Frontiers in Healthcare Research

ISSN: AAAA-BBBB
Journal homepahe: frontiersin-healthcare-research.org

Publisher: Rumah Sakit dr. M. Djamil, Padang, West Sumatra, Indonesia

The Effectiveness of a 4-Week Physical Exercise Program in Patients with Pulmonary Arterial Hypertension: A Pilot Study in Sumatra

Citra Kiki Krevani[*1,2], Muhammad Zakiy Azzuhdi[1,2], Feiky Herfandi Soegistiono[1,2], Putri Maulina[1,2]

[1]Department of Cardiology and Vascular Medicine, Dr. M. Djamil General Hospital, Padang, Indonesia

[2]Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Andalas, Padang, Indonesia

* Corresponding author.
E-mail address: krevani19@gmail.com

Article information

Submitted
30-11-2023

Accepted
30-12-2023

Published
19-01-2024

Abstract

Background: Pulmonary Arterial Hypertension (PAH) is known to induce a decline in functional capacity, attributed to mechanisms such as right ventricular dysfunction, chronotropic incompetence, ventilation abnormalities, and skeletal muscle dysfunction. Despite the recommendation of physical exercise programs, a standardized and easily implementable regimen for PAH patients is currently lacking. This study aims to investigate the influence of physical exercise on the 6-minute walking distance (6MWD), functional capacity, and pulmonary vascular resistance (PVR) in individuals with PAH.

Methods: This study employed a non-randomized clinical trial design involving adult patients with Pulmonary Arterial Hypertension (PAH), who were divided into intervention and control groups. Baseline characteristics, differences in 6-Minute Walking Distance (6MWD), peak VO2, and Pulmonary Vascular Resistance (PVR) before and after a four-week period (20 sessions, five times a week) of physical exercise were documented. The Shapiro-Wilk normality test was conducted before analyzing numerical data, followed by independent t-tests or Mann-Whitney tests to assess intergroup differences.

Results: The study included 32 PAH patients, with 16 subjects in each group. Baseline characteristics revealed a distribution of 22 females (68.75%) and 10 males (31.25%), with an age range of 18-55 years. Statistical analysis indicated no significant differences in baseline characteristics, hemodynamic data, and echocardiography between the two groups. However, there were significant differences between the control and intervention groups in terms of Δ6MWD (17.07 ± 48.30 (95% CI: -10.82 – 44.96) vs. 115.36 ± 54.69 meters (95% CI: 83.78 – 146.94), p-value < 0.001), ΔVO2 peak (159.42 ± 209.32 (95% CI: -92 – 707) vs. 14.5 ± 60.4 (95% CI: -77 – 148), p-value < 0.05), and ΔPVR (-1.36±0.67 (95% CI: -0.33-(-2.85)) vs. -0.34±0.30 (95% CI: -0.39-(0.63)), p-value < 0.05).

Conclusion: A four-week physical exercise program improved 6MWD, functional capacity, and PVR in patients with PAH.

Keywords: Pulmonary Arterial Hypertension, 4-week physical exercise program, 6-Minute Walking Distance (6MWD), functional capacity, Pulmonary Vascular Resistance (PVR).

Introduction

Pulmonary Arterial Hypertension (PAH) is a rare but debilitating condition associated with poor outcomes. According to data from The Global Burden of Disease in 2020, the worldwide prevalence of PAH ranges from 0.37 to 15 cases per 100,000 individuals, with an incidence ranging from 0.008 to 1.4 cases per 100,000 individuals annually. The one-year mortality rate for PAH reaches 40%[1]. Idiopathic, heritable, drug-induced, or toxin-induced PAH constitutes 52.6% of all global cases[2]. Recent registry data indicates an incidence of 6 cases per 1 million population, with a prevalence ranging from 48 to 55 cases per 1 million adult population. Idiopathic pulmonary arterial hypertension represents the most prevalent subtype (50-60%), followed by PAH associated with connective tissue diseases, congenital heart disease, and portal hypertension[3]. The Congenital HeArt Disease in adult and Pulmonary Hypertension (COHARD-PH) registry, the first prospective registry in Indonesia, reports that 80% of congenital heart disease (CHD) patients develop PAH due to delayed diagnosis

(Dinarti et al., 2020). In a study conducted at RSUP Dr. M. Djamil Padang from 2017 to 2021, Muslimah et al. reported 45 cases of PAH, primarily in the 55-64 age range, predominantly affecting females (73.3%), with CHD being the most common cause (68.9%)[4].

