

Significance of pulmonary hypertension probability in predicting six-minute walking distance in uncorrected acyanotic grown-up congenital heart disease at Sanglah General Hospital, Bali



Putu Sukma Parahita Aditya^{1*}, I Made Satria Yudha Dewangga²,
Ni Putu Veny Kartika Yantie³, Eka Gunawijaya³, I Wayan Wita⁴

¹Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia

²Division of Pediatric and Congenital Cardiology, Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia

³Division of Cardiology, Department of Child Health, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia

⁴Division of Preventive and Rehabilitative, Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia

*Corresponding author:

Putu Sukma Parahita Aditya;
Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia;
sukma.newworld@gmail.com

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ABSTRACT

Background: Pulmonary hypertension may cause impairment of functional capacity, which is a predictor of survival and quality of life in a patient with uncorrected acyanotic grown-up congenital heart disease. A six-minute walking test (6MWT) is a submaximal exercise test to measure these patients' functional capacity. This study aims to determine the significance of echocardiography parameters, such as Pulmonary Hypertension (PH) probability and Mean Pulmonary Artery Pressure (MPAP), as a predictor of functional capacity by 6MWT measurement.

Methods: Analytic observational study was used to determined walking distance as a measurement of functional capacity in acyanotic CHD patients. The probability of (PH) and MPAP was obtained from echocardiography and divided into three categories (low, intermediate, and high probability) based on guidelines defined by PH 2015. MPAP measured the d using the pulmonary valve acceleration time formula ($90 - 0.62 * PVAT$). The relationship between 6MWT distance with MPAP and probability of PH was measured using pearson correlation and one-way ANOVA. We included 43 patients from the Grown-Up Congenital Heart Disease (GUCH) registry who fulfills the inclusion criteria (age more than 18 years whom defect correction has not been done). All participants were given informed consent. Data were analyzed using SPSS version 20 for Windows.

Results: Forty-three patients were included in this study, with 35 females (81.4%) and 8 males with age range 18-75 years old. The most prevalent GUCH was an atrial septal defect (69.8%). Twenty-one (48%) patient was classified as high PH probability. There was a significant difference between the mild probability of PH with intermediate (MD=94.3 meters; $p < 0.001$) and high probability (MD=141.9 meters; $p < 0.001$). MPAP shows a strong correlation with walking distance ($r = -0.68$; $p < 0.001$).

Conclusion: GUCH patients with high and intermediate PH probabilities from echocardiography had a shorter walking distance and lowered functional capacity. MPAP is a reliable measurement to predict 6MWT in these patients.

Keywords: Grown-Up Congenital Heart Disease, Pulmonary Hypertension, MPAP, 6MWT, Functional Capacity

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INTRODUCTION

Congenital heart disease (CHD) can be categorized into cyanotic and acyanotic CHD.¹ Acyanotic lesions encompass stenosis, regurgitation of the heart valves, and defects that cause left to right shunt of the heart such as Atrial Septal Defect (ASD), Ventricular Septal Defect (VSD), or Patent Ductus Arteriosus (PDA).¹ This shunting of blood could cause increased blood volume and pressure in the pulmonary artery, resulting in increased vascular resistance and pulmonary hypertension in a chronic setting.¹

Pulmonary hypertension (PH) is defined by right heart catheterization (RHC) by an increase in MPAP of more than 25 mmHg.² Echocardiography can also be used in a hospital center without a catheterization facility or patients still waiting for RHC to measure pulmonary hemodynamic and predict pulmonary hypertension.² Several parameters, namely pulmonary systolic artery pressure, MPAP, and what we often use is the degree of PH probability that has a strong correlation to the results of catheterization.^{2,3}

