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Original Article

The effect of a physical exercise program on functional capacity in patients with pulmonary arterial hypertension at Dr. M. Djamil Padang Hospital

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Abstract

Background: Pulmonary arterial hypertension (PAH) has been known to cause a decreases functional capacity. The underlying mechanisms include right ventricular dysfunction, chronotropic incompetence, ventilation abnormalities, and skeletal muscle dysfunction. Although exercise training programs are recommended, there is currently no standardized exercise training program that is easy to implement in patients with PAH. We aimed to investigate the effect of exercise training program on functional capacity in patients with PAH.

Methods: This study was a non-randomized clinical trial in adult patients with PAH who were divided into intervention and control groups. Cardiopulmonary exercise test (CPET) results were assessed before and after a four-week supervised program (5 sessions/week). The program followed the FITT principle: frequency 5 times/week, intensity 60–85% of six-minute walk test (6MWT) distance, time 25–30 minutes/session including warm-up and cool-down, type supervised indoor walking. Shapiro-Wilk normality test was performed before analyzing the numerical data, followed by the independent t-test or Mann-Whitney U test to determine differences between groups.

Results: This study included 26 patients with PAH, 14 in the intervention group, and 12 in the control group, consisting of 17 women (65%) and 9 men (35%) aged 18-54 years. Statistical analysis showed no significant differences in the baseline characteristics between the two groups ($p > 0.05$). Characteristics of the CPET examination results before and after the exercise program. At baseline, there was no difference in VO2 peak in the intervention group and the control group (888.29 ± 435.99 (95% CI: 314-1823) vs 641.92 ± 231.98 (95% CI: 408 – 1111), p-value >0.05). After the physical exercise program, the intervention group showed a significant increase in VO_2 peak (1047.71 ± 456.05 (95% CI: 413-2175) vs 656.5 ± 223.85 (95%CI: 401–1105), p-value < 0.05). Therefore, ΔVO_2 peak in the intervention group was significantly higher (159.42 ± 209.32 (95%CI: -92 – 707) vs 14.5 ± 60.4 (95%CI: -77 – 148), p-value < 0.05).

Conclusions: A four-week structured walking exercise program significantly improved functional capacity in PAH patients.

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Keywords: pulmonary arterial hypertension, exercise training, VO_2

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Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease with a prevalence of 15–50 cases per million population, and it is more common in women. In Indonesia, atrial septal defect (ASD) represents the most frequent congenital cause. This condition is known to significantly reduce patients' functional capacity. Exercise programs have been shown to improve functional outcomes; however, a standardized regimen that is simple and allows patients to adapt quickly is still lacking. To the best of our knowledge, there are only limited studies investigating the effectiveness of physical exercise programs for PAH patients in Indonesia. Therefore, further research is required to evaluate the effects of structured exercise training on cardiopulmonary stress test capacity in this population.[1-3]

Methods

Study Design

This study is a non-randomized clinical trial conducted at the Integrated Heart Center of RSUP Dr. M. Djamil Padang from November 2022 to September 2023. The subjects in this study were all patients with PAH who visited the cardiology clinic of RSUP, Dr. M. Djamil Padang.

The inclusion criteria were as follows: age between 18-54 years old and not pregnant, while the exclusion criteria were acute coronary syndrome within the last month; WHO FC III-IV; resting heart rate > 120 beats/min; systolic blood pressure <85 mmHg or >180 mmHg; diastolic blood pressure> 100 mmHg; peripheral oxygen saturation at rest <85%; history of syncope <1 week prior; and musculoskeletal abnormalities or disorders. Diagnosis was based on right heart catheterization: mean pulmonary artery pressure ≥20 mmHg, pulmonary artery wedge pressure (PAWP) ≤15 mmHg, and pulmonary vascular resistance (PVR) >2 Wood units, consistent with ESC/ERS guidelines.

