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CORRELATION BETWEEN NT-PROBNP LEVELS AND RIGHT VENTRICULAR FUNCTION IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION

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ABSTRACT

Maladaptive pulmonary arterial hypertension (HAP) can cause changes in function in the right ventricle (VKa) due to failure to compensate for the increase *in afterload* over a long period of time. Functional changes in VKa can be assessed using echocardiography parameters and also biomarkers, one of which is NT-proBNP. This study aims to determine the echocardiography parameters that correlate with the NT-proBNP levels of HAP patients so that they can assess VKa function in HAP patients and become an alternative to *cardiac magnetic resonance* (CMR) examination as the *gold standard* that assesses VKa function. This study is a cross-sectional analytical research with a sample of 30 patients diagnosed with HAP. The data obtained was then analyzed using the Spearman test. The results of this study showed a moderate positive correlation between echocardiography parameters and NT-proBNP levels whose values were RVEF (r=0.372 and p=0.043), TAPSE (r=0.371 and p=0.044), FAC (r=0.377 and p=0.040) and S' (r=0.370 and p=0.044), respectively. The conclusion of this study is that echocardiography examination with RVEF, TAPSE, FAC, and S' parameters has a moderate correlation relationship with NT-proBNP levels so that these 4 parameters can be used as alternative CMR in assessing VKa function.

Keywords: echocardiography., biomarkers., cardiovascular., diagnostic techniques., cardiac function test., natriuretic peptides

INTRODUCTION

Pulmonary hypertension (PH) is a condition in which pulmonary arterial pressure rises above 20 mmHg at rest. The WHO categorizes pulmonary hypertension based on its cause. Pulmonary arterial hypertension (HAP) is part of group 1 pulmonary hypertension that has certain hemodynamic parameters. The incidence of HAP in the world is estimated at 25 cases per 1 million population, with women at a higher risk of developing HAP than men. However, the mortality rate in men is higher.[1,2]

In Indonesia, a study showed that the majority of HAP patients are young adult women aged 18-40 years, with many of them progressing to Eisenmenger syndrome and HAP. The incidence of HAP in Indonesia is not yet known, but it is estimated to be higher in developing countries. The main cause of PAH is pulmonary remodeling due to cell proliferation and decreased apoptosis, as well as vasoconstriction which plays a role in some cases. This increases pulmonary vascular resistance, makes the heart work harder and can lead to right heart failure.[3,4]

A thorough medical history, physical examination, and serological assessment of systemic or infectious diseases are essential in evaluating comorbidities to HAP. CMR (Cardiac magnetic resonance) is the gold standard for the evaluation of volume, mass, and fractional ejection of both ventricles. Echocardiogram is the first quantitative test performed on patients with HAP and is considered a useful screening tool.[5]

At the molecular level, VKa function can be assessed with NT-proBNP reported to have a close correlation with VKa function and survival in most types of HAP. The presence of pressure and volume overload in HAP patients results in an increase in ventricular wall pressure which then will occur the release of BNP hormone produced by cardiomyocytes in response to protect the cardiovascular system. NT-proBNP is a direct reflection of VKa dilation and impairment.[6]

Based on a study conducted in 2019 on 34 patients over 20 years of age, it was found that there was a correlation between the assessment of VKa function against NT-proBNP as a prognosis parameter. The study used CMR

as a parameter to assess VKa function in HAP patients. Indonesia has a ratio of 1.11 magnetic *resonance imaging* (MRI) units per million population. Most MRI devices are distributed in large cities at a relatively high cost. Echocardiography can provide a qualitative and quantitative assessment of VKa function, where to assess VKa dysfunction two echocardiography marks from three different categories are needed. Each echocardiography examination parameter has its drawbacks and limitations, so integrating and combining these parameters can more accurately assess VKa function.[5,7]

This study focused on the relationship between NT-proBNP levels and cardiac function in patients with pulmonary arterial hypertension, using echocardiography as an alternative to CMR in the evaluation of VKa function in HAP patients. The purpose of this study is to determine the echocardiography parameters including RVEF, TAPSE, FAC and S' which correlate with NT-proBNP levels of HAP patients so that they can assess VKa function in HAP patients and become an alternative *to cardiac magnetic resonance* (CMR) examination as the *gold standard* that assesses VKa function.