Physical exercise programs have been recognized for improving organ function in PAH patients. Exercise for pulmonary hypertensive patients can enhance hemodynamic conditions, improve right heart function, and strengthen respiratory muscles. At the molecular level, physical exercise demonstrates reductions in inflammatory processes, fibrosis, apoptosis, and smooth muscle cell proliferation in the pulmonary arterial wall[5].

Several studies indicate that low-intensity, individually tailored exercise can enhance functional capacity, quality of life, reduce disease progression, and increase life expectancy in PAH patients. In a study by Bussotti et al., a four-week physical exercise program resulted in a significant improvement in pulmonary cardiac functional capacity in 15 PAH patients. Grunig et al. conducted a study with a group of PAH patients engaging in moderate-intensity exercise 5-7 times per week for 10-30 days, followed by 3-7 times per week for 15 weeks. The results showed significant improvements in 6-minute walk test distance (6MWD), peak oxygen consumption (VO2 peak), and quality of life compared to a sedentary group[5-7].

Despite the recommendation of physical exercise for PAH patients, there is currently no standardized and easily adoptable exercise program for patients at RSUP Dr. M. Djamil Padang. To the best of the author's knowledge, research on the success of physical exercise programs for PAH patients in Indonesia remains limited.

Methods

Sample

This study is a non-randomized clinical trial conducted with two groups: the intervention group and the control group. The research took place at the Integrated Heart Center Installation of RSUP Dr. M. Djamil Padang from November 2022 to October 2023. The sample for this study includes all patients with pulmonary arterial hypertension attending the Cardiology Outpatient Clinic at RSUP Dr. M. Djamil Padang who meet the inclusion and exclusion criteria. Inclusion criteria are age ≥ 18 years, not pregnant, functional class I-II, with exclusion criteria including acute coronary syndrome in the last month, resting heart rate over 120 beats/minute, systolic blood pressure <85 mmHg or >180 mmHg, diastolic blood pressure >100 mmHg, resting peripheral oxygen saturation <85%, syncope within the last week, musculoskeletal abnormalities or disorders, and ejection fraction (EF) < 55%. Sampling for this study is done through consecutive sampling.

Procedure

Patients diagnosed with pulmonary arterial hypertension who have undergone right heart catheterization and meet the inclusion criteria, while not having exclusion criteria, are provided with informed consent for the study. If the patient agrees, they are given a patient consent form for the study. Patients are then assigned to either the intervention or control group. The patient's pharmacological treatment remains unchanged during the physical exercise program. Patients in the control group undergo baseline assessments, including the 6-minute walking test (6MWT), Cardiopulmonary exercise testing (CPET), and noninvasive measurement of pulmonary vascular resistance (PVR) through echocardiography. The same assessments are repeated after one month. Patients in the intervention group undergo a baseline 6MWT to determine the appropriate dose of physical exercise based on the 2019 Indonesian Society of Cardiovascular Rehabilitation Guidelines [8]. The intervention group follows a physical exercise program five times per week for four weeks (20 sessions). Pre-6MWT, pre-pulmonary exercise testing, and pre-PVR assessments are conducted before the exercise program, and post-6MWT, post-pulmonary exercise testing, and post-PVR assessments are performed afterward.

Statistic Test

Univariate analysis aims to provide an overview of the baseline characteristics of the study subjects. Characteristic data are presented in the form of frequency distribution tables. Bivariate analysis is conducted to examine the relationship between two variables: the independent variable and the dependent variable. Before performing bivariate analysis, the normality of the data is tested using the Shapiro-Wilk test to assess whether the data obtained are normally distributed. The statistical test used in this study is the independent t-test. Data are analyzed using the Statistical Package for Social Sciences (SPSS) for Mac version 27.

Results

There were a total of 49 patients with Pulmonary Arterial Hypertension (PAH), but 17 patients either declined to participate as samples or resided outside the city. The total number of research subjects obtained using consecutive sampling technique amounted to 32 patients with PAH, who were divided into two groups.

