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Short Communication

Role of phosphodiesterase-3 inhibitor in cardiorespiratory fitness and functional class of patients with pulmonary hypertension: A randomized, double-blind, placebo-controlled trial

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Abstract

Many patients with acyanotic shunt congenital heart disease (CHD) are diagnosed only in adulthood, by which time pulmonary hypertension (PH) has developed, impairing their functional class and cardiorespiratory fitness. While PH treatments are limited and expensive, cilostazol, a phosphodiesterase-3 inhibitor, has shown potential in reducing pulmonary artery pressure and improving heart function, offering hope for better patient outcomes. The aim of this study was to evaluate the effects of cilostazol on cardiorespiratory fitness and functional class in patients with acyanotic shunt CHD with PH using a randomized, double-blind, placebo-controlled trial. The trial was conducted at Dr. Kariadi Hospital, Semarang, Indonesia, from March 2022 to March 2023. Patients aged 14–75 years were randomly assigned to receive cilostazol (initially 200 mg, later adjusted to 100 mg) or placebo for three months. Cardiorespiratory fitness was assessed using the six-minute walk test (6MWT) and VO_2 max at pre-intervention and three months post-intervention. After three months, the mean 6MWT was not significantly different between cilostazol and placebo groups (319.65±50.52 vs 317.65±45.26 meters; p=0.090). Similarly, the VO_2 max was also not significantly different between cilostazol and placebo groups (10.74±2.59 mL/kg/min vs 10.73±2.8 mL/kg; p=0.099). However, the percentage of patients who had functional class improvement was significantly higher in the cilostazol group compared to the placebo group (90% vs 30%; p<0.001). This study indicated that cilostazol could improve functional class in acyanotic shunt CHD patients with PH. However, larger and more robust trials are warranted to confirm the potential benefits of cilostazol in this patient population.

Keywords: Congenital heart disease, acyanotic, cilostazol, cardiorespiratory fitness, six-minute walk test

Introduction

Congenital heart disease (CHD) is a structural abnormality of the heart that occurs as a result of improper formation of the heart and blood vessels during the heart formation period during the embryonic development. CHD is the most common congenital abnormality in newborns. The

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prevalence of CHD is nine to 10 per 1000 live births [1,2]. In Indonesia, the prevalence of children born with CHD is 45,000 annually [1,2]. A study in Dr. Kariadi Hospital, Semarang, Indonesia, between 2007 and 2008 found that the most common type of CHD was the acyanotic type; 68.8% of all CHD cases were acyanotic type with a left-to-right shunt [3]. Between four and 15% of CHD patients develop pulmonary hypertension (PH), and this rate is relatively high in Indonesia [3,4]. Data from the Congenital Heart Disease in Adult And Pulmonary Hypertension (COHARD-PH) Registry for 2012–2019 at Dr. Sardjito Hospital, Yogyakarta, Indonesia, found that the prevalence of patients with CHD and PH was 77.1% [4]. PH is a complication of CHD, especially in patients with shunts. Exposure to blood flow and pressure that increases continuously will trigger dysfunction and changes in the histological structure of the pulmonary vascular wall. This causes an increase in pulmonary vascular resistance (PVR). Patients with this condition will complain of shortness of breath, fatigue, and lower quality of life due to decreased functional capacity and fitness of the cardiorespiratory system.

Cardiorespiratory fitness can be measured objectively and quantitatively by measuring VO_2 max, which is the gold standard for assessing the amount of maximum oxygen consumption during a training test [3-5]. The exercise tolerance test is used to measure or predict a person's cardiorespiratory fitness [3,4]. One of the cardiorespiratory fitness tests is the six-minute walking test (6MWT) [5]. As PH progresses, increased PVR and cardiorespiratory dysfunction lead to reduced exercise tolerance and daily activity capacity. Patients then experience shortness of breath, fatigue, and a lower quality of life. Functional class, patient's ability to perform physical activities, is often evaluated using 6MWT or by measuring VO_2 max, which assesses cardiorespiratory fitness and overall functional capacity [4,5].