Consecutive sampling was conducted in this study. All subjects who presented consecutively and met the eligibility criteria were enrolled in the study until the required sample size was reached. Subjects were then allocated into the intervention group or the control group. The intervention group consisted of subjects who underwent treatment and were given a physical exercise program. In contrast, the control group consisted of subjects who underwent medical treatment and were not given a physical exercise program. Before undergoing a physical exercise program, patients were first examined using a six-minute walk test (6MWT) and cardiopulmonary exercise test (CPET) at the initial meeting.

The exercise program in this study was walking exercise, the dosage of which was given in accordance with the Cardiovascular Rehabilitation Guidelines by PERKI in 2019. At each walking session, the dosage administered to the patient was increased by 100-200 meters per session. Exercise intervention followed the FITT principle: Frequency: 5 sessions/week for 4 weeks; Intensity: 60–85% of 6MWT-derived walking distance; Time: 25–30 minutes/session, including 5-min warm-up and 5-min cool-down. Walking doses could be split into 2–3 intervals within one session depending on tolerance; Type: supervised indoor walking in the hospital's cardiac rehabilitation room, naturally ventilated (non-air conditioned). During se ssions, HR (bpm), BP (mmHg), and SpO_2 (%) were monitored. Supplemental oxygen (2 L/min, titrated) was provided when SpO_2 <90%.[4-5] At the end of the exercise program, the subjects underwent a CPET re-examina-

Table 1. Dose of physical exercise based on 6-minute walk test.

6MWD	Walking dose		
	60%	70%	85%
120 m	360 m	420 m	510 m
150 m	450 m	525 m	640 m
180 m	540 m	630 m	770 m
210 m	630 m	735 m	900 m
240 m	720 m	840 m	1030 m
270 m	810 m	945 m	1160 m
300 m	900 m	1050 m	1290 m
350 m	1050 m	1225 m	1490 m
400 m	1200 m	1400 m	1700 m

Description: The walking dose can be divided into 2x sessions or 3x sessions according to the patient's physical ability.

tion. The VO_2 peak values before and after the intervention in the intervention group were compared with those in the control group.

Statistical Analysis

Univariate analysis was performed to obtain an overview of the baseline characteristics of the study subjects, which are displayed in the form of a frequency distribution table. Bivariate analysis was performed to examine the relationship between the independent and dependent variables. Before bivariate analysis, data normality testing was performed using the Shapiro-Wilk test. An independent t-test was performed to compare the difference in VO_2 peak between the two groups if the VO_2 peak data were normally distributed, and the Wilcoxon test if the data VO_2 peak were not normally distributed. If the p-value was < 0.05, the null hypothesis (H0) was rejected, and there was a significant difference between the VO peak values before and after the rehabilitation program. Data were analyzed using the Statistical Package for Social Sciences (SPSS) for Mac version 27.

Results

This study included 30 subjects, 16 in the intervention group and 14 in the control group. The subjects included 20 women (66%) and 10 men (44%). Of the 30 subjects, four dropped out, leaving 26 subjects who completed the study. The 26 subjects included 17 (65%) females and 9 (35%) males. Two patients dropped out of the intervention group, and two dropped out of the control group. The dropouts in the intervention group were due to one patient's death and another patient's relocation, preventing him from completing the exercise program. Dropouts in the control group were due to patients not attending the post-test CPET examination.

At baseline characteristic data, there were no significant sample differences between the intervention group and the control group, except for the PVR data; also, it can be seen that the subjects who most often experienced PAH were female and had a low body weight. ASD was the most common cause of PAH with 7 (50%) patients in the intervention group and 5 (41.7%) patients in the control group. In addition, phosphodiesterase-5 inhibitors (PDE5I) were the most commonly used drugs, with 7 (39.28%) in the intervention group and 10 (83%) in the control group.

The characteristics of the CPET examination showed a statistically significant difference in the variables of exercise tolerance time and peak heart rate achievement (Table 3).