An assessment of the functional

capacity of adult patients with CHD has been investigated and illustrates the patients' quality of life.⁴ In general, there is a decrease in functional capacity in adult patients with CHD compared to healthy adults. Diller GP et al. showed that the functional capacity of adult CHD patients is equivalent to that of chronic heart failure patients, according to their class.⁴ Decreased functional capacity (peak VO_2 levels < 15.5 ml/kg/min) can predict increased risk mortality and hospitalization, both in duration and frequency (OR 2.9; $p < 0.01$).^{4,5} Six-minute

walking test (6MWT) could be used as an inexpensive, simple, and fast alternative method to determine functional capacity and estimate the prognosis of grown-up CHD patients.⁶ The 6MWT can also be used as an evaluation of therapy and prognosis.^{6,7} Kehmeier ES et al. stated that CHD patients with a 6-minute training distance over 482 meters had a strong association with a maximum VO₂ value > 15.5 ml/kg/minute.⁸

Based on those mentioned above, this study aims to determine whether echocardiography PH probability and MPAP is a predictor of functional capacity by 6-minute walking distance in grown-up CHD patients, especially patients awaiting RHC examination.

METHODS

Study population

This analytic observational study was surveyed at Integrated Cardiology Service, Sanglah General Hospital between February – April 2020. Consecutive sampling using grown-up CHD registry involving routine outpatient or during the inpatient stay. Patients were eligible for study inclusion if they were > 18 years old, diagnosed with acyanotic CHD, and haven't gotten percutaneous or surgical correction of the defect. Exclusion criteria were musculoskeletal disorders, cognitive disorders, chronic obstructive lung disease, an impaired vision that inhibits movement, disorders run due to other reasons, and tricuspid or pulmonary valve stenosis. The study was conducted according to the provisions of the Declaration of Helsinki and protocol approval was obtained from the local Ethics Committee. All patients gave written informed consent. Delineates screening, enrollment, and analysis of the study sample was conducted in this study.

MPAP and PH Probability

Echocardiography Philips EPIQ5 measured PH Probability and MPAP. PH probability was categorized into three categories (low, intermediate, high) based on the latest ESC guideline of pulmonary hypertension.³ MPAP (mmHg) was estimated using the Dabestani formula and PVAT ($90 - 0.62 * PVAT$) as a numeric variable.⁹

Six-Minute Walk Test

A six-minute walk test was performed standardized on a hospital corridor of 50-meter length. The test was conducted following the American Thoracic Society Guidelines and the recommendation of Guyatt and colleagues.^{10,11} Patient walked as fast as possible for 6 minutes. Rest was allowed when needed, and time was called out every 2 minutes. Blood pressure, heart rate, respiration rate, and peripheral oxygen saturation by pulse oximetry was measured before and after 6MWT. Classification of functional capacity was defined using walking distance, where 6-Minutes Walk Distances (6MWD) is more than 482 meter was classified as the adequate functional capacity and < 482 meters were classified as poor functional capacity.⁸

Statistical Analysis

All numeric variables were tested for distribution normality by the Saphiro-Wilk test. Pearson's correlation coefficient investigated the correlation between MPAP and 6MWD. One-way ANOVA analyzed the correlation between the degree of PH probability and 6MWD. Correlation between degree of PH probability and functional capacity was investigated using the Chi-square test. To determined that MPAP and PH probability is independently correlated to 6MWD, a linear regression test was used in multivariate analysis. Cut-off p values < 0.025 were used rather than 0,05 to maintain the power of the study remain adequate despite the small sample size. Data were analyzed using SPSS version 20 for Windows.

RESULTS

In this study collective of 43 patients, the median age was 35 years old with a range of 18-75 years old. Comparison of male: female was 1:4, where female patient consists of 81.4% of all patient. There were 6 (14%) participants included in the Eisenmenger syndrome category and all were included in the category of high PH probability. The mean MPAP obtained 26.78 mmHg (95% CI 22.04-31.51 mmHg). Of the total patients, 21 (48.8%) patients were categorized as high PH probability, while low and intermediate probability

were 11 samples (25.5%) (Table 1).

Based on the category of CHD diagnosis, the majority of patients included in the study had ASD in the number of 30 (69.8%), 9 VSD patients (20.9%), and 4 PDA patients (9.3%). The mean 6MWD was 391 ± 79.2 meters, with the lowest value being 214 meters (ASD Primum with Eisenmenger syndrome), and the highest value of 525 meters (small PDA L to R Shunt). A detailed overview of baseline characteristics and type of medication is presented in Table 1.

