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Original Article

Plasma NT-proBNP and pulmonary to systemic blood flow ratio in congenital heart defects with left-to-right shunts

Eko Kristanto Kunta Adjie, Ni Putu Veny Kartika Yantie, Made Gede Dwi Lingga Utama, Eka Gunawijaya, Ketut Ariawati, Ida Bagus Subanada, Anak Agung Ngurah Ketut Putra Widnyana

Abstract

Background Cardiac left-to-right shunts changes to the pulmonary-to-systemic blood flow ratio (Qp/Qs ratio). This ratio can be used to monitor the hemodynamics of the heart. Left-to right-shunts cause the release of amino terminal proB-ty natriuretic peptide (NT-proBNP) that can be utilized as a specific marker for the presence of heart failure in children with congenital heart defects (CHDs). Early intervention such as defect closure in CHD is important to prevent heart failure.

Objective To assess for a correlation between the level of NT pro-BNP and Qp/Qs ratio in CHD patients with left-to-right shunts.

Methods This cross-sectional, analytical study was conducted in 32 children who underwent cardiac catheterization at Sanglah General Hospital, Denpasar, Bali, and were recruited by consecutive sampling. NT-proBNP levels were measured by ELISA with a two-step sandwich assay system; Qp/Qs ratio using Fick rules. Statistical analyses included Shapiro-Wilk test, descriptive analysis for subject characteristics, and Pearson's correlation analysis. A P value of <0.05 was considered to be statistically significant. Age and defect size were analyzed as confounding factors by ***partial correlation test.***

Results The correlation value between NT-proBNP and Qp/Qs ratio was $r=0.384$ ($P<0.05$), after controlling for age and defect size as cofounding factors.

Conclusion There is a weak positive correlation between NT-proBNP levels and pulmonary-to-systemic blood flow ratio in patients with left-to-right shunt, after controlling for age and defect size as confounding factors. **[Paediatr Indones. 2020;60:310-5 ; DOI: 10.14238/pi60.6.2020.310-5**].

Keywords: *congenital heart disease; left-to-right shunt; NT-proBNP; pulmonary-to-systemic blood flow ratio*

Congenital heart disease (CHD) with a left-to-right shunt is the most common heart disease and the main cause of pulmonary to systemic blood flow ratio (Qp/Qs ratio) change in children. This ratio is a comparison between the blood flow from the heart to the lung and the blood flow from the heart to the rest of the body. If left untreated, these hemodynamic changes will lead to heart failure due to the inability of heart ventricles to distribute sufficient blood volume throughout the body accompanied by volume overload to the lungs and heart. This condition is known as decompensation. Echocardiography is typically used to assess Qp/Qs ratio, however, measurements performed during catheterization tend to yield more accurate results.[1]

Biomarkers have been increasingly used to predict and diagnose heart failure with high specificity

From the Department of Child Health, Universitas Udayana Medical School/Sanglah Hospital, Denpasar, Bali, Indonesia.

Corresponding author: Eko Kristanto Kunta Adjie. Department of Child Health, Universitas Udayana Medical School/Sanglah Hospital, Jalan Diponegoro, Dauh Puri Klod, Denpasar Barat, Bali 80113, Indonesia. Phone: +6281288823479. Email: anz1082@gmail.com.

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and sensitivity. The American Heart Association recommends the use of N-terminal pro B Type Natriuretic Peptide (NT-proBNP), which is an inactive pro-hormone fragment from B Type Natriuretic Peptide (BNP).[2,3] This biomarker is synthesized by cardiac ventricular myocytes in response to distention and overloading of the heart ventricles, especially the left ventricle. Increased levels of NT-proBNP are positively associated with the degree and prognosis of heart failure.[4] The NT-proBNP has several advantages as a marker of heart failure, as it is more stable at room temperature without the addition of anticoagulants and it has a longer half-life compared to other biomarkers.[4] Thus, NT-proBNP has an advantage over other heart markers in assessing heart failure.[5] However, this biomarker has not been well studied in relation to changes in Qp/Qs ratio.