Table 2. Baseline Characteristics.

Variable	Intervention group	Control group	p-value
Sex			
Male, n(%)	5 (55.6)	4 (44.4)	1.0
Female, n(%)	9 (44.4)	8 (47.1)	
Age (years)	24 (18-54)	27 (18-51)	0.13[b]
Height (cm)	159.4 ± 7.5	160.9 ±8.1	0.63[b]
Weight (kg)	44 (37-75)	49 (35-65)	0.37[b]
Body mass index (BMI) (kg/m^2)	17.1 (14.5-27.9)	18.4 (13.8-24.2)	0.8[a]
Etiology			
Ventricular septal defecr, n(%)	5 (35.7)	4 (33.3)	0.15
Atrial septal defect, n(%)	7 (50)	5 (41.7)	
Primary pulmonary hypertension, n(%)	0	3 (25)	
Patent ductus arteriosus, n(%)	2 (14.3)	0	
Right Heart Catheterization			
Mean Pulmonary Artery Pressure (mmHg)	45 (22-76)	48.5 (22-94)	0.54[a]
Pulmonary vascular resistance (WU)	2.57 (2.12-18)	10.45 (2.22-23.69)	0.01[a]
Echocardiography			
LVEF (%)	67.93±10.18	65.3±6.9	0.57[b]
TAPSE (mm)	2.15 (1.4-3.6)	1.9 (1-2.2)	0.07[a]
Drugs			
PDE5i, n(%)	7 (50)	10 (83.3)	0.11
Prostacyclin analogue, n(%)	3 (20)	5 (41.7)	0.40

CCB, n(%)	1 (7.1)	0	1
Diuretik, n(%)	1 (7.1)	2 (41.7)	0.58
MRA, n(%)	3 (21.4)	1 (8.3)	0.59
BB, n(%)	5 (35.7)	6 (50)	0.69
ACEi/ARB, n(%)	9 (64.3)	8 (66.7)	1

[a]Wilcoxon test (Mann-Whitney)
[b]Independent T-test
p-values for categorical variables (e.g., drugs) were calculated using chi-square or Fisher's exact test

Table 3. Cardiopulmonary exercise test characteristics.

No	Variable	Intervention group	Control group	p-value
1.	Resting systolic blood pressure (mmHg)			
	Pre-test	110.43 ± 23.86	112.67 ± 12.78	0.97[b]
	Post-test	112.43 ± 18.10	114.5 ±11.91	
	Δ pre-post test	2.0 ± 16.49	1.8 ± 2.4	
2.	Peak systolic blood pressure (mmHg)			
	Pre-test	146.5 ±23.9	138.83 ±10.75	0.89[b]
	Post-test	149.42 ±23.67	140.67 ±11.75	
	Δ pre-post test	2.92 ±25.75	1.83 ±9.40	
3.	Resting diastolic blood pressure (mmHg)			
	Pre-test	66.79 ±17.09	73.08 ±10.63	0.34[b]
	Post-test	72.14 ±12.71	73 ±8.53	
	Δ pre-post test	5.36 ±18.05	-0.08 ±7.26	
4.	Peak diastolic blood pressure (mmHg)			
	Pre-test	82.07 ± 11.24	85.42 ± 8.11	0.14[a]
	Post-test	83.00 ±7.07	81.67 ±7.89	
	Δ pre-post test	4.5 (-36–15)	0 (-20–2)	
5.	Resting heart rate (bpm)			
	Pre-test	94.86 ±11.98	85 ±3.86	0.85[a]
	Post-test	93.43 ±12.69	82.92 ±9.87	
	Δ pre-post test	-1.43 ±8.38	-2.08 ±9.05	
6.	Peak heart rate (bpm)			
	Pre-test	148.07 ± 17.93	136.58 ±29.45	0.008[a]
	Post-test	154.50 ±21.08	122.08 ±26.85	
	Δ pre-post test	6.5 (-49–36)	-7.5 (-98–13)	
7.	Resting SpO_2 (%)			
	Pre-test	97.43 ±2.31	95.00 ±4.16	0.40[a]
	Post-test	97.14 ±2.25	93.42 ±5.55	
	Δ pre-post test	0 (-3.0 –1.0)	-5.0 (-8 –3)	
8.	Peak SpO_2(%)			
	Pre-test	95.14 ±3.92	92.50 ±7.05	0.43[a]
	Post-test	94.93 ±5.97	90.58 ±8.84	
	Δ pre-post test	0 (-16.0 – 13.0)	-0.5 (28 – 18)	
9.	Exercise tolerance time (minutes)			
	Pre-test	8.3 ±2.51	7.21 ±2.83	0.002[a]
	Post-test	10.14 ±3.23	7.12 ±2.64	
	Δ pre-post test	2.3 (-1 – 5.5)	0 (-1 – 1)	
10.	Anaerobic Threshold (AT) (ml/min)			