Table 1. Characteristic of sample

Variable	Control Group				Intervention Group				*p-value*
	n	%	Median (min-max)	Mean ± SD	n	%	Median (min-max)	Mean ± SD	
Sex									
Male	4	25			6	37.5			0.704[a]
Female	12	75			10	62.5			
Age (year)			27 (18-55)				24 (18-54)		0.064[a]
Height (cm)			160 (148-171)				159 (148-173)		0.924[a]
Weight (kg)			48.50 (35-65)				44 (37-75)		0.384[a]
Body Mass Index (BMI) (kg/m^2)			18.47 (13.84-24.17)				17.18 (14.45-27.89)		0.356[a]
Systolic blood pressure (mmHg)				110.62±12.03				105.94±15.45	0.346b
Diastolic blood pressure (mmHg)				70.88±11.14				58.81±15.41	0.057b
Heart rate (x/m)				83.50±11.12				84.63±9.04	0.756b
Etiology									
Ventricular Septal Defect	4	25			6	37.5			
Atrium Septal Defect	9	56.3			8	50			0.14[a]
Primary Pulmonal Hypertension	3	18.8			0	0.00			
Patent Ductus Arteriosus	0	0.00			2	12.5			
Previous drugs treatment									
PDE5I	6	37.5			11	68.8			0.156[a]
Prostacyclin Analogues	0	0			0	0			
Combination (PDE5i + *Prostacyclin Analogues)*	8	50			3	18.8			0.135[a]
CCB	0	0.0			1	6.30			1.00[a]
Diuretic	3	18.8			1	6.30			0.60[a]
MRA	2	12.5			3	18.8			1.00[a]
BB	7	43.80			6	37.50			1.00[a]
ACEi/ ARB	11	68.8			11	68.8			1.00a
Right Heart Catheterization									
Mean Pulmonary Artery Pressure (mPAP)				46 ± 22.35				50.07 ± 23.28	0.64[b]
Pulmonary Vascular Resistance (PVR)				8.94 ± 7.84				7.36 ± 11.03	0.23[b]
Echocardiography									

LVEF (%)		64.5±8.89		66.75±10.02	0.507b
TAPSE (cm)	1.95 (1-3.40)		2.05 (1.40-3.60)		0.472[a]
RV FAC (%)		46.93±10.27		46.62±10.45	0.192b
RVS' (cm/s)	11 (7-14)		12.50(7-21)		0.056[a]
PAccT (ms)		102.81±18.98		105.94±15.45	0.392b
TRVmax (m/s)	4.32 (2.20-5.52)		3.99 (2.17-5.41)		0.451[a]
SPAP (mmHg)	89.64 (27.36-124.88)		71.65 (26.80-125)		0.376[a]
PVR	3.41 (1.82-7.46)		2.94(1.82-6.92)		0.638[a]
Hemodinamic					
Δ SBP rest		2.0 ± 16.49		1.8 ± 12.4	0.97[b]
Δ SBP maximum		2.92 ± 25.75		1.83 ± 9.40	0.89[b]
Δ DBP rest		5.36 ± 18.05		-0.08 ± 7.26	0.34[b]
Δ DBP maximum	4.5 (-36.0 –15.0)		0 (-20 –12)		0.14[a]
Δ HR rest		-1.43±8.38		-2.08±9.05	0.85[b]
Δ HR maximum	6.5 (-49 – 36)		-7.5 (-98.0 -13)		0.008[a]
Δ SpO2 pre-ULJP	0 (-3.0 –1.0)		-5.0 (-8 – 3)		0.40[a]
Δ SpO2 post-ULJP	0 (-16.0 –13.0)		-0.5 (-28 – 18)		0.43[a]
Δ Duration of ULJP (minute)	2.3 (-1 – 5.5)		0 (-1 – 1)		0.002[a]
Ventilation Eficiency					
Δ AT (anaerobic threshold)	64 (-222.0-569.0)		8 (-154.0 -175.0)		0.41[a]
Δ VE/VCO2		-2.49 ± 8.6		-2.28 ± 6.67	0.83[b]