There are no standardized therapy recommendations for PH that can be applied in all countries or regions because the results of studies have not shown satisfactory results. Surgical therapy for defect correction in CHD patients with severe PH where blood flow predominates from right to left is not recommended and some oral therapies are also not encouraging [3,5]. Phosphodiesterase-5 inhibitor class, such as sildenafil, could reduce pulmonary artery pressure (PAP) and improve 6MWT results [6], but the availability of the drugs is very limited due to high costs. Another oral PH drug available in Indonesia and approved by the Indonesian Food and Drug Administration is the beraprost class. A previous study showed that beraprost could improve the quality of life of PH patients, improve functional class and increase the 6MWT, but it did not significantly reduce pulmonary artery pressure, PH morbidity or mortality [6].

Cilostazol, a phosphodiesterase-3 inhibitor that has a vasodilating effect, has received approval from the Indonesian Food and Drug Administration for the treatment of chronic arterial occlusive disease [7]. Cilostazol is a standard therapy in patients with peripheral arterial disease and used in patients with cerebral vascular disease, as well as in patients with CHD who underwent stent placement [7]. A previous study examined PH-induced rats using monocrotaline and found that cilostazol was effective in reducing PH [8]. A study conducted in patients with peripheral arterial disease who were given cilostazol for three months and found improvement in right ventricular function and a significant reduction in PAP after cilostazol administration [9]. Improvements in PAP and right ventricular function would increase functional capacity class and cardiorespiratory fitness.

There have been no studies assessing the role of cilostazol in patients with shunt acyanotic CAD and PH, particularly in relation to improvement in functional class and cardiorespiratory fitness as measured by 6MWT. The aim of this study was to evaluate the efficacy of cilostazol, a phosphodiesterase-3 inhibitor, on cardiorespiratory fitness and functional class in patients with acyanotic shunt CAD and PH using a randomized, double-blind, placebo-controlled trial.

Method

Study design and patients

A randomized, double-blind, placebo-controlled clinical trial was conducted at Dr. Kariadi Hospital in Semarang, Indonesia, from March 2022 to March 2023. The sample consisted of patients with shunt acyanotic CHD and confirmed PH through right heart catheterization who were selected through purposive sampling. Eligible participants were between the ages of 14 and

75 years old, with a left ventricular ejection fraction (LVEF) of 55% or higher and pulmonary vascular resistance exceeding systemic pressure. Exclusion criteria included patients with the New York Heart Association (NYHA) class III or IV heart failure, chronic obstructive pulmonary disease (COPD), connective tissue diseases, or genetic disorders. Additionally, patients taking certain medications or those with other complicating conditions were excluded.

The sample size was calculated to ensure adequate statistical power for detecting differences between the cilostazol and placebo groups. A power analysis was performed prior to the study, taking into account the expected effect size and the standard deviations of key outcome measures (functional class improvement and cardiorespiratory fitness) as recommended previously [10]. Based on the calculation, the sample size of 42 patients could provide sufficient power to achieve meaningful conclusions while accounting for potential dropouts.

Randomization and blinding

Patients who met the eligibility criteria were provided with detailed information about the study, and those who agreed to participate provided written informed consent. Demographic characteristics and clinical data were collected through direct interviews and clinical assessments. Randomization was conducted using a computer program to generate random numbers, ensuring the patients were randomly assigned to either the cilostazol or placebo control group. Each patient was given an identity number, and neither the patients nor the researchers knew which group they belonged to, maintaining the double-blind nature of the study. Blinding was further ensured by using identical packaging for both the cilostazol and placebo capsules.

Intervention

Cilostazol and placebo were administered for a total of three months. The drug was self-administered by the patients, with instructions provided by a pharmacist to ensure proper use. Throughout the study, patients were monitored monthly for any side effects or adverse events. During the visits, clinical evaluations and assessments were performed to track the patient's progress and address any issues that arose.

