Using N-terminal pro-B natriuretic peptide to diagnose cardiac abnormalities in children with dyspnea

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Original Article

Using N-terminal pro-B-type natriuretic peptide to diagnose cardiac abnormalities in children with dyspnea

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Abstract

Background Malnutrition in hospitalized children has negative Background Dyspnea can be caused by various conditions, one of which is cardiac abnormality. Physical examination alone is not sufficient for distinguishing breathing ailments caused by heart abnormalities, especially in small children. N-terminal pro-B-type natriuretic peptide (NT-proBNP) has been used as a marker of heart disease.

Objective To evaluate the usefulness of NT-proBNP levels as a screening tool to diagnose cardiac abnormalities in children presenting with dyspnea.

Methods A cross-sectional study was conducted from August to October 2015 in pediatric patients aged 1 month to 18 years presenting with dyspnea in the Pediatric Ward, Mohammad Hoesin Hospital, Palembang, North Sumatera. All subjects provided blood specimens for NT-proBNP examinations and underwent echocardiography to assess for the presence of cardiac abnormalities. The diagnostic value was analyzed by ROC curve. We determined the optimal cut-off point, sensitivity, and specificity.

Results Fifty-eight subjects, with median age 9.5 (range 1-180) months, consisted of 39 children with and 19 children without cardiac abnormalities. Subjects' median NT-proBNP levels were significantly higher in those with cardiac abnormalities than in those without [1,775 (range 189-9,000) pg/mL vs. 759 (range 245-9,000) pg/mL, respectively, (P=0.002)]. In a ROC curve analysis the AUC value was 0.75, and at the optimal cut-off point of 1,235 pg/ml had sensitivity of 74.4% and specificity of 73.7%.

Conclusion The level of NT-proBNP can be used to screen for cardiac abnormalities in children presenting with dyspnea. **[Paediatr Indones. 2017;57:124-8 doi: http://dx.doi.org/10.14238/pi57.3.2017.124-8].**

Keywords: *NT-proBNP; dyspnea; cardiac abnormality*

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a hormone secreted primarily by ventricular cardiac myocytes in response to pressure and volume overload.[1] This hormone has been shown to be an accurate marker for heart disease and helpful in differentiating between heart disease and systemic diseases of the respiratory system in acute conditions. In infants and small children with dyspnea, it is particularly difficult to differentiate between heart failure or other diseases and the pathology.1 A previous study assessed the differences of NT-proBNP levels in healthy children vs. patients with heart failure and other diseases.[2] In addition, another study assessed the benefits of NT-proBNP examination to screen for children with congenital heart disease.[3]

In children, cardiac abnormalities, especially structural abnormalities, are major risk factors of heart failure. The main clinical manifestation most commonly found in children is dyspnea. Dyspnea

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can vary from tachypnea to respiratory distress. In acute conditions, it is often difficult to detect cardiac involvement in children with dyspnea, especially in infants and small children, so misdiagnoses happen frequently, leading to postponed management and poorer prognoses.[4]

The current diagnostic examination to assess for cardiac abnormalities is echocardiography. This test has limitations, as it is generally not available in district hospitals, and it is done by a cardiologist. Therefore, NT-proBNP testing could potentially be used mainly in hospitals with less access to echocardiography, in order to check for heart involvement in children who experience shortness of breath. As such, the initial management of the patient may not be hampered and outcomes can hopefully be improved.

Methods

A cross-sectional study was conducted in the Pediatric Ward of Dr. Mohammad Hoesin Hospital, Palembang, South Sumatera, from August to October 2015. Subjects were recruited by consecutive sampling. Inclusion criteria were patients with dyspnea over the age of 28 days to less than 18 years. Subjects' parents provided written informed consent. Subjects with obesity were excluded. The study was approved by the Committee for Medical Research Ethics, Sriwijaya University Faculty of Medicine. A total of 58 subjects were enrolled in this study. Patients with dyspnea underwent history-taking, physical examinations, and any other procedures in order for a a diagnosis to be made.