[a] p-value Wilcoxon test (Mann-Whitney). significant difference if p < 0.05
[b] p-value t-test independent. significant difference if p < 0.05
Abbr; PDE5i : phospodiesterase inhibitor; CCB: calcium chanel blocker; MRA : mineralocarticoid Receptor antagonis BB: beta blocker; ACEi/ARB : angiotensin converting enzym inhibitor/ angiotensin receptor antagonis; LVEF : levt ventricle ejection fraction; TAPSE : Tricuspid annular plane systolic excursion; RV FAC : richt ventricle fractional area change; RVS' : right ventricle S wave ; PAcct : pulmonary artery acceleration time; TRVmax : Tricuspid regurgitant velocity maximal; SPAP : sistolic pulmonary artery pressure; PVR : pulmonary vascular resistance; SBP: sistolic blood pressure; DBP : distolic blood pressure; HR : heart rate; CPET : cardiopulmonal exercise test : AT : anaerobic threshold; VE/VCO2 : ventilatory equation/ carbondioxcide production

The analysis of the characteristics of the ULJP examination included hemodynamic and ventilation efficiency characteristics conducted in both the intervention and control groups. The hemodynamic characteristics encompassed measurements of resting and maximum systolic and diastolic blood pressure. resting and maximum heart rate. peripheral oxygen saturation. as well as the duration of ULJP before and after the exercise program. The analysis of ventilation efficiency characteristics included VO2 values at anaerobic threshold (AT) and VE/VCO2. In the results of this study. there were statistically significant differences between the intervention and control groups in the variables of maximum heart rate achievement and ULJP duration.

Based on bivariate statistical analysis. there was no significant difference in 6MWD (meters) between the control group and the intervention group before the initiation of the physical exercise rehabilitation program (283.5 ± 84.18 (234.89 – 332.10) vs. 320.93 ± 43.59 (295.76 – 346.10). p-value = 0.311). However. after the four-week physical exercise rehabilitation program. a significant difference in 6MWD (meters) was observed between the control and intervention groups (300.57 ± 90.79 (248.15 – 352.99) vs. 436.28 ± 58.81 (402.33 – 470.24). p-value <0.001). Significant differences were also found in the Δ6MWD comparison between the control and intervention groups (17.07 ± 48.30 (-10.82 − 44.96) vs. 115.36 ± 54.69 (83.78 − 146.94). p-value

<0.001). This analysis indicates that the intervention group undergoing a four-week physical exercise rehabilitation program experienced a greater increase in 6MWD compared to the control group that did not undergo the program (Figure 1).

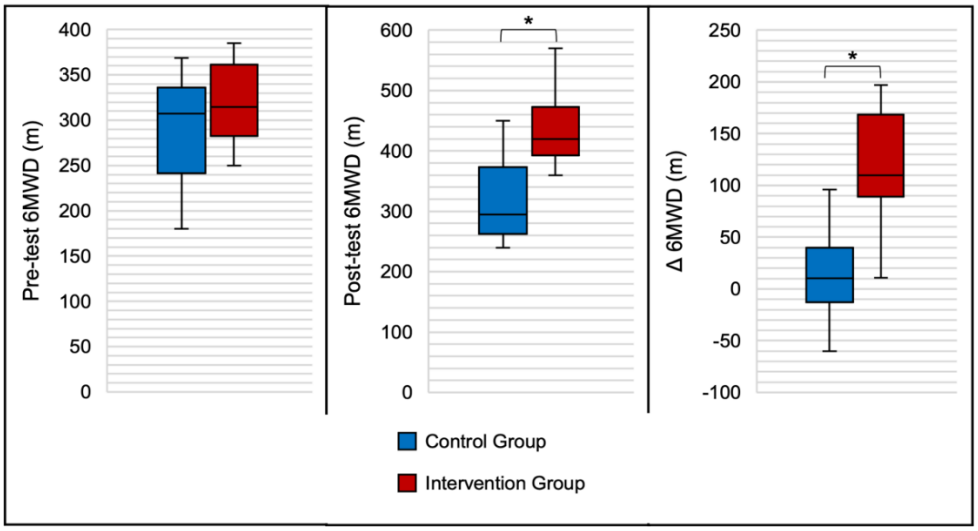

Figure 1. Differences in 6MWD between control group and intervention group.
* Significant difference if jika p-value < 0.05.

Based on bivariate statistical analysis. there was no significant difference in VO2 peak between the intervention group and the control group before the initiation of the physical exercise program (888.29 + 435.99 (314-1823) vs. 641.92 + 231.98 (408-1111). p-value = 0.136). Assessment after the four-week physical exercise program revealed a significant difference in VO2 peak between the intervention and control groups (1047.71 + 456.05 (413-2175) vs. 656.5 + 223.85 (401-1105). p-value = 0.013). Additionally. significant differences were found in the ΔVO2 comparison between the intervention and control groups (159.42 + 209.32 (-92 – 707) vs. 14.5 + 60.4 (-77 – 148). p-value = 0.018). This analysis indicates that the intervention group undergoing a four-week physical exercise program experienced a greater increase in VO2 peak compared to the control group that did not undergo the physical exercise program (Figure 2).