Initially, patients in the treatment group received 200 mg of cilostazol daily (once a day). However, after three consecutive days of 200 mg administration, the dosage was reduced to 100 mg (once a day) for patients who experienced adverse events, including headaches, dizziness, and gastrointestinal discomfort. These adverse events were managed with supportive care, such as hydration for headaches and antacids for gastrointestinal symptoms. No severe adverse events were reported, and the treatment regimen was well tolerated by the participants overall.

Cardiorespiratory fitness

All patients included in this study underwent 6MWT to measure their cardiorespiratory fitness before and three months after receiving the treatment. During the 6MWT, the patients were instructed to walk as far as possible in six minutes in a 15-meter-long, flat, straight hospital corridor [10,11]. The result of 6MWT was the distance in meters which was then converted to VO_2 max using Nury's formula [12]. VO_2 max = 0.053 (distance in meter) + 0.022 (age in year) + 0.032 (height in cm) – 0.164 (weight in kg) – 2.228 (sex*) – 2,287. For the variable "sex", male = 0 and female = 1. The VO_2 max was presented in milliliters per kilogram per minute (mL/kg/min).

Functional class

Functional class is a crucial metric in evaluating the clinical status of patients with CHD and PH since it provides a standardized way to assess the severity of symptoms and the patient's ability to perform daily physical activities. Functional class reflects the overall burden of the disease on their daily lives, offering valuable insight into their prognosis and therapeutic response. In this study, the World Health Organization (WHO) functional class [14] was employed, which specifically categorizes PH patients based on symptom severity and the impact on physical activity. The functional class was divided into four categories: (A) Class I represented patients who experience no limitations in physical activity; (B) Class II represented those who had slight limitations but could still perform daily tasks with minimal discomfort; (C) Class III indicated marked limitations, where even light activity caused significant symptoms like breathlessness and fatigue; and (D) Class IV included those who were severely symptomatic, often experienced

discomfort even at rest [14]. This study assessed functional class through clinical evaluation and physical performance tests using 6MWT.

Statistical analysis

Data normality was assessed using the Shapiro-Wilk test. For datasets with a normal distribution, hypotheses were tested using the parametric unpaired Student t-test. In contrast, for non-normally distributed data, non-parametric tests were applied: the Mann-Whitney U test was used for comparing medians between two groups, and the Chi-squared test was employed for categorical data analysis. A $p<0.05$ was considered statistically significant. Data analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 25 (IBM, New York, USA).

Results

Patients' characteristics

This study identified 42 patients as potential samples of which two underwent shunt closure surgery and were excluded. Therefore, 40 patients were randomized into two groups: cilostazol and placebo (20 patients per group). Until the end of the study none of the patients were excluded from the study. The flow diagram of the sample recruitment selection process is presented in **Figure 1**.