MATERIALS AND METHODS

This study uses secondary data conducted on HAP patients at the Integrated Heart Center Installation of Dr.M Djamil Padang Hospital in 2023-2024 after receiving the approval of the ethics commission of the research and development unit of Dr.M DJamil Hospital with the number DP.04.03/D.XVI.XI/311/2024.

Patients who are sampled are patients who have met the inclusion criteria and do not meet the following exclusion criteria:

2.1 Inclusion criteria

The inclusion criteria in this study are as follows:
1. Medical records of HAP patients with complete data.
2. Patients aged 18-65 years.

2.2 Exclusion criteria
1. Patients with left ventricular dysfunction based on echocardiography examination with a left ventricular ejection fraction value of $< 55\%$
2. Patients with heart valve abnormalities with moderate/severe lesion severity
3. Patients with a history of permanent pacemaker insertion.
4. Patients with coronary heart disease, fibrosis, lung tumors, pulmonary embolism or obstruction of lung disease, and myocardial infarction.
5. Patients with diabetes mellitus and obesity.
6. Patients with sepsis, liver disorders, and cancer.
7. Patients with glomerular filtration rate $\leq 30\text{mL/min}/1.73 \text{ m}^2$

This research was conducted from May to November 2024 with a total of 30 samples used in this study. Data processing for this study was carried out using *Microsoft Excel* and *the Statistical Package for The Social Sciences* (SPSS) application.

1. RESULT

Characteristics of Research Subjects

In this study, subjects with the following characteristics were obtained.

Table 1. Characteristics of research subjects

Characteristic	n=30 (%)
Gender	
Man	7 (23,3)
Woman	23 (76,7)
Age (years)*	39.80 ± 13.19
Etiology	
PJB	20 (66,7)
Non-PJB	10 (33,3)
Body Mass Index (kg/m2)*	19.88 ± 2.51
Heart Rate (times/minute)*	79.77 ± 16.76
Blood Pressure (mmHg)*	104.90 ± 13.90
Systolic	68.17 ± 16.83
Diastolic	
Laboratory Examination*	
Hemoglobin (g/dL)	14.02 ± 2.05
Glomerular Filtration Rate (mL/min/1.73 m2)	70.49 ± 19.53

*Data is presented in Mean±SD form

In this study, it was found that HAP patients were more female than male with an average sample age of 39.8. The most common etiology in patients is CHD with average BMI, heart rate, blood pressure, and hemoglobin levels in patients are normal. The glomerular filtration rate in HAP patients was found to decrease.

Table 2. Characteristics of NT-proBNP Levels

Variable	Median	Minimum	Maximum
NT-proBNP (pg/mL)	1414,50	113	12649

Examination of NT-proBNP levels in HAP patients found a median value of 1414.550pg/mL which indicates that the level of NT-proBNP in the sample has increased.

Table 3. Characteristics of Echocardiography

Variable	Median	Minimum	Maximum
RVEF (%)	46	24	58
TAPSE (cm)	1,95	0,9	3,4
FAC (%)	39,6	22	59
S' (cm/s)	12,2	5	18

In this study, the characteristics of echocardiography examination include RVEF, TAPSE, FAC, and S'. On echocardiography examination, it was found that the median value of each parameter was within normal limits. In the RVEF examination, it was found that the minimum and maximum values were 24% and 58%, respectively. In TAPSE, a minimum value of 0.9cm and a maximum of 3.4cm were found, while in the FAC examination, a minimum value of 22% and a maximum of 59% were found, and S' found a minimum value of 5cm/s and a maximum of 18cm/s.

Table 4. The Relationship of NT-proBNP Levels to Right Ventricular Function

	Function of the right ventricle	Value r	Value p
NT-proBNP	RVEF	0,372	0,043
	TAPSE	0,371	0,044
	FAC	0,377	0,040
	S'	0,370	0,044

The data normality test using the Shapiro-Wilk test on the level of NT-pro BNP with right ventricular function which includes 4 examination parameters RVEF, TAPSE, FAC, and S' showed a $p<$ value of 0.05, which means that the data were not normally distributed. Inversion transformations don't change the distribution. Bivariate analysis using the Spearman test showed a meaningful relationship between NT-proBNP levels and a moderate positive correlation.

