

Value of plasma NT-ProBNP concentration in the diagnosis of congenital heart in children

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ABSTRACT

Objective: Research the value of plasma NT-ProBNP concentration in diagnosing congenital heart disease in children. **Objects and methods of study:** Controlled study on 80 children with congenital heart disease at the Vietnam National Children's Hospital from April 2018 to August 2019. **Results:** NT-ProBNP concentrations in all types of congenital heart disease were higher than in the control group ($p < 0.05$). NT-ProBNP concentration was highest in the left-right shunt group and lowest in the cyanotic congenital heart disease group with a statistically significant difference ($p > 0.05$). NT-ProBNP concentration was highest in the severe heart failure group, followed by the moderate, mild and no heart failure groups and were all higher than the control group ($p < 0.01$). NT-ProBNP concentration was the highest in the severe pulmonary hypertension group, followed by the moderate, mild, and no pulmonary hypertension groups and were all higher than the control group ($p < 0.05$). The optimal cutoff point of NT-ProBNP is 671 pg/ml, which is valuable for diagnosing congenital heart disease with a sensitivity of 90.2%, a specificity of 53.1% and an area under the curve of 0.735. **Conclusion:** NT-ProBNP levels are increased in congenital heart disease in children. Increased NT-ProBNP concentrations are associated with left-right shunting, degree of heart failure and pulmonary hypertension. **Keywords:** NT-ProBNP, congenital heart disease, children.

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INTRODUCTION

Congenital heart disease (CHD) is a defect of the heart and/or large blood vessels that is present at birth. Congenital heart disease can cause dangerous complications such as heart failure, pulmonary hypertension, Eisenmenger syndrome, etc., and even death if not detected early and treated promptly [1]. Therefore, early diagnosis and timely treatment of congenital heart disease are very important. Currently, echocardiography is of prime value in the diagnosis of congenital heart disease, helping to evaluate the structure and function of the heart. However, in reality,

echocardiography is a highly specialized technique, so it is difficult to perform regularly in departments as well as medical facilities. Therefore, there is a need for a disease diagnosis method that is easy to perform and gives quick results.

Currently, the role of biomarkers such as B-type Natriuretic Peptide (BNP, NT-ProBNP) and Troponin, CK-MB, etc in the assessment of cardiovascular diseases has been confirmed [2], [3]. Regarding the mechanism, B-type Natriuretic Peptide is released due to an increase in pressure and volume of the ventricles, especially the left ventricle. In congenital heart disease, structural abnormalities of the heart chambers and blood vessels cause changes in the pressure and volume of the heart

chambers [4], [5]. Because of this, it causes the release and increase of BNP and NT-ProBNP concentrations in plasma. However, currently in Vietnam, research on the role of B-type Natriuretic Peptide in children's congenital heart disease is still very limited. Therefore, we conducted the study "Value of plasma NT-ProBNP concentration in the diagnosis of congenital heart disease in children" to support early diagnosis of congenital heart disease.

OBJECTS AND METHODS

Objects

Disease group: 80 children with congenital heart disease came for examination and treatment at the Vietnam National Children's Hospital.

Control group: 80 clinically evaluated healthy children of the same age and gender as the disease group. For each child in the disease group, we selected 1 child in the control group of the same age and gender.

Criteria for selection

Disease group: The children were diagnosed with congenital heart disease by cardiologists at the Vietnam National Children's Hospital when structural abnormalities of their heart were identified by ultrasound.

Control group: healthy children evaluated clinically and paraclinically.

Criteria for exclusion

Exclude from the study both the controlled group and the patient group if the children have any of the following diseases: kidney failure, endocrine disease, severe infection, pneumonia, obesity, severe anemia.

Time and location

Time: from April 2018 to August 2019.

Location: At the Clinic of the Cardiovascular Department – Vietnam National Children's Hospital.

Methods

Design: Cross-sectional description with comparison and convenience sampling.

Steps to conduct the study

- Disease group: after being diagnosed with congenital heart disease, plasma NT-ProBNP concentration will be measured, when no treatment has been used.

- Control group: quantification of plasma NT-ProBNP concentration at the time the children came for medical examination.

Quantification of plasma NT-ProBNP concentration by electrochemiluminescence immunoassay on Roche's Cobas e601 machine at the Department of Biochemistry, Vietnam National Children's Hospital. In the study, we compared plasma NT-ProBNP concentrations between the patient group and the control group. In addition, we compared plasma NT-ProBNP concentrations between congenital heart disease types, heart failure degree, and pulmonary artery pressure degree.

The study's variables

- Age, gender

- Types of congenital heart disease: left-right shunt, cyanotic congenital heart, and other congenital hearts.