Only a few studies refer about BNP and pediatric left-to-right shunt correlated with Qp-Qs ratio.[6,7] However, correlation between NT-proBNP and Qp/Qs ratio were never been assessed. This study was conducted in the hope that it will be able provide information on the correlation between plasma levels of NT-proBNP and pulmonary-to-systemic blood flow ratio in patients with CHD with left-to-right shunts. This information could be used to determine whether or not defect closure should be performed without relying on other more complicated examinations whose interpretation requires experts which, in certain settings, might be a limited resource.

Methods

This cross-sectional study was conducted from August to October 2018 at Sanglah General Hospital, Bali, to assess for a correlation between plasma NT-proBNP levels and pulmonary-to-systemic blood flow ratio in patients with left-to-right shunt congenital heart disease. Inclusion criteria were patients with left-to-right CHD aged 3 months to 18 years who had parent consented to participate in the study after receiving a thorough explanation about the study. Exclusion criteria were patients with the following acute illness and comorbidities: severe anemia, sepsis, chronic kidney disease, severe pneumonia and moderate-to-severe narrowing of the heart's large blood vessels (coarctation of the aorta, pulmonary stenosis, and aortic stenosis). Subjects were recruited using a consecutive sampling technique. Nutritional status was defined based on anthropometric measurement of weight in kilogram and height in centimeter. Data was plot to weight to height Z-score (WHZ) chart and classified as malnourished if WHZ <-3SD, undernourished if WHZ -3SD to -2SD, well-nourished if WHZ -2SD to 2 SD, or overweight if WHZ is more than 2SD.

Patients diagnosed with left-to-right shunt congenital heart disease who came to our hospital and meet the study criteria were included as subjects in the study until the minimum required sample size of 30 subjects was obtained. The VSD considered as small if diameter <3 mm, moderate if diameter 3-8 mm, and large if > 8 mm.[8] Small defects of ASD had a diameter > 3 mm to < 6 mm, moderate defects measured > 6 mm to < 12 mm, and large defects were > 12 mm.[9] Size of PDA was considered small if < 1.5 mm, moderate if 1.5 mm and 3 mm, and large if > 3 mm.[10] A modified Ross score for heart failure was used for clinical severity evaluation. Heart failure staging was defined with total score >2. The symptoms of heart failure were graded on a scale of 0, 1, or 2 points, according to severity. Patients classified as having mild heart failure (3-6 points), moderate heart failure (7-9 points), or severe heart failure (10-12 points).[11]

Blood samples were collected in EDTA-coated tubes and immediately placed in a cooling box at 4°C, followed by centrifugation. Plasma was stored at -80°C if the NT-proBNP measurements could not be immediately performed. Plasma NT-proBNP levels were measured in subjects venous blood by ELISA (*Elecsys 2010*, Roche Diagnostic) with a two-steps sandwich assay system with streptavidin-coated microtiter plates. Complete blood count also performed for anemia clasification according to WHO. Mild anemia with hemoglobin levels at 10.0-10.9 g/dL; moderate anemia at 7.0-9.9 g/dL, while severe anemia at less than 7.0 g/dL.[12]

The Qp-Qs ratio was measured using the Fick rule formula (**Figure 1**) during catheterization. Pulmonary-to-systemic blood flow ratio can be calculated by Doppler echocardiography and cardiac catheterization performed simultaneously. Echocardiography was regarded as operator-dependent and less accurate than diagnostic catheterization.[7] If Qp/Qs ratio was greater than 1.8:1, an intervention

must be considered. whereas if Qp/Qs was less than 1.5:1, there was no significant change in pulmonary to systemic blood flow ratio.[10]

Shapiro-Wilk test was used to assess data normality. A descriptive analysis was also conducted to determine sample characteristics. Pearson's correlation analysis was conducted after the normalization of data distribution with log and inversion. Results with P values <0.05 were considered to be statistically significant. Partial correlation test was conducted after controlling for age and defect size with a linearity test. Ethical clearance for this study was granted based on the criteria of the Institutional Review Board of the Universitas Udayana Medical School/Sanglah Hospital Denpasar, Bali, Indonesia. Permission was also obtained from the Research and Development Unit of Sanglah General Hospital, Bali, Indonesia.