From the Pearson correlation, we found a strong correlation between MPAP and 6MWD with an inversive relationship (the higher the MPAP, the lower the 6MWD) with a significant correlation coefficient $r = -0.687$ ($p < 0.005$). Figure 1 shows the Pearson correlation scatter plot.

Analysis of the relationship between PH probabilities (low, intermediate, and high probability) and physical abilities based on 6MWD (low and good functional capacity) was performed by chi-square test. From the cross-tabulation results, a value of zero is obtained in the high PH probability and good functional capacity group, making comparative test calculations difficult. The group of patients with a high and moderate probability of PH was being grouped into one category to facilitate the calculation. Moderate and high PH probability has significantly increased the risk of low functional capacity (6MWD < 482 meters) with a P.R. value of 2.13 (95% CI=1.11-4.08) (with $p < 0.001$). A detailed overview of the chi-square test will be presented in Table 2.

To analyze whether there are differences in the 6MWD from each of the PH probability categories, a one way ANOVA test was used. The highest 6MWD was found at low PH probability ($481 \text{ m} \pm 36.2$) and lowest at high PH probability ($339 \pm 63 \text{ m}$). Post-hoc analysis was carried out to determine the mean difference and significance of each PH probability group (Figure 2). A significant difference in the 6MWD was found between the low vs. intermediate probability (mean difference 94.3-meter, $p < 0.001$) and low vs. high probability groups (mean difference 141.9-meter, $p < 0.001$) (Figure 2). There was a mean difference of 47.56 meters that were not statistically significant between

Table 1. Baseline Characteristic Classified by PH Probability

Parameter	Low PH Probability (N=11)	Intermediate PH Probability (N=11)	High PH Probability (N=21)
Gender, n (%)			
Male	2 (18.0)	2 (18.0)	4 (19.0)
Female	9 (82.0)	9 (82.0)	17 (81.0)
Age (Years), Median (Min-Max)	23 (18-55)	38 (28-48)	35 (21-75)
Height (cm) (mean±SD)	157±10.4	156±7.7	159±6.1
Obesity (BMI > 27 kg/m ²), n (%)	2 (18.0)	2 (18.0)	0 (0.0)
Average BMI (mean±SD)	20.4±5.1	24±3.4	21.9±2.4
Medication, n (%)			
Diuretic	7 (63.0)	4 (36.0)	16 (76.0)
ACE-inhibitor or ARB	8 (72.0)	4 (36.0)	16 (76.0)
Beta-Blocker	7 (63.0)	7 (63.0)	13 (61.0)
Mineralocorticoid RA	5 (45.0)	5 (45.0)	13 (61.0)
PDE 5 Inhibitor	0 (0.0)	1 (9.0)	6 (28.0)
Prostasiklin agonist	0 (0.0)	3 (27.0)	6 (28.0)
Endothelin receptor antagonist	0 (0.0)	1 (9.0)	0 (0.0)
Eissenmenger Syndrome, n (%)	0 (0.0)	0 (0.0)	6 (28.0)
MPAP (mean±SD)	11.7±7.8	20.8±7.7	37.7±12.9
Systolic BP pre-6MWT (mean±SD) (1)	118±7.0	102±11.4	103±14.2
Diastolic BP pre-6MWT (mean±SD) (1)	73±9.7	66±8.6	65±8.2
Systolic BP pre-6MWT (mean±SD) (2)	118±7.0	102±11.4	103±14.2
Diastolic BP pre-6MWT (mean±SD) (2)	73±9.7	66±8.6	65±8.2
RR pre-6MWT (mean±SD)	17±2.0	16±2.0	16±2.0
HR pre-6MWT (mean±SD)	73±9.7	70±12.0	74±13.5
Systolic BP post-6MWT (mean±SD)	127±13.5	108±12.5	109±13.5
Diastolic BP post-6MWT (mean±SD)	79±7.7	72±8.9	74±8.9
RR post-6MWT (mean±SD)	21±2.0	22±3.0	24±3.0
HR post-6MWT (mean±SD)	88±10.1	79±21.0	95±17.0
SpO ₂ pre-6MWT (mean±SD)	97±1.2	98±0.9	93±5.2
SpO ₂ post-6MWT (mean±SD)	98±0.8	97±2.1	92±9.0