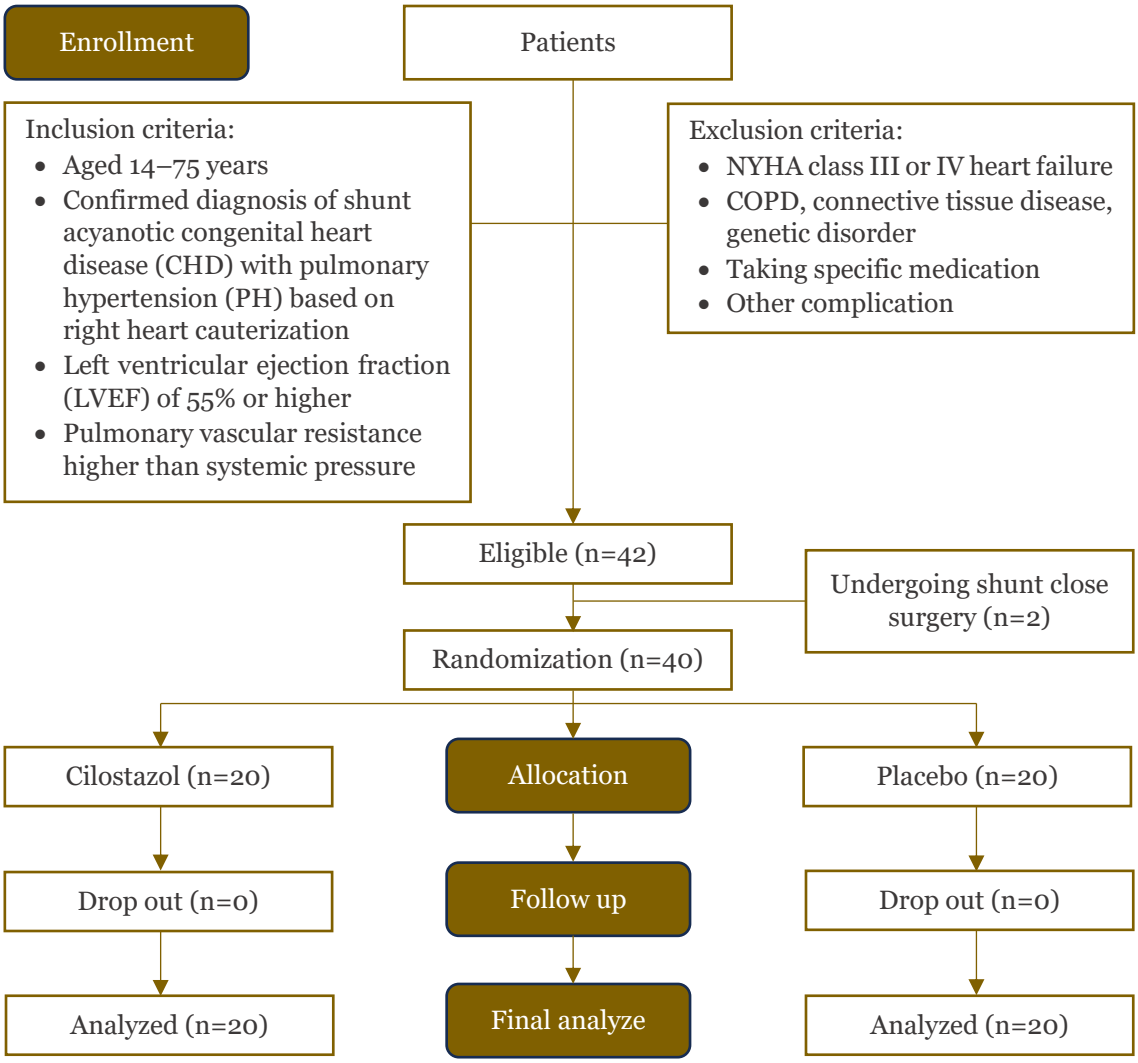

Figure 1. CONSORT flowchart diagram of participant recruitment. COPD: chronic obstructive pulmonary disease; NYHA: New York Heart Association.

The demographic data and clinical characteristics of the study samples of treatment and control groups are presented in **Table 1**. The cilostazol group had a mean age of 36.9±13.30 years, and the placebo group had a median of 30±9.82 years. Both groups were predominantly female, with 90% women in the cilostazol group and 80% in the placebo group. In the cilostazol group, 65% of patients were in functional class II, while the placebo group had 80% in the same class. The atrial septal defect was the most common type of CHD, present in 80% of the cilostazol group and 70% of the placebo group (**Table 1**).

The results of the right heart catheterization examination in the cilostazol group obtained an average mean pulmonary arterial pressure (mPAP) of 51±21.17 mmHg, the median pulmonary vascular resistance index (PVRi) value was 4.41, and the median pulmonary vascular resistance (PVR)/systemic vascular resistance (SVR) ratio was 0.16 (**Table 1**). The placebo group had an average mPAP of 55.15±26.05 mmHg, a median PVRi value of 3.58 and a median PVR/SVR ratio of 0.15 (**Table 1**). The results of the initial 6MWT examination in the cilostazol group had an average of 270±60.3 meters, and in the placebo group, 270.7±43.65 meters (**Table 1**). The mean value of VO_2 max in the cilostazol and placebo group was 8.11±2.88 mL/kg and 8.25±2.73 mL/kg, respectively (**Table 1**). These data indicated that the basic demographic and clinical characteristics between the cilostazol and placebo groups were not statistically different.