Results

The study was conducted with 32 subjects, consisting of 8 males and 24 females. The subjects' mean age was 46.97 (SD 55.63) months and median age was 22.5 months. There were 6 subjects with small-size defects, 12 with medium-size defects, and 14 with large-size defects. General characteristics of subjects (gender, age, type of CHD, defect size, nutritional status, Hb level, and Ross heart failure score) are described in **Table 1**. **Table 2** shows the mean NT-proBNP and flow ratio used in the correlation analysis (4,389.5 pg/mL and 1.77, respectively). Normality test revealed that the NT-proBNP level and flow ratio data were not normally distributed, thus they were normalized using inversion and log. Pearson's correlation test revealed a weak positive correlation between NT-proBNP and flow ratio (r=0.309). Partial correlation test after controlling for age and defect size showed that NT-proBNP and flow ratio had a correlation value (r) of 0.384. A two-tailed significance test indicated that this correlation was statistically significant (P=0.036).

Discussion

A total of 32 subjects had median age of 22.5 months, ranging from 3 months - 16.5 years. A study noted that most CHD cases occurred in subjects with a median age of 11 years (range 4-22 years).[11] Most of our subjects were female (24). Less number of subject in this study cause of sex difference with previous study, in which CHD incidence in female patients was higher (20.1/1,000 births) compared to males (16.4/1,000 births).[12] We identified CHD at a younger age range, most likely due to physiologic anemia levels after the age of 3 months, which causes clinical symptoms of heart failure in large size CHD. This might also due

$$\text{Flow through a circuit} = \frac{O_2 \text{ consumption } (VO_2)}{\text{Difference in } O_2 \text{ content between the arterial and venous limbs of the circuit}}$$

$$Qp = \frac{VO_2 \text{ (L/min) x 100}}{\text{(PV sat - PV sat) x Hb (g/dL) x 1.36 mL/g x 10}}$$

$$Qs = \frac{VO_2 \text{ (L/min) x 100}}{\text{[Ao sat - mixed venous (SVC) sat] x Hb (g/dL) x 1.36 mL/g x 10}}$$

$$\frac{Qp}{Qs} = \frac{\text{Ao sat - SVC sat}}{\text{PV sat - PA sat}}$$

Figure 1. The Fick rules formula[9]
Qp=blood flow to the lungs (L/min/m^2), Qs=systemic blood flow (L/minute/m^2), PVsat=pulmonary vein oxygen saturation (%), Aosat=aorta oxygen saturation (%), PAsat=pulmonary artery oxygen saturation (%), SVCsat=superior vena cava oxygen saturation (%), Hb=hemoglobin level (g/dL)

Table 1. Characteristics of subjects

Characteristics	(N = 32)
Gender, n	
Female	24
Male	8
Median age (range), months	22.5 (3-198)
Type of CHD, n	
VSD	8
ASD	5
PDA	19
Size of defect, n	
Small	6
Moderate	12
Large	14
Nutritional status, n	
Well-nourished	13
Undernourished	14
Malnourished	5
Mean hemoglobin (SD), g/dL	12.08 (1.54)
Anemic status, n	
No anemia	23
Mild anemia	6
Moderate anemia	3
Severe anemia	0
ROSS score for stage of heart failure, n	
Mild	12
Moderate	8
Severe	0
None	12

Table 2. NT-proBNP levels and flow ratios

Variables	Mean (SD)	Median (range)
NT-proBNP, pg/mL	4,389.50 (8919.11)	529.35 (92.64-29525)
Flow ratio	1.77 (0.89)	1.39 (0.65- 3.85)

Table 3. Partial correlation analysis of NT-proBNP and flow ratio before and after controlling for age and defect size

NT-proBNP adjustment, pg/mL	FR (Qp/Qs ratio)	
	r	P value
Non-adjusted	0.309	0.085
Adjusted	0.384	0.036

to the fact that neonatal CHD screening has not been routinely conducted in Indonesia.

Malnutrition is often found in CHD patients with left-to-right shunt possibly due to increased metabolism, decreased nutritional intake, and reduced systemic perfusion as a response to cardiac compensation. Such poor nutritional status may result in increased morbidity and mortality.[13] In our study, 60% of subjects were undernourished or malnourished. Only 5 (16%) subjects were classified as malnourished and failed to thrive. This low number was likely due to periodic evaluations for nutritional status and early interventions performed upon recognition of signs for decreased nutritional status. We provided nutritional counseling, evaluation, and meal-planning for each patient who showed decreased nutritional status.