	Pre-test	565.29 ±256.75	462.5 ±159.23	0.41[a]
	Post-test	678.43 ±227.27	480.92 ±147.93	
	Δ pre-post test	64 (-222.0 – 569.0)	8 (-154.0 – 175.0)	
11.	VE/VCO_2			
	Pre-test	46.53 ±7.44	60.69 ±15.00	0.83[b]
	Post-test	44.04 ±7.52	58.40 ±14.18	
	Δ pre-post test	-2.49 ±8.6	-2.28 ±6.67	

[a]Wilcoxon test (Mann-Whitney)
[b]Independent T-test

The results of the normality test of the VO_2 peak at the initial measurement showed that the data were not normally distributed; therefore, the non-parametric Wilcoxon (Mann-Whitney) test was performed to compare the VO_2 peak values at the initial measurement, the measurement after four weeks of research, and the ΔVO_2 peak (Table 3).

Table 4. Bivariate analysis of VO_2.

	Group	N	Mean ± SD	Median (min-max)	p-value*
VO_2 peak pre-test (ml/min)	Intervention	14	888.29 ± 435.99	839 (314 – 1823)	0.136
	Control	12	641.92 ± 231.98	578.5 (408 – 1111)	
VO_2 peak post-test (ml/min)	Intervention	14	1047.71 ± 456.05	999 (413 – 2175)	0.013
	Control	12	656.5 ± 223.85	537.5 (401 – 1105)	
ΔVO_2 peak pre-post test(ml)	Intervention	14	159.42 ± 209.32	120 (-92 – 707)	0.018
	Control	12	14.5 ± 60.4	-1.5 (-77 – 148)	

*Wilcoxon test (Mann-Whitney)

Based on the bivariate analysis, there was no significant difference in VO_2 peak between the intervention group and the control group before the physical exercise program was conducted (888.29 ± 435.99 (314-1823) vs 641.92 ± 231.98 (408-1111), p = 0.136). After the four-week physical exercise program, a significant difference was found in VO2 peak between the intervention and control groups (1047.71 ± 456.05 (413-2175) vs 656.5 ± 223.85 (401-1105), p = 0.013). In addition, a significant difference was found in the comparison of ΔVO_2 between the intervention group and the control group (159.42 ± 209.32 (-92 – 707) vs 14.5 ± 60.4 (-77 – 148), p-value = 0.018). The results of this analysis indicate that the intervention group who underwent a four-week physical exercise program experienced a more significant increase in VO_2 peak than the control group who did not undergo a physical exercise program (Table 3).