- Degree of heart failure: heart failure is classified based on the revised Ross criteria with levels: no heart failure, mild heart failure, moderate heart failure, severe heart failure.

- Systolic pulmonary artery pressure: assessed on ultrasound with levels: no increase, slightly increased, moderate, severe.

- Plasma NT-ProBNP concentration: the unit is pg/ml.

Data processing and analysis

Data were processed using SPSS software version 22. Data were presented as: median with 25th and 75th Interquartile range (IQR) for non-standard distribution. The Mann - Whiney test was used to compare the median of two independent samples for non-standard distribution.

Ethical considerations in the study

The child's family explained the study content and provided consent to participate. Patient information was

guaranteed to be confidential. The study did not affect the patient's health.

RESULTS

General characteristics

Table 1. Distribution by age and gender

Gender, age	Disease group		Control group	
	n	%	n	%
Boy	43	53.8	43	53.8
Girl	37	46.2	37	46.2
< 1 year old	53	66.3	53	66.3
1 year old - 5 year old	23	28.7	23	28.7
5 year old - 15 year old	4	5	4	5
Total	80	100%	80	100%

Age: in the congenital heart group and control group, the most common age group is under 1 year old (66.3%). *Gender:* in both the heart failure group and the control group, boys accounted for 53.8%, and girls accounted for 46.2%.

Table 2. Classification of congenital heart disease and associated disorders

Characteristics	Quantity	Percentage
CHD	Left-right shunt	37 46.3%
	Cyanotic CHD	33 41.2%
	Other CHD	10 12.5%
Heart Failure (HF)	Severe HF	13 16.2%
	Moderate HF	21 26.2%
	Mild HF	35 43.8%
	No HF	11 13.8%
Pulmonary hypertension	Severe	10 12.5%
	Moderate	20 25.0%

Mild	30	37.5%
No increase	11	13.7%
Unknown	9	11.3%

The left-right shunt congenital heart group accounts for the highest proportion with 46.3%, followed by cyanotic congenital heart (41.2%). The severity of heart failure is mainly mild (43.8%) and moderate (26.2%). Most patients have pulmonary hypertension with varying degrees (88.7%), and there were 9 cases where systolic pulmonary artery pressure could not be determined on echocardiography.

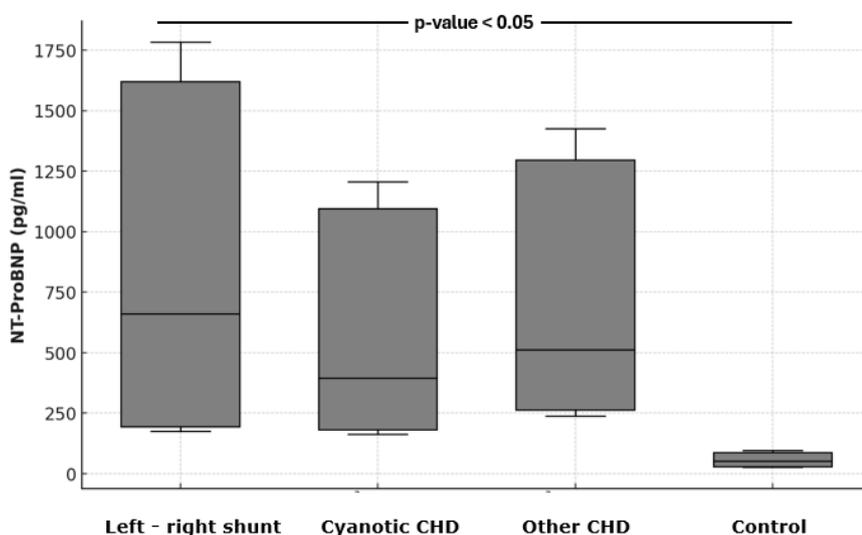


Figure 1. NT-ProBNP concentration in the congenital heart group and control group

NT-ProBNP concentrations in all types of congenital heart disease were higher than in the control group ($p < 0.05$). NT-ProBNP concentration was highest in the left-right shunt group and lowest in the cyanotic congenital heart group and there was a difference between types of congenital heart disease ($p < 0.05$).