In our study, 23 (72%) subjects had no anemia, 6 (19%) had mild anemia, and 3 (9%) had moderate anemia. A previous study reported that 96% of patients with left-to-right shunt and malnutrition were anemic at various levels proportionate to their nutritional status. Such anemia may be caused by low iron micronutrient intake.[14] Anemia may aggravate the condition of these patients, as the ventricles work harder to provide adequate tissue oxygenation. Anemia can increase the left-to-right shunt flow ratio due to increased ventricular volume, increased metabolic activity and ventricular remodeling, which in turn aggravates cardiac ventricular compensation.[15] Early intervention and monitoring on our patients provides low number of patient with anemia.

Twelve out of 32 of our patients had mild heart failure, 8/32 had moderate heart failure, and none had severe heart failure. The process of compensation, remodeling, and increased metabolism in left-to-right shunts, if left untreated, leads to heart failure. Administering anti-failure drugs that contain ACE-inhibitors can prevent increased systemic resistance and diuretics can overcome volume overload.[16] Our low number of subjects with severe heart failure might have been due to the anti-failure therapy, monitoring heart function, and routine echocardiography, supported by control of anemia and nutritional status.

Left-to-right shunts in CHD cause an increase in flow ratio due to increased blood flow to the lungs through the defect.[17] Changes and increases in flow ratio depend on the defect type, size, and location, which affect the size of the left-to-right shunt, leading to differences in pressure on the heart structure, especially in the ventricular wall. These factors affect the extent of cardiac myocyte stretching, expansion, and overload as a form of compensation and change in cardiac anatomy.[17] The non correlation between NT-proBNP level and flow ratio in this study was not statistically significant due to the low number of subjects with heart failure, as well as routine

monitoring and provision of anti-failure drugs. In addition, differences in defect locations may have affected ventricular dilatation in the subjects, and the difference in flow ratio may have caused non-normal distribution of the NT-proBNP level data. After calculating the partial correlation by controlling for age and defect size, we found a significant correlation between NT-proBNP and flow ratio, with a P value of 0.036 and an r value of 0.384.

A previous study reported that hemodynamic changes in left-to-right shunts, which increases with age, will, in turn, increase pulmonary flow due to lower pulmonary resistance. This hemodynamic change also decreases NT-proBNP levels.[18] This causes left-to-right shunts to be asymptomatic at the beginning of life, with clinical symptoms appearing as the patient ages. Functional changes and compensation mechanisms that occur with increasing age include changes in heart rate, cardiac systolic and diastolic function, and contractility. The compensation mechanisms cause left ventricular hypertrophy and decreased pulmonary compliance.[19]

The defect size and location can increase blood flow to the pulmonal circulation. which increases pulmonary venous flow which causes increased flow to the left atrium. Older CHD patients will experience greater left-to-right shunt flow compared to younger patients with the same defect size. The diastolic filling phase slows with age, resulting in a difference in the proportion of diastolic filling in the passive phase. The ventricular filling shifts to the final diastolic phase and the atrium enlarges due to aging, because the atrium plays a major role in increasing the left diastolic ventricular volume.[20] Such mechanism lead to an increase in left ventricular preload phase pressure and increased stroke volume due to increased left ventricular end-diastolic pressure and left atrial pressure.[21]

Mechanical stress increases NT-proBNP secretion, as suggested by Koch *et al.*[22] who showed that CHD patients with left-to-right shunts had increased in plasma NT-proBNP that positively correlated with defect size, pulmonary arterial pressure, flow ratio, and pulmonary resistance. This result supports the concept that NT-proBNP is produced by the ventricles as a response to mechanical stress volume overload, ultimately affecting the NT-proBNP level and flow ratio in CHD patients with left-to-right shunt. The results of this analysis are consistent with changes in left-to-right shunts and NT-proBNP which are influenced by age, and the size and location of the defect.

We found a weak positive correlation between NT-proBNP and flow ratio, which might have been due the lack of homogeneity in defect locations among subjects. In conclusion, this study provides evidence of a weak positive correlation between NT-proBNP and pulmonary-to-systemic blood flow ratio.

Conflict of Interest

None declared.

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