Dyspnea was defined to be breathing problems, as judged by an increased respiratory rate above the normal frequency, according to age. Normal limits were defined as: <60 breath per minute (bpm) for < 2 month-olds, <50 bpm for 2 – 12 month-olds, <40 bpm for 1-5-year-olds, and <30 bpm for 5–18-year-olds. Cardiac abnormality was defined as heart failure, congenital heart disease, or acquired heart disease, found on echocardiography examination. Echocardiography, the gold standard for diagnosing cardiac abnormalities, was performed by a pediatric cardiologist on the day blood specimens were obtained. Subjects were classified into two groups, those with and without cardiac abnormalities.

Venous blood specimens (3 mL) were obtained from the subjects and stored in heparinized tubes. Specimen stability was a maximum of 8 hours at room temperature. The *Roche Cardiac proBNP+ and Cobas h 232* instrument was used to determine NT-proBNP levels in 150μL serum by an immunoassay method as per instructions of the manufacturer. Laboratory results were expressed in picogram per milliliter (pg/mL).

Statistical analysis was performed using *PASW 18.0 for Windows* software. Data are presented as median, minimum, and maximum because NT-proBNP levels were non-normally distributed. The Mann-Whitney U test was used for comparisons between groups, and a receiver-operating characteristic (ROC) curve was used to obtain area under the curve (AUC), and a cut-off point with optimal sensitivity and specificity.

Results

Subjects were predominantly female (60.3%) and mostly in the 2 to 12 month age group (43.1%). There were no significant differences in sex, age, or nutritional status distribution between the two groups. In general, the nutritional status of subjects was mostly classified as well-nourished (58.6%). Although severely undernourished subjects were found only in the cardiac abnormality group, the overall proportion of nutritional status between the two groups was not significantly different (P=0.141). The median age of all subjects was 9.5 months (range 1-180). Characteristics data of subjects are presented in **Table 1**.

Subjects with cardiac abnormalities were grouped into congenital heart disease or acquired heart disease. In the congenital heart disease group, the most common diagnosis was ventricular septal defect (VSD) in 12 subjects, whereas in the acquired heart disease group, the most common diagnosis was rheumatic heart disease (RHD) in 4 subjects. The distribution of diagnoses and subjects' median NT-proBNP levels are shown in **Table 2**.

Comparison between subjects with and without cardiac abnormality (P=0.002); between congenital and acquired heart diseases (P=0.011)

Median NT-proBNP levels were significantly

Table 1. Characteristics of subjects

Characteristics	With cardiac abnormality (n=39)	Without cardiac abnormality (n=19)	Total N=58	P value
Gender				
Male	13 (33.3)	10 (52.6)	23 (39.7)	0.131
Female	26 (66.6)	9 (47/4)	35 (60.3)	
Nutritional status, n(%)				
Severely	7 (17.9)	0	7 (12.1)	0.141
undernourished	11 (28.2)	6 (31.6)	17 (29.3)	
Undernourished	21 (53.9)	13 (68.4)	34 (58.6)	
Well-nourished				
Age group, n(%)				
1-2 mo	3 (7.7)	3 (15.8)	6 (10.3)	0.571
>2-12 mo	16 (41.0)	9 (47.4)	25 (43.1)	
>1-5 yr	9 (23.1)	2 (10.5)	11 (19.0)	
>5-15 yr	11 (28.2)	5 (26.3)	16 (27.6)	
Median age (range), mo	12 (1-174)	6.5 (1.5-180)	9.5 (1-180)	

Table 2. Median NT-proBNP levels in subjects with and without cardiac abnormalities

