JMedSci

Journal of the Medical Sciences
(Berkala Ilmu Kedokteran)

Volume 55, Number 1, 2023; 34-43
https://doi.org/10.19106/JMedSci005501202305

Pulmonary vascular resistance/systemic vascular resistance (PVR/SVR) ratio changes after sildenafil therapy in uncorrected congenital heart disease-associated pulmonary arterial hypertension

Evita Devi Noor Rahmawati*, Putrika Prastuti Ratna Gharini, Anggoro Budi Hartopo, Lucia Kris Dinarti, Dyah Wulan Anggrahini

Department of Cardiology and Vascular Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta

Submitted: 2022-02-28
Accepted : 2022-05-23

ABSTRACT

Pulmonary vascular resistance (PVR) to systemic vascular resistance (SVR) ratio is a prognostic predictor in congenital heart disease (CHD)-associated pulmonary arterial hypertension (PAH) after defect correction. Sildenafil, widely used as a PAH drug, can decrease PVR with minimal or without changes in SVR, resulting in decreased PVR/SVR ratio after treatment. However, there is limited evidence that PVR/SVR ratio reduced after sildenafil therapy in uncorrected CHD-associated PAH patients. This study aimed to investigate the decreasing of the PVR/SVR ratio after ≥ 1-year oral sildenafil therapy in adult uncorrected CHD-associated PAH. A total of 30 uncorrectable CHD-associated PAH subjects derived from the COHARD-PH registry were included in this study. Right heart catheterization (RHC) was performed during the first visit and further evaluations were conducted after ≥1-year oral sildenafil therapy. The PVR/SVR ratio at the baseline and after the evaluation was collected. The primary outcome of this study was the changes in PVR/SVR ratio from baseline to evaluated RHC. Characteristic analysis of subjects with decreased PVR or PVR/SVR ratio was perforemd as the secondary outcome. The mean PVR and SVR were not different from baseline and evaluated RHC (15.98± 10.67 vs. 18.38±13.93 WU, p=0.206 and 36.65±13.99 *vs.* 39.34±15.46 WU, p=0.262). There was no significant difference in the baseline PVR/SVR ratio and the evaluated PVR/SVR ratio after ≥1-year sildenafil therapy (0.48 ±0.32 vs. 0.49±0.36; p=0.882). As much as 15 subjects (50%) experienced decreased PVR/SVR ratio. However, there was no significant difference in the characteristics, including age, Eisenmenger syndrome, type of shunts, baseline PVR, PAH-specific treatment, and baseline NT-proBNP level (p>0.05). In conclusion, sildenafil therapy does not change PVR/SVR ratio in adults with uncorrected CHD-associated PAH.

Keywords:
congenital heart disease;
pulmonary arterial hypertension;
pulmonary vascular resistance;
sildenafil;
systemic vascular resistance

ABSTRACT

Rasio resistensi paru (Rp) terhadap resistensi sistemik (Rs) atau selanjutnya disebut Rp/Rs merupakan sebuah prediktor pada hipertensi arteri paru (HAP) yang berhubungan dengan penyakit jantung kongenital setelah koreksi defek. Sildenafil, obat HAP yang banyak digunakan, dapat menurunkan Rp dengan minimal atau tanpa perubahan pada Rs, yang menghasilkan penurunan rasio Rp/Rs setelah terapi. Namun belum terdapat bukti bahwa terapi sildenafil oral dapat menurunkan Rp/Rs pada pasien HAP yang berhubungan dengan penyakit jantung kongenital yang belum dikoreksi. Penelitian ini bertujuan untuk mengkaji penurunan Rp/Rs pada HAP yang berhubungan dengan penyakit jantung kongenital yang belum dikoreksi setelah terapi sildenafil ≥1 tahun. Sebanyak 30 subyek dengan HAP akibat penyakit jantung kongenital yang belum dikoreksi diambil dari data registrasi COHARD-PH. Kateterisasi jantung kanan (KJKa) dilakukan pada awal dan dilakukan evaluasi setelah

*corresponding author: evitadevi.dr@gmail.com

terapi sildenafil oral selama ≥ 1 tahun. Rasio resistensi paru terhadap resistensi sistemik awal dan evaluasi didapatkan dari KJKa tersebut. Luaran utama dari studi ini adalah perubahan Rp/Rs. Analisis karakter subyek dengan nilai Rp yang turun atau Rp/Rs yang turun dilakukan sebagai luaran sekunder. Hasil penelitian menunjukkan rerata Rp maupun Rs tidak berbeda dari awal dibandingkan dengan evaluasi (15,98±10,67 vs. 18,38±13,93 WU, p=0,206 dan 36,65±13,99 vs. 39,34±15,46 WU, p=0,262). Tidak terdapat perbedaan bermakna pada Rp/Rs awal dan evaluasi setelah terapi sildenafil oral selama ≥1 tahun (0,48 ±0,32 vs. 0,49±0,36; p=0,882). Sebanyak 15 subyek (50%) mengalami penurunan Rp/Rs, namun tidak didapatkan perbedaan signifikan dari karakteristik subyek, termasuk usia, sindrom Eisenmenger, tipe defek, Rp awal, terapi spesifik HAP dan level NT-proBNP awal. Simpulan, terapi sildenafil tidak mengubah Rp/Rs pada HAP yang berhubungan dengan penyakit jantung kongenital yang belum dikoreksi.