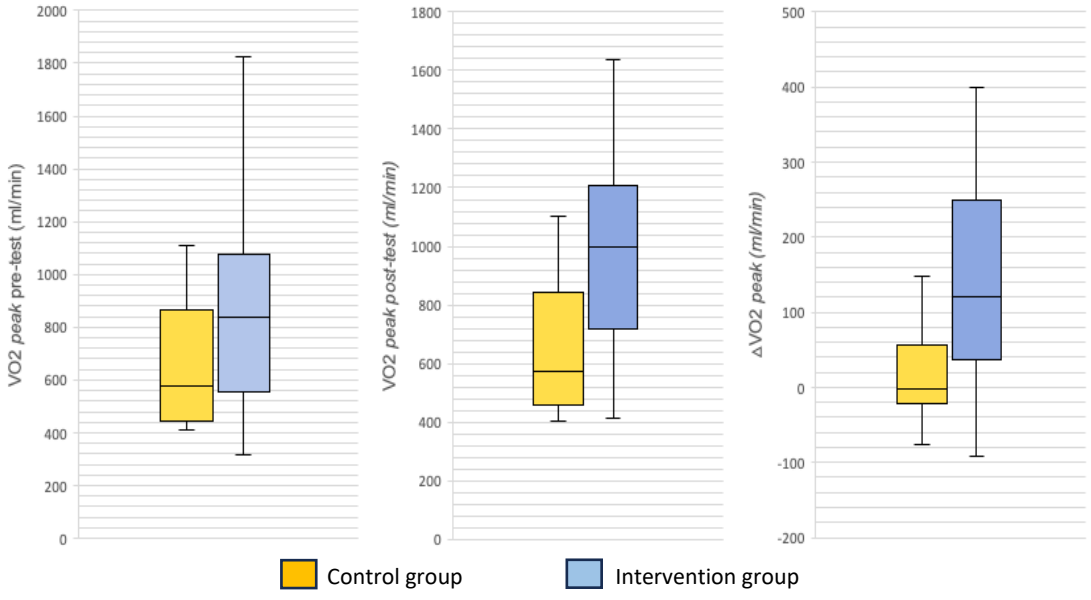

Figure 2. Difference in VO2 between control group and intervention group

Based on bivariate statistical analysis. it is observed that there is no significant difference in Pulmonary Vascular Resistance (PVR) values measured by echocardiography between the control group and the intervention group before the initiation of the physical exercise program (3.41 (1.46-7.46) vs. 2.94 (1.82-6.92) Wood Units (WU). p-value = 0.638). However. after the four-week physical exercise program. a significant difference in PVR values was found between the control and intervention groups (3.70 (1.35-7.56) vs. 2.03 (1.10-4.07) WU. p-value = 0.004). Significant differences were also noted in the ΔPVR comparison between the control and intervention groups [-0.01 (-0.39-(0.63) vs. -1.07 (-0.33-(-2.85)] WU. p-value 0.000). This analysis indicates that the intervention group undergoing a four-week physical exercise program experienced a greater reduction in PVR values compared to the control group that did not undergo the physical exercise program (Figure 3).