Discussion

Several variables did not show a statistically significant difference between the intervention and control groups, except for the PVR data, likely due to the consecutive sampling method, which could lead to the potential for uneven sample division of the intervention and control groups. Nevertheless, there was no statistically significant difference in VO_2 peak values between the intervention and control groups before the exercise program (Table 3). This study showed that most PAH patients are young adult women who have a low body weight and a significant age difference ranging from 18 to 54 years. The data from this study are in line with previous studies that show that PAH is more common in women aged 30-60 years. However, the life expectancy of women with PAH is better than that of men, which is thought to be related to the influence of estrogen. The phenomenon known as the "estrogen paradox" in women suggests that this hormone can interact with other factors to increase chronic effects and damage pulmonary vessels. Conversely, it can have a protective effect in patients with PAH. However, the exact cause of this paradox remains unknown.[6-7]

Previous studies have shown that low body weight is more common in patients with PAH, and patients with low body weight were 2.9 times more likely to be found in the PAH population than in the general population. Low body weight is also known to be associated with a worse prognosis, especially in younger patients.[8] This study found that ASD was the most common cause of PAH in the study subjects, in line with the COHARD-PH registry, which

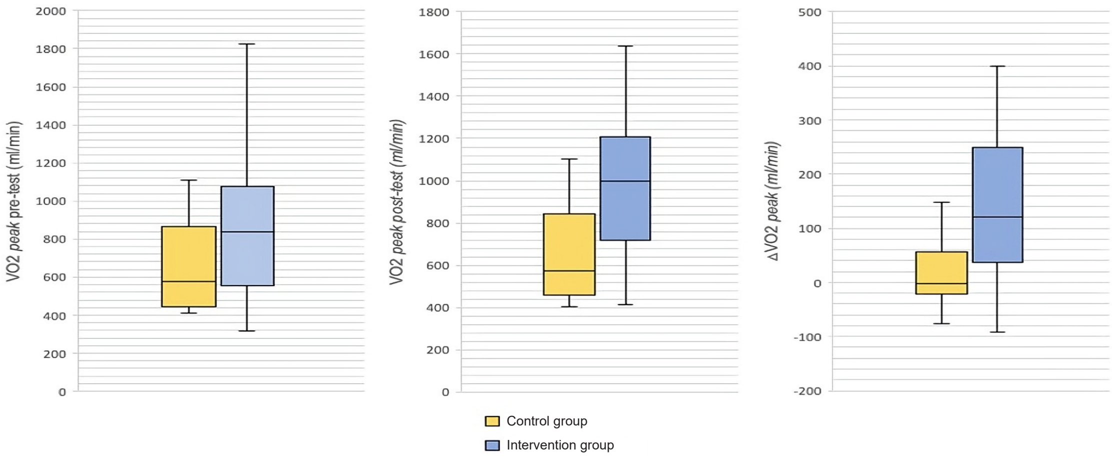

Figure 1. VO_2 peak difference between the intervention and control groups.

reported that ASD is the most common congenital heart disease that causes PAH in Indonesia, at 73.4%.[9]

This study also found that PDE5Is were the most common specific PAH treatment administered to the study subjects. PDE5Is, especially sildenafil, have been shown to be safe and effective in improving exercise capacity, hemodynamics, and outcomes in patients with PAH. In a study by Oudiz et al., sildenafil improved the functional capacity and ventilatory efficiency in patients with PAH. This is due to the improvement of pulmonary blood flow, which causes an improvement in ventilation efficiency.[10] However, PDE5Is are also effective in treating PAH, but they also have side effects, such as headache, redness, and muscle pain. In addition, there are some contraindications to the use of PDE5Is, such as ischemic heart disease, congestive heart failure, and hypertension. Therefore, not all study subjects used PDE5Is.[11-12]

Based on the results of this study, it was found that there were no statistically significant differences in some characteristics of the CPET between the two groups after the four-week research period except for the HR peak and time to exercise intolerance data. The intervention group showed better exercise endurance than did the control group after the physical exercise program. Several studies have shown that exercise programs can increase exercise tolerance time.[13-14]