PH: Pulmonary Hypertension; BMI: Body Mass Index; 6MWT: 6-Minutes Walking Test; SD: Standard Deviation; RR: Respiratory Rate; HR: Heart Rate; BP: Blood Pressure; MPAP: Mean pulmonary artery pressure; ACE: Angiotensin-Converting Enzymes; RA: Receptor Antagonist; SpO₂: Oxygen Saturation

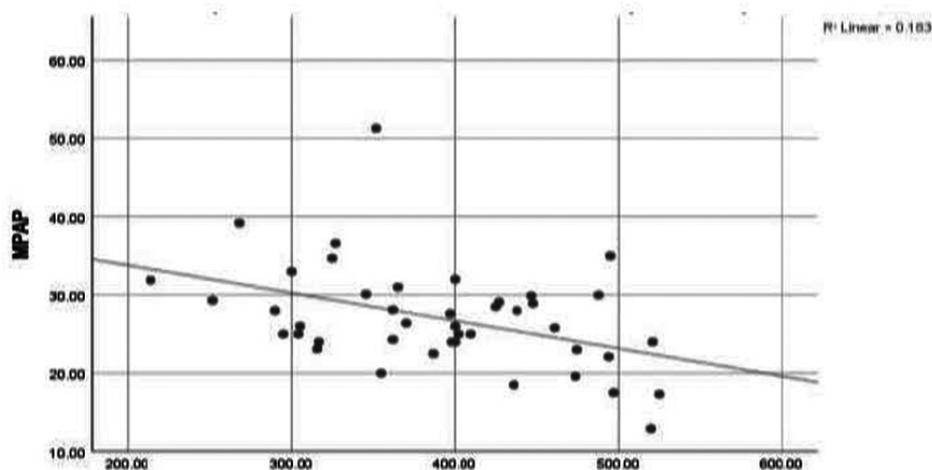


Figure 1. Scatter plot correlation between MPAP and 6MWT (Pearson correlation R² = 0.183; p < 0.001)

intermediate and high PH probabilities (p = 0.049). Figure 2 shows a stem diagram of mean difference for every PH probability probability

A linear regression test was used to analyze the significance of all variables to 6MWD. In the final equation the significant values obtained are MPAP (Beta = -0.69), and body mass index (Beta = -0.25). From the model summary, the correlation coefficient value is 0.75, with adjusted R² 0.56 and the significance value p ANOVA < 0.001. The equation for predicting 6MWT distance is: Distance 6MWT = 498 (constant) - 3.5 (MPAP) - 5 (body mass index) (Table 3).

DISCUSSION

Descriptive data of this study showed that the majority of acyanotic CHD who became study participants were women, with a percentage reaching 81.4% with a total of 35 female subjects. This is consistent with the higher prevalence of women in acyanotic CHD cases, especially ASD, where women's percentage is higher (67%). In contrast, relatively similar percentages of men and women are found in VSD cases.¹² A higher percentage was obtained from the COHARD-PH registry, a single descriptive center study in Indonesia on adult CHD where female presentations were 78.46%. ASD was the most prevalent CHD (69.8%) following previous descriptive studies where Secundum ASD the most common type of disease (73.4%).¹³ Eisenmenger's syndrome was found in 6 patients (14%), which was lower than the prevalence in Indonesia's previous study (18.7%).