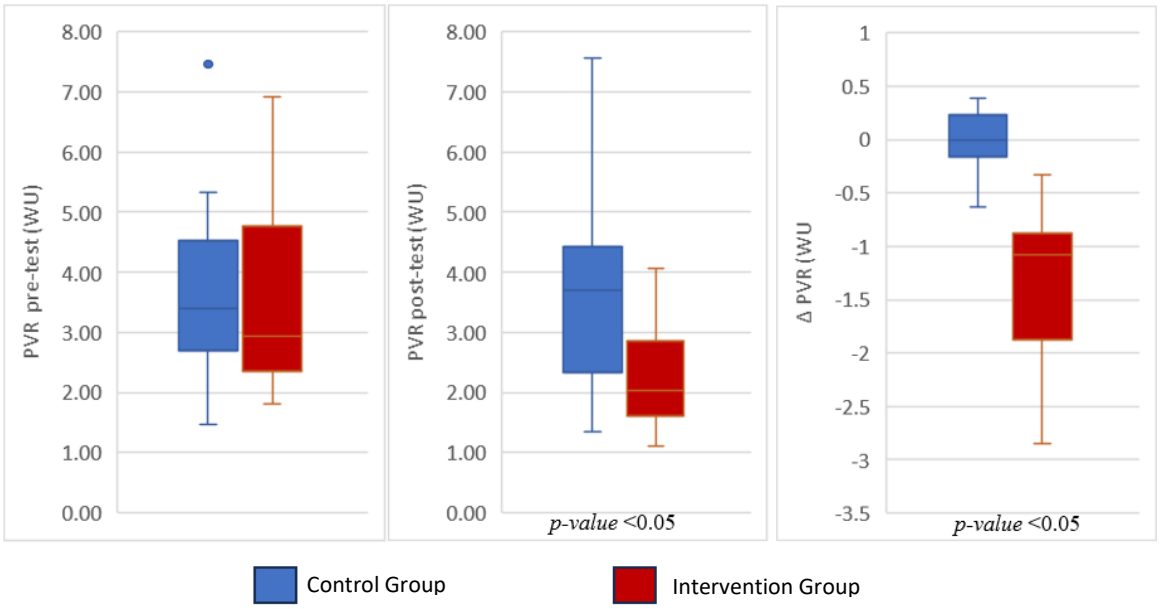

Figure 3. Difference in PVR between control group and intervention group

Discussions

This study indicates that the majority of PAH patients are females. The higher proportion of females with PAH is consistent with several global registries recording that PAH is more prevalent in females and less so in males. but with a worse prognosis[9,10]. The COHARD-PH registry in Indonesia also states that the majority of PAH-CHD patients are females (78.46%)[11]. Previous study also mentioned that PAH patients at RSUP Dr. M. Djamil from 2017-2021 were mostly females[4]. Another studied the effects of estrogen and serotonin on rats induced with PAH. stating that there is an interaction between estrogen and serotonin inducing the proliferation of smooth muscle cells in the pulmonary artery. thereby increasing the risk of PAH[12].

Based on the results of this study. it is known that there is no statistically significant difference in some ULJP characteristics between the two groups after the four-week research period. except for HR peak data and ULJP duration. This suggests that the intervention group shows better exercise endurance than the control group after the physical exercise program. Several studies have shown that physical exercise can improve ULJP tolerance time[13,14]. Research by De Man et al. showed better exercise endurance in the physical exercise program group. This is supported by evidence of increased capillarization in the quadriceps muscles and oxidative enzyme capacity. especially in type 1 (slow twitch) muscle fibers. indicating an improvement in muscle work predominantly using aerobic metabolism[4]. However. this difference may be due to the limited sample size and the short exercise time. resulting in an accidental increase in one of the hemodynamic parameters. This is mentioned in the study by Grunig et al.. which found a significant increase in maximum

blood pressure. HR peak. and maximum peripheral saturation in the intervention group. possibly due to chance[7].

Furthermore. this study found that there was a significantly greater increase in 6MWD in PAH patients undergoing physical exercise rehabilitation compared to those who did not undergo this program. Physical exercise rehabilitation programs have been identified as beneficial approaches in the management of PAH. A prospective study on PAH patients showed that physical exercise rehabilitation significantly improved their 6MWD and exercise capacity[15]. Factors that can influence the increase in 6MWD in PAH patients undergoing physical exercise rehabilitation programs include better cardiorespiratory adaptation and increased strength of respiratory muscles. Physical exercise is known to improve right ventricular function. reduce pulmonary vascular resistance. and improve the quality of life of PAH patients[16]. Additionally. physical exercise rehabilitation programs focusing on high-intensity interval training are known to be effective in improving exercise capacity and respiratory muscle function in PAH patients[17]. The molecular mechanisms underlying the increase in 6MWD in PAH patients undergoing physical exercise rehabilitation programs have also been investigated. Regular physical exercise can affect various signaling molecules involved in the regulation of cardiovascular and muscle adaptation. For example. physical exercise has been shown to increase the expression of angiogenic factors such as vascular endothelial growth factor (VEGF) and Fibroblast Growth Factor (FGF). which can enhance angiogenesis and muscle perfusion[18]. Additionally. physical exercise can stimulate the production and release of neurotrophic factors such as Brain-Derived Neurotrophic Factor (BDNF). which plays a role in muscle maintenance and adaptation[19].