De Man et al. showed improved exercise endurance in the exercise program group, supported by evidence of increased capillaryization in the quadriceps muscle and oxidative enzyme capacity, especially in type 1 muscle fibres (slow twitch), which indicates an increase in muscle work that predominantly uses aerobic metabolism.[14] However, this difference may be due to the limited number of samples and the short duration of the exercise, which may have caused an increase in one of the hemodynamic parameters to occur by chance. A study by Grunig et al. also found a significant increase in maximum blood pressure, peak heart rate, and maximum peripheral saturation in the intervention group, which is likely due to a chance.[15]

A previous study found that the blood pressure of PAH patients is often low but still tolerable owing to the use of vasodilators. HR at rest is associated with the prognosis of PAH patients. In a study by Hildenbrand et al., resting HR below 82 beats per minute was associated with better long-term prognosis in patients with PAH.[16] In another study, it is mentioned that high resting HR at the initial measurement without other known causes can indicate right ventricular failure.[17-18]

Exercise programs are expected to lower PVR and increase cardiac output, thereby lowering resting HR in patients with PAH. In addition, it is also expected to increase pulmonary blood flow and reduce right-to-left shunts, thereby improving peripheral oxygen saturation in patients with PAH. In this study, there were no significant differences in resting HR or resting/exercise oxygen saturation between the intervention and control groups. This may be due to the relatively short duration of the exercise program, which may have needed to be longer to produce significant differences in some hemodynamic parameters. In a study by Elkhen et al., the exercise program did not show a significant improvement in resting systolic blood pressure, resting

HR, resting diastolic blood pressure, or maximum diastolic blood pressure in patients with PAH who underwent 15 weeks of exercise training compared to the control group.[4,15,19-20]

In this study, there was no significant difference in ventilation efficiency between the intervention and control groups after four weeks of exercise. However, both groups showed a simultaneous improvement in ventilation efficiency after four weeks, as evidenced by an increase in VO_2 at AT and a decrease in VE/VCO_2. Pulmonary vascular remodelling in patients with PAH leads to perfusion deficits in the pulmonary arteries, which can increase the ventilation-perfusion ratio (V/Q) and alveolar dead space fraction (Vd/Vt), and cause ventilatory inefficiency that contributes to decreased functional capacity. The improvement in efficiency observed in the control group may be due to the use of medications, such as sildenafil. A study by Oudiz et al. showed that sildenafil significantly increased AT and decreased VE/CO_2 compared with the control group. This is related to the increase in pulmonary blood flow, which improves ventilatory efficiency.[10]

Previous studies have shown that physical exercise significantly increases the VO_2 peak. However, there was no significant difference in ventilation efficiency parameters, which suggests that an acute exercise program does not improve ventilation-perfusion. Still, the increase in functional capacity is due to improvements in skeletal muscle strength and endurance. However, no studies have confirmed this finding.[21-22]

In this study, there was a significantly more significant increase in VO_2 peak in patients with PAH who underwent an exercise program than in those who did not undergo an exercise program. Physical exercise is beneficial for the management of PAH. Although different exercise protocols have been used in various studies, physical exercise can improve functional capacity in patients with PAH[2-3,20,23]

Several mechanisms can influence the improvement in functional capacity in subjects who undergo an exercise program, such as improvement in right ventricular function, increased adaptation and strength of the respiratory muscles, and increased strength and endurance of the skeletal muscles. At the molecular level, physical exercise can reduce inflammatory mediators such as Th17 lymphocytes, Tumor Necrosis Factor α (TNF-α), IL-1, and IL-6, which play a role in inducing inflammation in patients with pulmonary hypertension.[24-25]