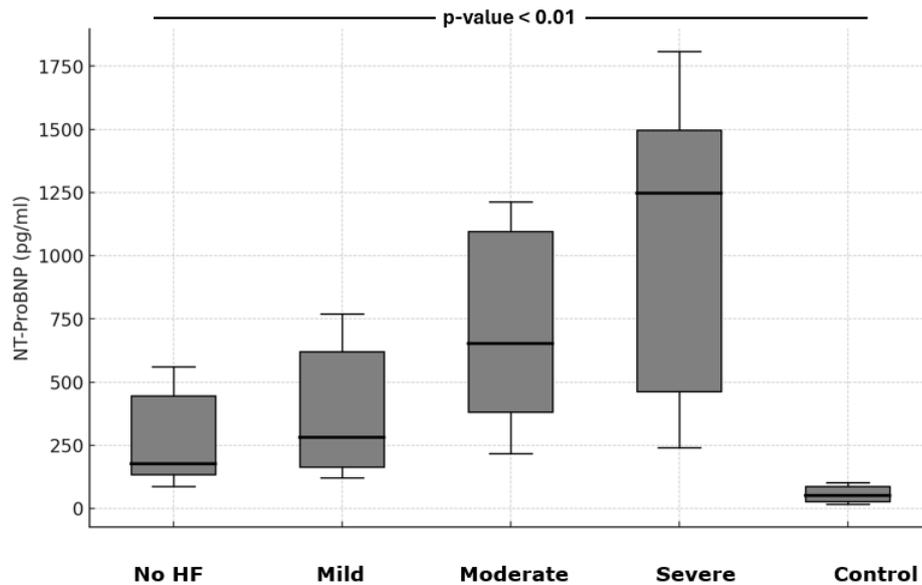


Figure 2. NT-ProBNP concentration in different levels of HF versus the control group

NT-ProBNP concentration was highest in the severe heart failure group, followed by the moderate, mild, and no heart failure groups, the difference was statistically significant ($p < 0.01$). NT-ProBNP concentrations in the congenital heart disease groups, including the group without heart failure, were higher than the control group with a statistically significant difference ($p < 0.01$).

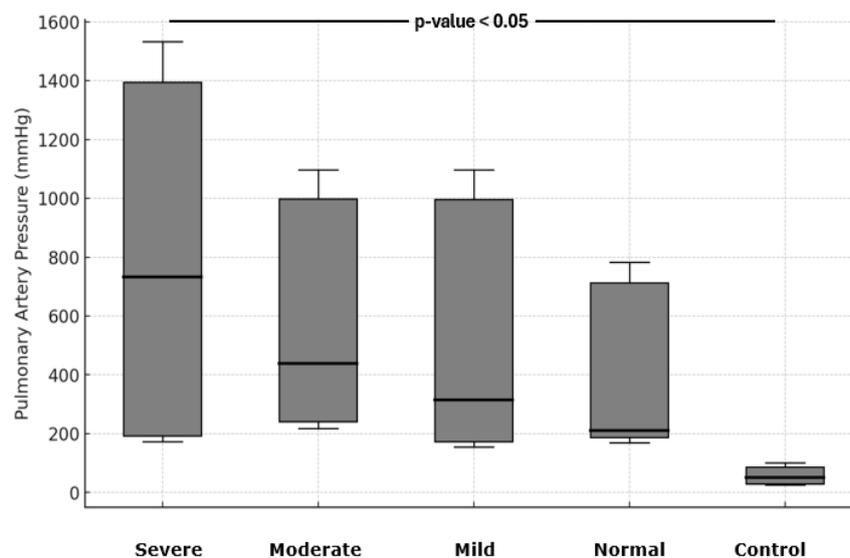


Figure 3. NT-ProBNP concentration between levels of pulmonary hypertension versus the control group.

NT-ProBNP concentration was the highest in the severe pulmonary hypertension group, followed by the moderate, mild, and no pulmonary hypertension groups, and were all higher than the control group with differences between groups with statistical significance ($p < 0.05$)

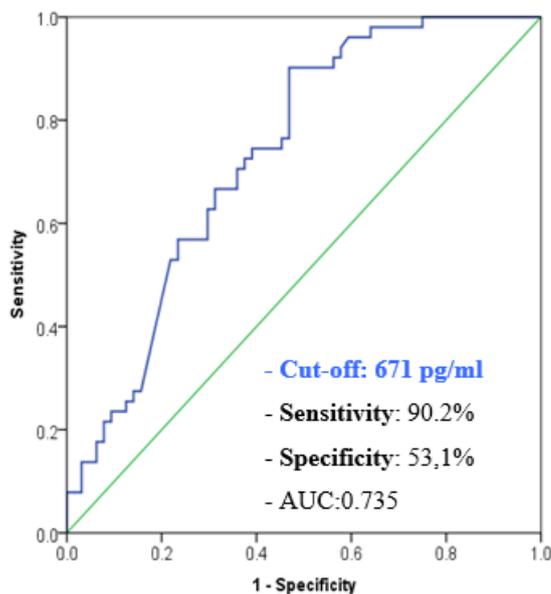


Figure 4. Roc curve of NT-ProBNP in the diagnosis of congenital heart disease

The optimal cut-off point of NT-ProBNP is 671 pg/ml, which is valuable for determining the border between the congenital heart group and the control group with a sensitivity of 90.2%, a specificity of 53.1% and an area under the curve is 0.735.