In this study. it was found that there was a significantly greater increase in VO2 peak in PAH patients undergoing physical exercise compared to those who did not undergo the exercise program. Physical exercise programs are known as beneficial approaches in the management of PAH. Although various studies have different protocols. they consistently show that physical exercise programs can improve functional capacity in PAH patients[6,20-22]. There are several mechanisms that can influence the increase in functional capacity in subjects undergoing physical exercise programs. such as improvement in right ventricular function. increased adaptation and strength of respiratory muscles. and increased strength and endurance of skeletal muscles. Additionally. 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[7,22].

In this study. a significant decrease in PVR was found. indicating a greater reduction in PVR in the intervention group undergoing a 4-week physical exercise program compared to the control group. The decrease in PVR values in the intervention group aligns with the study conducted by Ehlken. providing physical exercise for a total of 15 weeks in PAH patients[20]. Physical exercise is known to reduce the processes of inflammation. fibrosis. apoptosis. and proliferation of smooth muscle cells in the pulmonary artery. leading to a decrease in pulmonary vascular resistance[5]. Previous study conducted physical exercise for 5 weeks in rats induced with PAH. and the results showed a 46% reduction in the thickness of the pulmonary artery diameter compared to the control group[23]. Another study also conducted research on rats induced with PAH. and the pulmonary vascular resistance values measured using echocardiography at the end of the study correlated with a decrease in the thickness of the pulmonary artery wall[24]. Thus, it can be concluded that physical exercise is beneficial for inhibiting pulmonary vascular remodeling. the main cause of increased pulmonary vascular resistance and mean pulmonary artery pressure.

Conclusions

This study demonstrates the effectiveness of a 4-week physical exercise program, as evidenced by the significant improvement in the differences in 6MWD. VO2 peak and PVR measured by echocardiography. Therefore, this exercise program can be implemented as part of the rehabilitation program for PAH patients at RSUP M Djamil especially and in various other cardiovascular health centers as a safe easy and effective management effort to enhance the quality of life and prognosis. Some limitations of this study include not measuring other variables that contribute to the increase in VO2 peak such as respiratory muscle strength skeletal muscle strength increased pulmonary blood flow and molecular changes in PAH patients after the

exercise program. Additionally in this study, right heart catheterization measurements were not repeated after patients underwent the exercise program to reassess PVR invasively.

Acknowledgements

Thank you to the Research and Development Division of RSUP M Djamil for facilitating this research especially regarding funding. Gratitude also goes to the members of the Integrated Heart Services Installation as well as the faculty and staff of the Department of Cardiology and Vascular Medicine at the Faculty of Medicine, Andalas University for their support in the implementation of this study.

Declarations of competing interest

No potential competing interest was reported by the authors.