Some studies have shown that physical exercise can improve right ventricular function, as assessed by a decrease in systolic pulmonary arterial pressure and an increase in pulmonary perfusion flow.[4,15,19] This suggests that physical exercise also plays a role in lowering PVR. However, it is still unknown whether reverse remodelling of pulmonary vessels occurs.[25] Gonzalez et al. also found that physical exercise can increase respiratory muscle strength, as evidenced by a significant increase in Pimax after an eight-week exercise program. In addition, exercise programs increase the strength and endurance of skeletal muscles.[14,26] Other studies have shown that physical exercise is not effective in improving the functional capacity and quality of life in patients with pulmonary hypertension. This may be due to several factors, such as small study sample size, inconsistent patient selection criteria, low intensity and frequency of exercise, variability of exercise programs, different study durations, and heterogeneity of the patient population.[27]

Further research with a larger sample size, more consistent patient selection criteria, higher intensity and frequency of exercise, and longer study duration is needed to determine whether physical exercise is effective for patients with pulmonary hypertension. Based on the above discussion, this study shows that an exercise program can improve the functional capacity of patients with PAH; in this case, an increase in VO_2 peak. To the best of our' knowledge, this study is the one that uses the most easily adaptable exercise program, but can significantly improve functional capacity in patients with PAH. The results of this study support the importance of physical exercise as a non-pharmacological approach in the management of PAH.

Limitation

This study demonstrated the benefits of exercise in PAH patients as measured by VO_2 peak, yet several limitations should be acknowledged. First, the study did not assess other variables that may contribute to improvements in VO_2 peak, such as right ventricular function, PVR, respiratory muscle strength, skeletal muscle strength, pulmonary blood flow, or molecular changes following exercise. Second, the baseline data revealed a significant difference in PVR between the intervention and control groups, which could have introduced bias, since the intervention group had a lower baseline PVR. Nevertheless, the baseline VO_2 peak values were not significantly different between the two groups prior to the exercise program. Finally, because consecutive sampling was used—a non-probability technique—there is a possibility of selection bias, which may limit the generalizability of the findings.

Conclusion

This study showed that PAH is more common in young adult women with low body weight, the most common diagnosis being atrial septal defect, and the most common treatment is PDE5I. The study showed a significant increase in the peak HR and exercise intolerance time in the intervention group. However, there were no significant differences in other hemodynamic characteristics such as blood pressure and peripheral oxygen saturation. In addition, the ventilation efficiency variables in both groups after the four-week study period, such as anaerobic threshold and VE/VCO_2 ratio before and after the physical exercise program, also did not show a significant difference. The study showed a significant increase in VO_2 peak in PAH patients who underwent a physical exercise program compared to PAH patients who did not undergo the program. This study can be continued with a multivariate analysis by measuring other variables that can affect VO_2 peak measurement results. Physical exercise can be performed as a routine rehabilitation therapy for PAH patients as safe, easy, and effective management to improve patient quality of life.

List of Abbreviations

6MWT Six-Minute Walk Test
6MWD Six-Minute Walk Distance
CPET Cardiopulmonary Exercise Test
DBP Diastolic Blood Pressure
HR Heart Rate
LVEF Left Ventricular Ejection Fraction
mPAP Mean Pulmonary Artery Pressure
PAH Pulmonary Arterial Hypertension
PAWP Pulmonary Artery Wedge Pressure
PVR Pulmonary Vascular Resistance
SBP Systolic Blood Pressure
TAPSE Tricuspid Annular Plane Systolic Excursion

Ethical Clearance

Ethical approval was obtained from the Ethics Committee of RSUP Dr. M. Djamil Padang (No. LB.02.02/5.7/329/2023). All patients provided written informed consent.

Publication Approval

Institutional approval for publication has been obtained.

Authors Contributions

F. H. S.: Conceptualization, study design, patient recruitment, data collection, data analysis, statistical analysis, manuscript drafting and editing; C. K. K.: Conceptualization, study design, exercise session supervision, and critical revision for important content; R. H.: Conceptualization, study design, exercise session supervision, and critical revision for important content.

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Conflict of Interest

The authors declare no conflict of interest.

Availability of Data and Materials

Data are available from the corresponding author upon reasonable request.

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