DISCUSSION
Sample Characteristics Overview

Based on a study of 30 HAP patients, it was found that women were the group most diagnosed with HAP (76.7%), in line with NIH and REVEAL data showing that women are four times more at risk of developing HAP than men. Research by Breanne EM, et al. also shows that the majority of HAP patients are female (70%), although men have more severe hemodynamic disorders. One of the influencing factors is the hormone estrogen which has an impact on the proliferation of smooth muscle cells in the pulmonary blood vessels. In addition, mutations in the BMPR2 gene were found in 42% of female patients with HAP.[8,9]

Analysis of age characteristics showed that the highest incidence of HAP occurred at an average age of 39.8 years, with the study of Humbert, et al. showing an average age of 50 ± 16 years. HAP patients generally have undiagnosed congenital heart disease at a young age, and the age of over 35 years is at higher risk of developing HAP due to pulmonary hypercirculation. Based on etiology, congenital heart disease was the most common cause of HAP (66.7%), with the secondary type of ASD. In CHD patients, complaints have not appeared at a young age, but when they are over 3 years old due to pulmonary hypercirculation and excess right heart volume over a long period of time, it can induce the occurrence of HAP.[2,10]

The average Body Mass Index (BMI) of HAP patients was 19.88 ± 2.51 kg/m², in line with COHARD-PH research which found that the average BMI in CHD patients was 19.5 ± 6.9 kg/m2.[2] The average heart rate of HAP patients was 79.77 ± 16.76 times/minute, indicating an increase in heart rate in response to afterload. The average systolic and diastolic blood pressure were 104.90 ± 13.90 and 68.17 ± 16.83, respectively, close to the data found by Gholamreza, et al.[11] The average hemoglobin level of HAP patients was 14.02 ± 2.05 g/dL. This is not much different from the research conducted by Panagiota, et al.[12] The average glomerular filtration rate (LFG) was 70.49 ± 19.53 mL/min/1. 73 m², indicates mild kidney damage due to a long-term increase in blood pressure in the arterioles and glomeruli causing sclerosis of the blood vessels so that the nephrons will be damaged. Initially, the body can compensate for the reduced number of nephrons by adapting in the form of increased blood flow, increased LFG, and increased urine

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excretion in nephrons that are still functioning, but when this lasts for a long time, the lesions that form will increase and lead to glomerular obstruction and decreased kidney function.[13,14]

The Relationship of NT-proBNP Levels to Right Ventricular Function

The results of the analysis of the relationship between NT-proBNP levels and right ventricular function using the Spearman correlation test were obtained if each echocardiography parameter had a meaningful relationship with a moderate positive correlation with NT-proBNP levels where FAC (r=0.377 and p=0.040), TAPSE (r=0.371 and p=0.044), S' (r=0.370 and p=0.044) and RVEF (r=0.372 and p=0.043) can be concluded if the four parameters can be used as parameters in assessing VKa function in HAP patients. This is in line with the research conducted by Mariangela, et al. who found a correlation (r=0.51) between NT-proBNP levels and VKa function examined using echocardiography.[5] The results of this study are not much different from the study conducted by Qimou Li, et al. which concluded that FAC, TAPSE, RVEF, and S' can be useful parameters for assessing the hemodynamics of VKa in a non-invasive manner.[15]

According to research conducted by Robert, et al. on 14 HAP patients, changes in NT-proBNP were found to correlate with changes in RAP (r=0.49), heart index (r=-0.45), final diastolic volume index VKa (r=0.59), and VKa ejection fraction (r=-0.81). NT-proBNP levels have also been shown to correlate with VKa function where this is related to pressure and volume overload in HAP patients resulting in increased pressure of the ventricular wall which then triggers cardiomyocytes to release the hormone NT-proBNP to maintain fluid balance by dilating blood vessels, increasing sodium excretion, and preventing vasoconstriction.[16,17] Elevated levels of NT-proBNP may reflect progressive VKa dilatation and impaired systolic function so that it may indicate VKa dysfunction in HAP patients. This can be found in an echocardiography examination, where the higher the NT-proBNP level, the FAC and TAPSE values found will decrease. This is related to the function of VKa, where FAC and TAPSE indicate a decrease in heart muscle contraction when pumping blood in VKa. In this study, it was found that in some samples of HAP patients there was no increase in NT-proBNP levels, this was due to the fact that the heart was still able to compensate for the pressure and volume overload that existed so that NT-proBNP was not excreted. Decreased levels of NT-proBNP may also occur in patients who have received previous heart failure therapy, but this does not indicate that the patient's condition has improved and is free from risks or complications due to heart failure. Effective therapy can help improve the function of the heart pump, so that the production of NT-proBNP in response to increased pressure in VKa will be reduced.[16,18]