References

1. Emmons-Bell S, Johnson C, Boon-Dooley A, Corris PA, Leary PJ, Rich S, et al. Prevalence, incidence, and survival of pulmonary arterial hypertension: A systematic review for the global burden of disease 2020 study. Pulm Circ. 2022 2(1):e12020.
2. Levine DJ, Gale S, Burgoyne DS. Improving economic and quality of life burden in pulmonary arterial hypertension: a review of clinical data and strategies to slow progression. Am J Manag Care. 2021;27(3):e86-e92.
3. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022;43(38):3618-3731.
4. Raihani MU, Yanni M, Asri E. Gambaran karakteristik pasien hipertensi arteri pulmonal di RSUP Dr. M. Djamil Padang tahun 2017-2021. E-Repository Universitas Andalas. 2021.
5. Eichstaedt CA, Benjamin N, Xanthouli P, Marra AM, Grünig E. The role of rehabilitation in patients with pulmonary arterial hypertension. Curr Opin Pulm Med. 2019;25(5):398-404.
6. Bussotti M, Gremigni P, Pedretti RFE, Kransinska P, Di Marco S, Corbo P, et al. Effects of an Outpatient Service Rehabilitation Programme in Patients Affected by Pulmonary Arterial Hypertension: An Observational Study. Cardiovasc Hematol Disord Drug Targets. 2017;17(1):3-10.
7. Grünig E, Eichstaedt C, Barberà JA, Benjamin N, Blanco I, Bossone E, et al. ERS statement on exercise training and rehabilitation in patients with severe chronic pulmonary hypertension. Eur Respir J. 2019;53(2):1800332.
8. PERKI. Panduan Rehabilitasi Kardiovaskular. Jakarta: PERKI; 2019.
9. Cheron C, McBride SA, Antigny F, Girerd B, Chouchana M, Chaumais MC, et al. Sex and gender in pulmonary arterial hypertension. Eur Respir Rev. 2021;30(162):200330.
10. Martin YN, Pabelick CM. Sex differences in the pulmonary circulation: implications for pulmonary hypertension. Am J Physiol Heart Circ Physiol. 2014;306(9):H1253-64.
11. Dinarti LK, Hartopo AB, Kusuma AD, Satwiko MG, Hadwiono MR, Pradana AD, Anggrahini DW. The COngenital HeARt Disease in adult and Pulmonary Hypertension (COHARD-PH) registry: a descriptive study from single-center hospital registry of adult congenital heart disease and pulmonary hypertension in Indonesia. BMC Cardiovasc Disord. 2020;20(1):163.
12. White K, Dempsie Y, Nilsen M, Wright AF, Loughlin L, MacLean MR. The serotonin transporter, gender, and 17β oestradiol in the development of pulmonary arterial hypertension. Cardiovasc Res. 2011;90(2):373-82.
13. Chan L, Chin LMK, Kennedy M, Woolstenhulme JG, Nathan SD, Weinstein AA, et al. Benefits of intensive treadmill exercise training on cardiorespiratory function and quality of life in patients with pulmonary hypertension. Chest. 2013;143(2):333-343.
14. de Man FS, Handoko ML, Groepenhoff H, van 't Hul AJ, Abbink J, Koppers RJ, et al. Effects of exercise training in patients with idiopathic pulmonary arterial hypertension. Eur Respir J. 2009;34(3):669-75.
15. Chia KSW, Shiner CT, Brown K, Holloway CJ, Moreyra C, Bart N, et al. The exercise in pulmonary arterial hypertension (ExPAH) study: A randomized controlled pilot of exercise training and multidisciplinary rehabilitation in pulmonary arterial hypertension. Pulm Circ. 2022;12(2):e12069.
16. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European

Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37(1):67-119.
17. Zhang X, Xu D. Effects of exercise rehabilitation training on patients with pulmonary hypertension. Pulm Circ. 2020;10(3):2045894020937129.
18. Laddha AP, Kulkarni YA. VEGF and FGF-2: Promising targets for the treatment of respiratory disorders. Respir Med. 2019;156:33-46.
19. Schäfer K, Tello K, Pak O, Richter M, Gierhardt M, Kwapiszewska G, et al. Decreased plasma levels of the brain-derived neurotrophic factor correlate with right heart congestion in pulmonary arterial hypertension. ERJ Open Res. 2023;9(2):00230-2022.
20. Ehlken N, Lichtblau M, Klose H, Weidenhammer J, Fischer C, Nechwatal R, et al. Exercise training improves peak oxygen consumption and haemodynamics in patients with severe pulmonary arterial hypertension and inoperable chronic thrombo-embolic pulmonary hypertension: a prospective, randomized, controlled trial. Eur Heart J. 2016;37(1):35-44.
21. Ozemek C, Berry MJ, Arena R. A Review of Exercise Interventions in Pulmonary Arterial Hypertension and Recommendations for Rehabilitation Programing. J Cardiopulm Rehabil Prev. 2019;39(3):138-145.
22. Harbaum L, Renk E, Yousef S, Glatzel A, Lüneburg N, Hennigs JK, et al. Acute effects of exercise on the inflammatory state in patients with idiopathic pulmonary arterial hypertension. BMC Pulm Med. 2016;16(1):145.
23. Colombo R, Siqueira R, Becker CU, Fernandes TG, Pires KM, Valença SS, et al. Effects of exercise on monocrotaline-induced changes in right heart function and pulmonary artery remodeling in rats. Can J Physiol Pharmacol. 2013;91(1):38-44.
24. Handoko ML, de Man FS, Happé CM, Schalij I, Musters RJ, Westerhof N, et al. Opposite effects of training in rats with stable and progressive pulmonary hypertension. Circulation. 2009;120(1):42-9.