The mean of 6MWD patients in this study was 391 meters (95% CI 364 - 412 meters). This distance is lower than the normal 6MWT value in a healthy population (571 ± 90 meters) but is higher than the mean distance of patients with chronic heart failure with reduced ejection fraction (301 ± 80.18 meters).^{14,15} The Diller et al. study also found a decrease in the VO₂ peak from cardiopulmonary exercise testing in adult CHD patients compared to healthy subjects (21.7 ± 8.5 vs. 45.1 ± 8.6 ml/kg.min, P < 0.001).⁴ The COHARD study with PJB patients obtained a mean 6MWT 356.5 ± 99.9 m.¹³ Research from Kehmeier and colleagues

Table 2. Cross-tabulation and chi-square test of PH probability and Functional class

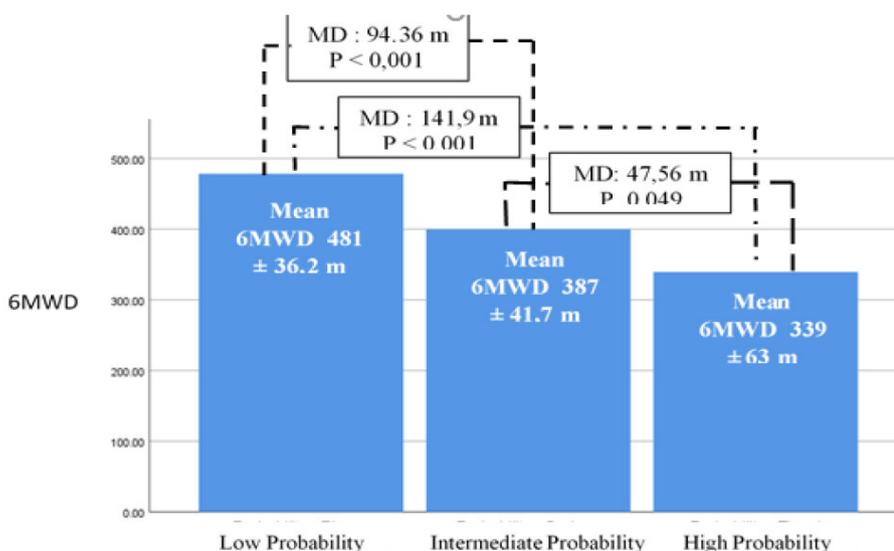
Variables	Adequate Functional Capacity (N=7)	Low Functional Capacity (N=36)	PR	95% CI	p
High and Moderate PH Probability, n (%)	1 (14.3)	31 (86.1)	2.13	1.11-4.08	<0.001
Low PH Probability, n (%)	6 (85.7)	5 (13.9)			

PH: Pulmonary Embolism; PR: Prevalence Ratio; CI: Confidence Interval; *p-value was considered significant if less than 0.05

Table 3. Linear regression all variables to 6MWD with a backward method

Step		Unstandardized Coefficients		Standardized Coefficients	t	p
		B	Std. Error	Beta		
1	Constant	487.41	217.15		2.24	0.03
	Eisenmenger Syndrome	-19.82	33.24	-0.08	-0.59	0.55
	Male	33.67	26.16	0.16	1.28	0.20
	PASP (mmHg)	-0.39	0.48	-0.13	-0.81	0.41
	MPAP (mmHg)	-2.82	0.86	-0.55	-3.28	0.00
	Height (cm)	0.76	1.37	0.07	0.55	0.58
	BMI (kg/m ²)	-4.72	2.83	-0.22	-1.66	0.10
	Age (years)	-0.62	0.70	-0.11	-0.88	0.38
	ACE-Inhibitor	23.32	42.33	0.14	0.95	0.34
	Beta-Blocker	-19.47	23.60	-0.12	-0.82	0.41
	MRA	-27.0	25.23	-0.17	-1.07	0.29
	PDE-5 Inhibitor	11.86	33.16	0.056	0.35	0.72
	Protasiklin Agonist	-14.25	28.37	-0.07	-0.50	-0.61
	Dual Endothelin Receptor	-8.83	74.42	-0.07	-0.50	0.61
11	Constant	498.45	53.63		11.18	0.00
	MRA	-31.76	16.62	-0.20	-1.90	0.06
	MBAP (mmHg)	-3.53	0.54	-0.69	-6.48	0.00*
	BMI (kg/m ²)	-5.39	2.30	-0.25	-2.34	0.04*