Table 1. Basic demographic and clinical characteristics of the study sample between intervention and control groups (n=40)

Patients' characteristics	Cilostazol (n=20)	Placebo (n=20)	*p*-value
	n (%)	n (%)	
Age (year), mean±SD	36.9±13.30	30±9.82	0.084
Sex			0.494
Female	18 (90%)	16 (80%)	
Male	2 (2%)	4 (20%)	
Height (cm), mean±SD	155±9.16	162±7.89	0.528
Weight (kg), mean±SD	46.85±10.22	57.5±14.87	0.128
BMI (kg/m²), median (range)	17.66 (14.61–28.01)	20.45 (9.41–26.67)	0.960
WHO functional class			0.484
I	3 (15%)	1 (5%)	
II	13 (65%)	16 (80%)	
III	4 (20%)	3 (15%)	
Type of congenital heart disease			0.737
Atrial septal defect	16 (80%)	14 (70%)	
Ventricular septal defect	3 (15%)	4 (20%)	
Patent ductus arteriosus	1 (5%)	2 (10%)	
Systolic pressure (mmHg), mean±SD	107.85±13.84	105.65±14.13	0.528
Diastolic pressure (mmHg), mean±SD	69.35±12.22	65.45±11.05	0.128
Right heart catheterization			
mPAP (mmHg), mean±SD	51±21.17	55.15±26.05	0.960
PVRi, median (range)	4.41 (0.1–40.82)	3.58 (0.19–31.95)	0.903
PVR/SVR, median (range)	0.16 (0.01–1.09)	0.15 (0.01–1.59)	0.351
Initial 6MWT (meter), mean±SD	270±60.3	270.7±43.65	0.528
Initial VO_2 max (mL/kg/min), mean±SD	8.11±2.88	8.25±2.73	0.960

6MWT: six-minute walking test; mPAP: mean pulmonary arterial pressure; PVRi: pulmonary vascular resistance index; PVR/SVR: pulmonary vascular resistance – systemic vascular resistance ratio

Efficacy of cilostazol in improving cardiorespiratory fitness

After three months of treatment, the effects of cilostazol on cardiorespiratory fitness were assessed. Based on the 6MWT assessment, the cilostazol group had an average of 319.65 meters compared to 317.65 meters in the placebo group, suggesting slightly better in the cilostazol group compared to the placebo group with a mean difference of 2.0 meters (95%CI: -28.7–32.7) (**Table 2**). However, the analysis indicated no significant difference between both groups with p=0.090 (**Table 2**). Similarly, the mean final VO_2 max in the cilostazol was slightly higher compared to the placebo group (10.74 mL/kg/min vs 10.73±2.8 mL/kg/min), with a mean difference of 0.01 mL/kg/min (95%CI: -1.71–1.73) (**Table 2**). The mean final VO_2 max had no significant difference between both groups with p=0.099.

Table 2. Comparison of 6MWT and VO_2 max between cilostazol and placebo at the end of treatment

Variable	n	Mean±SD	Mean difference (95%CI)	*p*-value
Final 6MWT (meter)				
Cilostazol	20	319.65±50.52	2.0 (-28.7–32.7)	0.090
Placebo	20	317.65±45.26		
Final VO_2 max (mL/kg/min)				
Cilostazol	20	10.74±2.59	0.01 (-1.71–1.73)	0.099
Placebo	20	10.73±2.8		

The comparisons of Δ6MWT and ΔVO_2 max between cilostazol and placebo groups are presented in **Table 3**. The median value of Δ6MWT in the cilostazol and placebo group was 49 meters and 39.5 meters, respectively, and there was no significant difference between the two groups, with p=0.062 (**Table 3**). The median of ΔVO_2 max in the cilostazol group was higher than the placebo group, with a median value of 2.27 mL/kg vs 1.81 mL/kg; however, this difference was also not statistically significant (p=0.074) (**Table 3**).