Diagnoses	n	Median NT-proBNP (range), pg/mL
With cardiac abnormalitiy	39	1,775 (189-9,000)
Congenital heart disease	28	1,617 (189-9,000)
Acquired heart disease	11	2,989 (1,251-9,000)
Without cardiac abnormalitiy		
Bronchiolitis	19	759 (245-2,996)
Bronchopneumonia	1	651
Bronchopneumonia with complications	7	972 (717-2,996)
Asthma bronchiale	5	707 (249-1,959)
Malignancy	2	502 (245-759)
Meningitis	2	1,040 (571-1,509)

higher in subjects with cardiac abnormalities [1,775 (range 189-9,000) pg/mL] compared to subjects without cardiac abnormalities [759 (range 245-2,996) pg/mL] (P=0.002). **Figure 1** shows the comparison of median NT-proBNP levels between the two groups. The ROC curve analysis (**Figure 2**) showed that NT-proBNP performed well in differentiating subjects with and without cardiac abnormalities who present with dyspnea (AUC 0.75). The optimal cut-off of 1,235 pg/mL gave the highest diagnostic accuracy based on ROC curve analysis, with sensitivity of 74.4% and specificity of 73.7%.

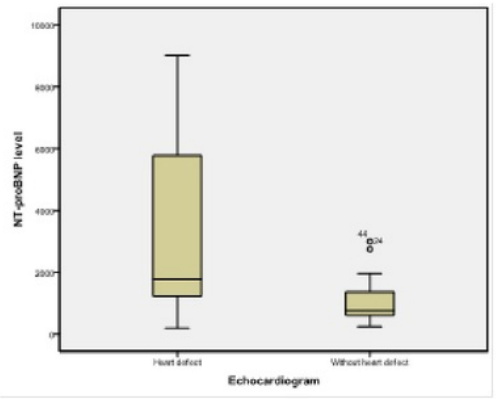

Figure 1. Median NT-proBNP level comparison between subjects with and without heart defects

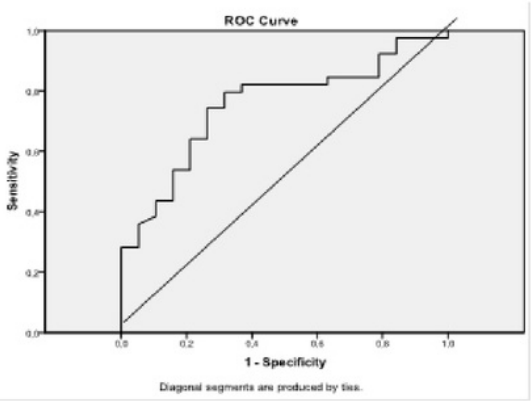

Figure 2. ROC curve for NT-proBNP levels in diagnosing cardiac abnormalities in children with dyspnea

Discussion

The median NT-proBNP level in 39 subjects with cardiac abnormalities was 1,775 (189-9,000) pg/mL. The minimum value, 189 pg/mL, in this group was a subject with a moderate perimembranous outlet (PMO) VSD aged 2 years and 10 months, who had received heart failure treatment during the NT-proBNP examination. In the 19 subjects without cardiac abnormalities, most had bronchopneumonia, with and without complications. The median NT-proBNP level in those without cardiac abnormalities was 759 (245-2,996) pg/mL. In this group there were two data outliers with values of 2,747 pg/mL and 2,996 pg/mL (maximum). Both of these patients were diagnosed with bronchopneumonia, which caused hypoxia and may have stimulated the production of NT-proBNP.[5] Cohen *et al*. comparing NT-proBNP levels in the groups of healthy children, children with acute lung disease, and children with heart failure. They found that NT-proBNP levels in children with acute lung disease (including pneumonia) were elevated compared to that of healthy children, but the increase was not as high as in the group of children with heart failure.[6]

In our study, median NT-proBNP levels were significantly higher in the cardiac abnormality group than in those without cardiac abnormalites, as diagnosed by echocardiography (P=0.002). Cohen *et al*. found that NT-proBNP levels in children with heart failure were much higher than in those with acute pulmonary diseases and healthy children.6 In addition, Maher *et al*. compared NT-proBNP levels in 30 patients with heart disease to 70 patients with respiratory diseases and infections. They found that NT-proBNP levels in patients with heart disease were much higher than in patients with respiratory disease and infections.[7]