According to research conducted by Qimou, Li et al., the use of echocardiography with a multiparametric method is clinically meaningful rather than a single-parameter assessment of VKa function. This relates to each parameter representing a different VKa function.[15] According to research conducted by Liz, et al., it was found that echocardiography examination correlated with VKa function (r=-0.4) where echocardiography examination

in HAP patients included an assessment of the structure and function of the right heart, estimated pressure in the VKa, right atrium, and lungs so that this could rule out other causes of increased pulmonary pressure. Given the complexity of the VKa structure, echocardiography allows for better visualization of the myocardial fibers and endocardial boundaries of the VKa, making the calculation of the volume and ejection fraction of the VKa more accurate.[19,20]

On echocardiography examinations, the accuracy and reproducibility of echocardiography measurements are limited due to operator-dependent interpretation. Echocardiography also relies on the angle and volume affected by the anatomical shape of the VKa while CMR can produce accurate measurements of the structure and function of the VKa and pulmonary arteries compared to echocardiography because it produces high-resolution images without interference from bones or air so that CMR can assess the function and volume of the VKa, ejection fraction, and mass in the VKa without relying on the operator examining it.[21,22] Echocardiography remains an option for assessing VKa function given the relatively expensive cost of CMR and tends to be limited.[23]

The correlation results of TAPSE and NT-proBNP in this study are in line with the study conducted by Troisi, et al. where TAPSE is moderately correlated with NT-proBNP levels (r=0.33) in HAP patients. TAPSE itself assesses the displacement of the annulus of the tricuspid valve during the systolic phase where TAPSE can assess the longitudinal function of the VKa free wall.[24] The correlation analysis between RVEF and NT-proBNP in this study is not much different from the study conducted by Mariangela, et al. where (r=0.51) it was found that the value of RVEF has a strong correlation with NT-proBNP levels.[5] The results of FAC analysis in this study are not much different from the research conducted by Efren, et al. where (r=0.50) FAC is moderately correlated with NT-proBNP levels.[25] The correlation results of S' and NT-proBNP in this study are not much different from the results of the study conducted by Susan, et al. where (r=0.42) it was found that S' and NT-proBNP levels were moderately correlated. S' can assess the peak speed of the systolic annulus of the tricuspid valve so that it can indicate the speed of movement of the VKa when it contracts.[26,27]

2. CONCLUSIONS AND SUGGESTIONS
Conclusion

Based on the research that has been conducted on the relationship between NT-proBNP levels and right ventricular function in HAP patients at Dr. M Djamil Padang Hospital, the following conclusions are obtained:

1. Description of the characteristics of HAP patients is found if the patient is female with an average age of 39.8 years with the most etiology of CHD. The average BMI, heart rate, blood pressure, hemoglobin levels in HAP patients were found to be within normal limits, while LFG in patients was found to decrease.

2. The median value of NT-proBNP levels in HAP patients was 1414.5pg/mL which indicates an increase in NT-proBNP levels in HAP patients.

3. The median value of the echocardiography examination with 4 parameters was found within normal limits. The median values of each parameter were as follows: RVEF 46%, TAPSE 1.95cm, FAC 39.6%, and S' 12.2cm/s.

4. The relationship between NT-proBNP levels and right ventricular function was found to be significant with a moderate positive correlation.

Suggestion

Based on the research that has been carried out, there are several suggestions in this study, namely:

1. Echocardiography examination can be used as an alternative to NT-proBNP in checking for signs of heart failure in HAP patients.

2. Echocardiography examination of RVEF, TAPSE, FAC, and S' parameters can be used to assess VKa function in HAP patients as an alternative to CMR.

3. Further research is expected to use a combination of VKa function parameters. Combining multiple echocardiography parameters can improve the accuracy of VKa function examination.

4. Further research can make heart failure patients an inclusion criterion for the sample used.

5. Subsequent research may use a larger sample number than this study.

6. Further research may exclude HAP patients who have received heart failure therapy.

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