Table 3. Comparisons of Δ6MWT and ΔVO_2 max between cilostazol and placebo

Indicator/group	n	Median (min-max)	Mean (meter)	*p*-value
Δ6MWT				
Cilostazol	20	49 (9–111)	49.65±28.17	0.062
Placebo	20	39.5 (7–99)	46.95±33.34	
ΔVO_2 Max				
Cilostazol	20	2.27 (0.2–5.13)	2.28±1.39	0.074
Placebo	20	1.81 (0.09–4.94)	2.18±1.71	

Efficacy of cilostazol in improving WHO functional class

WHO functional class in this study was grouped into improved and not improved by comparing WHO functional class before and after treatment. Of the patients, 18 (90%) and 6 (30%) treated with cilostazol and placebo, respectively, had improved the WHO functional class (**Table 4**). Our analysis also confirmed that the percentage of patients who had improved WHO functional class after treatment was higher in cilostazol and placebo (90% vs 30%, p<0.001) (**Table 4**).

Table 4. Efficacy of cilostazol in improving WHO functional class

Group	WHO functional class improvement				*p*-value
	Yes		No		
	n	%	n	%	
Cilostazol	18	90.0	2	10.0	<0.001
Placebo	6	30.0	14	70.0	
Total	24	60.0	16	40.0	

Comparison of adverse effects

During this study, four side effects were reported in both groups: headache, palpitation, hypotension, and diarrhea (**Table 5**). Chi-squared tests were performed to assess their relationship with cilostazol administration. Headaches were reported by seven participants in the cilostazol group and four in the placebo group (p=0.292). Palpitations occurred in seven participants receiving cilostazol and one in the placebo group (p=0.024). Hypotension was observed in one cilostazol recipient (p=0.312) and diarrhea in two (p=0.150). Among these, only palpitations showed a statistically significant association with cilostazol use.

Table 5. Adverse effects reported between cilostazol and placebo groups

Adverse event	Cilostazol group (n=20)	Placebo group (n=20)	*p*-value
Headache	7 (35%)	4 (20%)	0.292
Palpitations	7 (35%)	1 (5%)	0.024
Hypotension	1 (5%)	0 (0%)	0.312
Diarrhea	2 (10%)	0 (0%)	0.150

Discussion

Patients with acyanotic CHD and PH often suffer from right ventricular dysfunction, which contributes to reduced cardiorespiratory fitness [14-16]. Cilostazol is expected to enhance cyclic adenosine monophosphate (cAMP) levels and inhibit adenosine uptake, promoting vasodilation. It has demonstrated positive chronotropic and inotropic effects in previous studies [9,17,18]. In the present study, improvements in cardiorespiratory fitness and WHO functional class in patients receiving cilostazol were observed, although only the WHO functional class was statistically significant.

Cardiorespiratory fitness, assessed via 6MWT and VO_2 max values in the present study, served as a critical marker for functional capacity in PH patients. In this study, patients treated with cilostazol exhibited a modest increase in 6MWT distance and a slight improvement in VO_2 max compared to the placebo group. While these changes were not statistically significant, the observed trends suggested that cilostazol may enhance exercise tolerance. These findings align with cilostazol's pharmacological effects, including vasodilation and improved cardiac output through positive inotropic and chronotropic mechanisms [9,17,18], which could theoretically increase oxygen delivery to tissues and improve exercise performance. The results of our study were also in line with a previous study, which reported significant increases in walking distance among patients with intermittent claudication treated with cilostazol, despite no improvement in VO_2 max [19]. The variations between these findings may stem from differences in the underlying pathophysiology of PH, peripheral arterial disease, and heart failure. In PH, the unique effects on pulmonary circulation and right ventricular function may necessitate more targeted interventions to further enhance exercise capacity beyond cilostazol's vasodilatory actions [19].