BMI: Body Mass Index; Mean pulmonary artery pressure; ACE: Angiotensin-Converting Enzymes; MRA: Mineralocorticoid Receptor Antagonist; R=0.75; R²=0.56; p<0.001; *Statistically significant if p-value less than 0.05

**Figure 2.** One-way Anova of a degree of PH Probability and 6MWD (MD: mean difference).

found higher 6MWD in acyanotic CHD patients with an average of 530 meters, even with a smaller number of samples. The percentage of PH in these studies was smaller than COHARD (41.2% vs. 77%) by excluding patients with Eisenmenger syndrome in subgroup analysis.⁸

Comparative analysis between the probability of PH (mild, moderate, high) and functional capacity (good and less) cannot be analyzed with a 3x2 table because no patient with a high PH probability has a good functional capacity (zero number of patients). To be able to analyze the correlation, the author transformed high and intermediate PH probability into one category. Chi-square analysis found a significant relationship between intermediate-high PH probability and low functional capacity with PR 2.13 and p < 0.001. Previous studies have

showed several parameters of pulmonary hemodynamic by echocardiography and 6MWD and obtained similar results. Nesheim and colleagues found a significant correlation of MPAP and 6MWD on WHO type 1 PH with a p-value of 0.019.¹⁶ Research from Satuti and colleagues found differences in the 6MWD of the PH group based on PASP assessed by echocardiography, where severe PH (PASP > 60 mmHg) had an average of 278 meters and mild PH (PASP < 45 mmHg) had a mean of 394 meters, $p = 0.01$.¹⁷ The role of PH severity on 6MWD can also be seen from Kehmeier and colleagues' study where there is a significant difference in 6MWD between left-to-right shunt CHD and Eisenmenger syndrome.⁸ This poorer functional capacity in high PH probability may be caused by several mechanisms. Elevated pulmonary vascular resistance in PH will cause an increase right ventricle (R.V.) afterload, causing dilatation, impaired systolic function, and a leftward shift of the interventricular septum, which in turn lowers cardiac output. Perfusion-ventilation mismatched, which is showed by the increase of VE/VCO_2 slope in PH patient while exercise will also cause desaturation and chemoreflex activity. This process will decrease the oxygen supply to musculoskeletal muscles and reduce functional capacity.¹⁸

A strong correlation between 6MWD and VO_2 peak was shown by Ross and colleagues ($R = 0.68$, $p < 0.001$). These studies examined data from 11 studies and found a formula to calculate VO_2 peaks from 6MWT distance accurately: Average peak VO_2 (ml/kg/min) = $4.498 + 0.023 * \text{average distance of 6MWT (m)}$.^{6,19}

By knowing the average distance of each PH probability category, the cardiologist can also know the average VO_2 and functional capacity in the form of METs. Functional capacity (METs) can be used as a reference in educating grown-up acyanotic CHD patients regarding the recommended intensity of physical activity for regular exercise. ESC and American Heart Association (AHA) guidelines recommend providing physical activity therapy for patients with CHD.^{2,5} Physical activity can improve fitness, improve quality of life, and reduce the risk of morbidity such as obesity.

This study limitation is this study is there is not yet information regarding functional capacity difference of different subtype of CHD. Further research with medium and long-term follow-up and larger sample to study exercise capacity and prognosis of grown-up acyanotic CHD for every sub-type

CONCLUSION

GUCH patients with high and intermediate probability of PH from echocardiography had shorter walking distance than patients with low PH probability (low vs. intermediate probability with mean difference 94.3-meter, $p < 0.001$, low vs. high probability with mean difference 141.9-meter, $p < 0.001$). Patient with high and intermediate PH probability was also associated with lower functional capacity, and 6MWT < 482 m (PR value 2.13, 95% CI 1.11-4.08, $p < 0.001$). MPAP is a reliable measurement to predict 6MWT in these patients with equation Distance 6MWT = 498 (constant) - 3.5 (MPAP) - 5 (body mass index).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

ETHICS CONSIDERATION

Ethics approval has been obtained from the Faculty of Medicine's ethics committee, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia.

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