DISCUSSIONS

Our research results show that the concentrations in the congenital heart group are higher than the control group, with the highest being in the left-right shunt group and the lowest being in the cyanotic congenital heart group with significant statistical differences ($p < 0.05$) (Figure 1). Similarly, research conducted by author Andrei A. Svobodov showed that Pro-BNP concentrations in patients with congenital heart disease are elevated and reflect the severity of hemodynamic disorders. This shows that in congenital heart disease, there are hemodynamic changes due to structural abnormalities that cause pressure and volume overload of the heart chambers, especially the

left ventricle, leading to an increase in NT-ProBNP concentration.

Especially in congenital heart disease with left-right shunting, hemodynamic disorders due to intracardiac shunting cause increased aorto-pulmonary flow, leading to volume overload and right and left ventricular pressure, increasing NT-pro-BNP [5]. This is also the reason the NT-ProBNP concentration in the left-right shunt group was higher than the other groups (Figure 1). Therefore, quantifying NT-ProBNP concentration helps indirectly evaluate the degree of shunting and aorto-pulmonary flow, so it is valuable to determine the time of intervention to treat congenital heart disease [2], [3]. Eindhoven et al also showed that in children with complex cyanotic congenital heart disease, NT-

ProBNP concentrations were higher than in the age-matched control group even though the children had no symptoms of heart failure. According to the author, in cyanotic congenital hearts, a direct cause of the release and increase in NT-ProBNP concentration is hypoxia. In this study, results showed a general increase in Natriuretic Peptide concentrations in complex congenital heart disease, although there were differences in this index between types of congenital heart defects [2]. Similarly, study conducted by Butnariu A and colleagues showed that in children with congenital heart disease, NT-ProBNP concentrations were 4 times higher than in the control group ($p < 0.001$) [3].

Our study results showed that NT-ProBNP concentration was highest in the severe heart failure group, followed by the moderate, mild, and no heart failure groups. In the congenital heart group without heart failure, NT-ProBNP concentrations were still higher than the control group with a statistically significant difference ($p < 0.01$). Chowdhury RR et al. suggested that increased NT-ProBNP concentrations could be considered as a marker of the severity of heart failure in children with congenital heart disease [4]. Most studies show that Natriuretic Peptides in general and especially NT-ProBNP have a very close correlation with the clinical severity of heart failure with or without congenital heart disease. Therefore, currently, the method of quantifying NT-ProBNP concentrations has become routine and has high sensitivity and specificity in the diagnosis and prognosis of heart failure treatment in children.

Our study results also showed that NT-ProBNP concentrations were highest in the severe pulmonary hypertension group, followed by the moderate, mild, and no pulmonary hypertension groups with statistically significant differences between the groups ($p < 0.05$). However, in the congenital heart group without pulmonary hypertension, NT-ProBNP concentrations were still higher than the control group ($p < 0.05$) (Figure 3). This shows that in

pulmonary hypertension, more blood flows to the lungs and causes an increase in right ventricular pressure and volume, leading to the release of NT-ProBNP. Although the mechanism of NT-ProBNP release is mainly from the left ventricle, studies show that NT-ProBNP concentrations also increase in right ventricular hemodynamic disorders [6], [7]. Similarly, Takatsuki et al. also showed that this index increased corresponding to the increase in pulmonary artery pressure. Specifically, every increase of 1 unit of LogNT-ProBNP corresponds to an increase of 3.4 m2 in the pulmonary resistance index. Therefore, the author believes that NT-ProBNP concentration can predict clinical and hemodynamic changes in pulmonary hypertension [8].

Our study results show that the optimal cut-off point of NT-ProBNP is 671 pg/ml, which has value in diagnosing congenital heart disease. This cutoff point determined the boundary between the congenital heart group and the control group with a sensitivity of 90.2%, a specificity of 53.1%, and an area under the curve of 0.735. According to the report of Wu Y et al., the cutoff point of NT-ProBNP is 499 fmol/ml (1726 pg/ml) which has value in diagnosing congenital heart disease. The author also affirmed that using the quantitative method of NT-ProBNP concentration combined with clinical signs will improve the accuracy of diagnosis [5]. Meanwhile, according to research by author Elsharawy S, the cutoff point of NT-ProBNP is 101 fmol/ml (349 pg/ml) which has the value of diagnosing congenital heart disease with a sensitivity of 90% and a specificity of 80% [9].

CONCLUSIONS

In a controlled study of 80 children with congenital heart disease at the Vietnam National Children's Hospital, we found NT-ProBNP levels are increased in congenital heart disease in children. Increased NT-ProBNP concentrations are associated with left-right shunting, degree of heart failure, and pulmonary hypertension.

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