In our study, the WHO functional class, a recognized metric for assessing the severity of PH, was notably improved among patients in the cilostazol group compared to the placebo group. A total of 90% of cilostazol-treated patients moved to a better functional class, compared to only 30% in the placebo group. This trend suggested a potential clinical benefit of cilostazol in alleviating PH symptoms and enhancing patients' daily functioning, proven as statistical analysis showed significantly different results. Such improvement reflects a meaningful enhancement in quality of life. This finding aligned with a previous study highlighting cilostazol's positive impact on functional capacity, quality of life and symptom relief in cardiovascular conditions [19].

The side effect profile of cilostazol in this study is largely in line with what has been previously reported [20]. Palpitation, the only adverse event with a statistically significant difference between the groups, is a known side effect of cilostazol due to its mechanism as a phosphodiesterase-3 inhibitor, which can increase heart rate and cause vasodilation. This was also observed previously, although this side effect is generally well-tolerated [21].

Some factors could explain the lack of statistical significance of 6MWT and VO_2 max values despite observed clinical trends. The relatively short duration of cilostazol administration (three months) may not have been sufficient to yield substantial hemodynamic or functional improvements. Additionally, the sample size was relatively small, which limits the power of the study to detect significant differences. PH is a complex and progressive disease, and longer treatment durations could potentially reveal more pronounced benefits. For example, a study by Sahin *et al.* [9] which demonstrated significant improvements in right ventricular function and a decrease in PAP after six months of cilostazol treatment, suggested that a longer duration of therapy may be necessary to observe significant hemodynamic benefits. This comparison highlights the importance of extended follow-up periods in future research. Similarly, Ito *et al.* [17] findings on the variability of cilostazol's effects based on the underlying cause of PH suggested that patient selection and the etiology of PH are critical factors that could influence treatment outcomes [17]. Inflammatory processes and structural vascular changes may differentially impact the effectiveness of cilostazol, and future studies should stratify patients based on these factors to provide more nuanced insights.

Future studies on cilostazol for managing PH in acyanotic CHD patients therefore should consider several recommendations based on our limitations and findings. First, prolonged cilostazol administration may be necessary to assess long-term effects, as improvements in right ventricular function and PAP may take longer to manifest, emphasizing the need for longer follow-up periods. Additionally, expanding the sample size will enhance statistical power,

allowing for more robust conclusions, particularly regarding subtle improvements in objective measures like VO_2 max and 6MWT. Detailed subgroup analyses based on factors such as the etiology of PH, patient age, sex, and disease severity will help identify which groups benefit the most from cilostazol therapy. Furthermore, exploring cilostazol in combination with other therapies targeting pulmonary vascular resistance or right ventricular function could yield more comprehensive results. Advanced hemodynamic assessments using tools like echocardiography and right heart catheterization should be incorporated to better understand cilostazol's mechanisms of action. Lastly, patient-reported outcome measures will provide insights into quality-of-life improvements, symptom relief, and overall well-being, ultimately offering a clearer understanding of cilostazol's role in this patient population and identifying more targeted therapeutic approaches.

Conclusion

This study found that cilostazol treatment in acyanotic CHD patients with PH could improve the WHO functional; however, it did not improve cardiorespiratory fitness (6MWT and VO2 max). Cilostazol's positive chronotropic and inotropic effects, as observed in peripheral arterial disease, suggested that its benefits may relate more to symptom relief and functional improvements rather than direct enhancements in fitness. Future research should focus on extended time of cilostazol use, larger samples, and combining it with other therapies. Advanced diagnostic tools and quality-of-life assessments are crucial to uncover their full therapeutic potential, particularly in specific patient subgroups.

Ethics approval

This study was performed after receiving the ethical approval of its protocol by the Ethics Committee of the Kariadi General Hospital (Protocol Number 994/EC/KEPK-RSDK/2022), aligning with the ethical principles stated in the Declaration of Helsinki.

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None.

Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

This study used artificial intelligence (AI) tools and methodologies in the following capacities. ChatGPT was used for language refinement (improving grammar, sentence structure, and readability of the manuscript). We confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were solely made by the authors.

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