In this study, we assessed the usefulness of NT-proBNP levels as a screening tool to diagnose cardiac abnormalities in pediatric patients who presented with dyspnea. We obtained an AUC value of 0.75, and an optimal cut-off point of 1,235 pg/mL, with sensitivity of 74.4% and specificity of 73.7%. Hammerer-Lercher *et al*. also analyzed NT-proBNP levels retrospectively among 23 children with heart disease and 119 children with non-cardiac diseases (kidneys, lungs, CNS, and others), who were aged over 1 month to 3 years. They reported an AUC value 0.87 and a cut-off point of 2,000 ng/L, with sensitivity 74% and specificity 95%. This study was similar to our study, in terms of variety of cases for comparison, although their age range was smaller (children aged 1 month to 3 years).[8] Their specificity was higher than ours, 95% *vs*. 73.7%, respectively, and our subjects were children with dyspnea, which can be caused by various mechanisms. Furthermore, in most cases dyspnea can also increase NT-proBNP levels. In subjects without cardiac abnormalities, most had bronchopneumonia, which in severe circumstances can also lead to heart failure and increase NT-proBNP levels, even when not accompanied by structural heart abnormalities.[5]

The use of NT-proBNP level as a screening tool to detect congenital heart defects, was made by Moses *et al.* in 2011. They analyzed NT-proBNP levels in 119 children with congenital heart disease and 33 healthy children (with no evidence of abnormalities of the heart), aged 5 days to 12 years. They found that median NT-proBNP levels were 372 (range 60-3000) pg/mL in children with acyanotic congenital heart disease, 1,023 (range 182-3000) pg/ml in those with cyanotic congenital heart disease, and 120 (range 60-380) pg/mL in normal patients. Their AUC value was 0.79, with a cut-off point of 98 pg/mL, with sensitivity 82% and specificity 46%.[3] The study was similar to ours, in terms of subject age and study design. However, Moses *et al*. included pediatric patients admitted to the Cardiology Division at Penang Hospital, Malaysia, who had suspected congenital heart defects based on prior examination at the hospital.[3] We included children who presented with shortness of breath.

Previous studies compared NT-proBNP levels in children with heart disease which had caused heart failure to that of children with lung disease, or to that of a control group of healthy children, and concluded that the hormone was very beneficial in differentiating between the groups.[6-8,16,17] In our study, NT-proBNP levels were compared among children with various diseases who experienced dyspnea. Most of these diseases can also increase NT-proBNP levels.[5,9-15] The cut-off point obtained from our study (1,235 pg/mL) was higher compared that of previous studies that only compared NT-proBNP levels in heart disease with a certain diagnosis.[3,16,17] Additionally, different methods and instruments were used to measure NT-proBNP levels. A previous study reported a cut-off

point of 2,940 pg/mL to distinguish heart disease from pulmonary disease and healthy children, and their AUC was 1.0.6 Another study reported a cut-off point of 415 pg/mL to distinguish children with heart disease from children with non-cardiac illness, and an AUC of 0.958.[16] In addition, Elsharawy et al. reported a cut-off point of 854 pg/ml to distinguish children with VSD who have heart failure from healthy children, with an AUC of 0.98.17 Furthermore, Moses et al. had a cut-off point of 98 pg/ml and AUC of 0.79 to distinguish children with heart defects and those with suspected but unproven heart defects.[3]

In conclusion, NT-proBNP level can be used to diagnose cardiac abnormalities in children who present with dyspnea. Advanced study is still required with a larger sample size of non-cardiac abnormalities, so that NT-proBNP levels can be compared by group with particular organ abnormalities which lead to dyspnea.

Conflict of Interest

None declared.

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