±4.41	16.97±3.19	0.001*
LV EDD (mm)	32.03±7.65	27.21±4.34	0.004*
RV diameter (mm)	18.57±4.58	16.20±3.27	0.025*
ESPAP	48.83±12.08	12.13±2.78	0.001*

LV: Left ventricle, FS: Fraction shortening, ESD: End systolic diameter, EDD: End diastolic diameter, RV: Right ventricle, RVOT: Right ventricular outflow tract, ESPAP: Estimated systolic pulmonary artery pressure

Table 3. Plasma levels of NT- pro BNP in PH patients with favorable and unfavorable prognosis

Prognosis	Number	Percent	NT-pro BNP	P value
Favorable	23	76.7%	67±28.1	<0.001*
Unfavorable	7	23.3%	174.8±31.8	

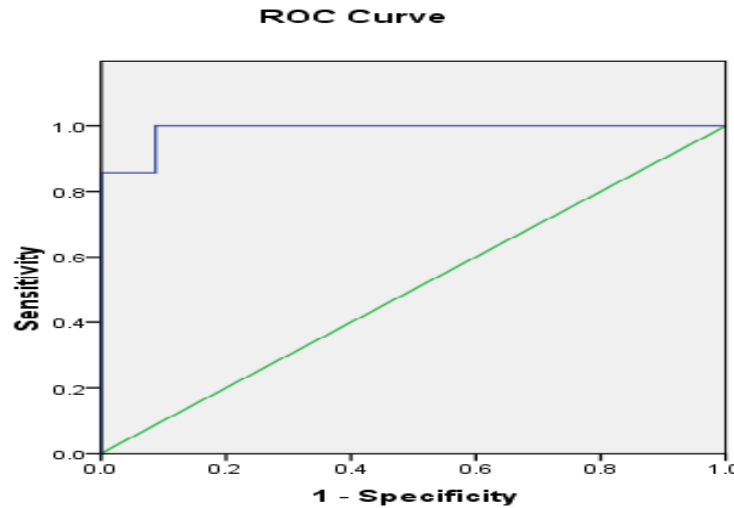


Fig. 1. Receiver operating characteristic (ROC) curves of prognostic value of NT pro BNP for detection of bad prognosis showed sensitivity of 100%, specificity of 92% at cutoff value of 103 pg/ml

infants and children. Echocardiography is an alternative to catheterization but it is operator dependent with frequent false calculation [10]. So, the presence of rapid easy non invasive accurate biomarker with reasonable cost, which can add diagnostic and prognostic information, will be invaluable. Therefore, we investigated the prognostic value of NT pro BNP to predict bad prognosis in children with PH due to CHD as early detection of these high risk children will allow for further investigation and intervention.

Table 4. Correlation between plasma levels of NT pro-BNP and both clinical and echocardiographic variables in children with PH due to CHD

Variables	NT pro- BNP	
	r	P value
Age (months)	0.053	0.779
RR	0.055	0.774
HR	0.724	0.001*
ESPAP	0.644	0.001*
LV FS	-0.510	0.004*
LV E'/A' ratio	-0.733	0.001*
RVOT FS	-0.701	0.001*
RV E'/A' ratio	-0.471	0.009*
LV ESD	0.634	0.001*
LVEDD	0.734	0.001*
RV diameter	0.488	0.005*

RR: Respiratory rate, HR: Heart rate, ESPAP: Estimated systolic pulmonary artery pressure, LV: Left ventricle, FS: Fraction shortening, ESD: End systolic diameter, EDD: End diastolic diameter, RV: Right ventricle, RVOT: Right ventricular outflow tract

In our study, we found that plasma level of NT-pro BNP was significantly elevated in patients with PH compared to control group. This elevation of plasma NT-pro BNP most probably results from increased RV wall stretching and hypertrophy. This agrees with the results of Barst et al. [11] who found that plasma NT-pro BNP level was elevated in patients with PH. Also, this is in agreement with the study done by McCullough et al. [4] who found that plasma NT-pro BNP level was increased in patients with high pulmonary pressure.

Our study showed that there was more significant increase of plasma level of NT-pro BNP in PH cases with unfavorable prognosis (hospital readmission or death) than those with favorable prognosis. ROC curve analysis showed that the predictive value of plasma NT-pro BNP to detect adverse outcome in children with PH due to CHD was high with sensitivity of 100%, specificity of 92% and accuracy of 98% at a cutoff value of 103 pg/ml. This is in agreement with the result of Fijalkowska et al. [12] who reported that high plasma NT-pro BNP level was found to be useful biomarker in identifying poor long-term prognosis in patients with PH. Moreover, Andreassen et al. [13] reported that NT-pro BNP had a specificity of 100% as a prognostic biomarker for detecting poor prognosis and mortality in PH patients.

The present study showed that there was strong correlation between NT-pro BNP levels and both

clinical and echocardiographic findings in children with PH. NT-pro BNP levels had significant positive correlation with heart rate. This was in agreement with other investigators [13,14] who found significant positive correlation of NT-pro BNP and heart rate.

Our study reported that there was significant positive correlation between NT-pro BNP levels and pulmonary pressure. This comes in agreement with Andreassen et al. [13] and Samadi et al. [9] who found significant positive correlation between NT-pro BNP levels and pulmonary pressure in patients with pulmonary hypertension.

The current study revealed that NT-pro BNP levels had significant negative correlation with right ventricular function and significant positive correlation with right ventricular dimension. This is similar to the findings of Fijalkowska et al. [12] who reported that NT-pro BNP level was related to right heart morphology and dysfunction as assessed by echocardiography. Our study agrees also with Nagaya et al. [15] and Gan et al. [16] who concluded that plasma NT-pro BNP level reflected right ventricular function in all patients with idiopathic pulmonary hypertension and high level of NT pro BNP was associated with bad prognosis. Furthermore, our results come in agreement with the results of Van Albada et al. [17] who suggested that NT-pro BNP may have additional value in the management of children with pulmonary arterial hypertension if tracked over time. Additionally, they observed that a high level of NT-pro BNP is indicative of poor survival.

Moreover, we found that NT-pro BNP level has significant negative correlation with left ventricular function and significant positive correlation with left ventricular dimensions as detected by echocardiography. This is in agreement with other investigators [14,18,19].

Interestingly, there is lack of data available for relating plasma NT-pro BNP concentration to the echocardiographic characteristics of pediatric patients with PH. We observed correlation of plasma NT-pro BNP concentration with echocardiographic indexes of RV function and dimension. These findings could be of practical importance, indirectly suggesting that NT-pro BNP assessment could replace or reduce the number of echocardiographic examinations conducted during follow-up.

5. CONCLUSION

NT pro-BNP may serve as a reliable biomarker for predicting adverse outcome in children with PH due to CHD.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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