INTRODUCTION

Pulmonary hypertension (PH) is a pathological disorder in the cardio-pulmonary system that involves multiple clinical conditions. Distinct classifications based on clinical, pathological, and hemodynamic findings and treatment strategies are used to categorize the multiple clinical conditions found in PH. Congenital Heart Disease (CHD) is one condition that could lead to PH development over time.[1]

The incidence of CHD is approximately 8 over 1000 birth worldwide, and 30% of uncorrected CHD patients develop pulmonary arterial hypertension (PAH). The estimation of prevalence and incidence of PAH were 15.0 cases/million and 2.4 cases/million annually, respectively.[2] The spectrum of CHD that contributes to PAH development is Eisenmenger syndrome, PAH associated with prevalent systemic-to-pulmonary shunts, PAH with small/coincidental defects, and PAH after defect correction.[1] In less developed countries, such as Indonesia, a significant number of the adult with uncorrected CHD is looking for help because of the emerging symptoms and signs of complication.[3] Unfortunately, the availability of approved PAH targeted therapy in Indonesia is limited.

A previous study showed a positive correlation between mean pulmonary arterial pressure (mPAP) before correction and severity of pulmonary vascular morphology in lung tissue biopsy. However, due to the risk of bleeding and the need for specialized expertise for interpretation, the lung tissue biopsy was no longer used.[4] The indication of defect correction relies on hemodynamic parameters and vasoreactivity tests taken from right heart catheterization (RHC) in recent years. Hemodynamic parameters such as pulmonary vascular resistance (PVR), pulmonary vascular resistance to systemic vascular resistance ratio (PVR/SVR), and vasoreactivity test are used as predictors of surgical outcomes for CHD-associated PAH with shunt who undergoes defect correction. A progressive increase in PVR is known to be correlated with right heart failure and even death. Nonetheless, there was no proof whether these parameters could predict which patients develop PAH after the defect correction.[5]

Sildenafil, a phosphodiesterase inhibitor type 5 (PDE-5 inhibitor), is a widely used PAH drug that effectively induces smooth muscle relaxation and vasodilatation in pulmonary vascular.[6] The previous study has shown the effect of sildenafil in symptom improvement, functional capacity, and hemodynamics in PAH patients with any causes.[7] Sildenafil shows a decreasing PVR with minimal or without changes in SVR, resulting in decreased PVR/SVR ratio after treatment.

According to the European Society of Cardiology (ESC) guideline, right heart catheterization evaluation should be done in 6-12 months after first catheterization (based on hospital rules) or 3-6 months after treatment changes or when deterioration happens.[1] In this study, we investigated the changes in PVR/SVR ratio in uncorrected CHD-associated PAH patients with shunt after sildenafil therapy for 1-year in Dr. Sardjito General Hospital, Yogyakarta as well as the characteristics of patients who show a decrease in PVR/SVR ratio.

MATERIALS AND METHODS

Data collection

It was an observational analytic study with a self-controlled case study design. Data was collected from the PAH registry of Dr. Sardjito General Hospital (COHARD-PH registry) from January-May 2020. The PAH was defined as mPAP > 20 mmHg, PVR ≥ 3 WU, and pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg from RHC.[8] The inclusion criteria of this study were: 1) male or female aged ≥ 18 years old PAH associated CHD with shunt patient; 2) undergo RHC evaluation with minimal separate 1 year after baseline and between RHC baseline and evaluation patient took sildenafil; 3) uncorrected defect; 4) hemodynamic data in RHC baseline and evaluation were available. Patients with complex CHD (more than one defect) were excluded. The minimal sample size of this study was 29 subjects. This sample size was yielded from the calculation below for the numeric analytic pair study:

$$n_1 = n_2 = \left\{ \frac{(Z_\alpha + Z_\beta)\ S}{X_1 - X_2} \right\}^2$$

$$n_1 = n_2 = \left\{ \frac{(1{,}96 + 1{,}28)\ x0{,}3}{0{,}2} \right\}^2$$

$$n_1 = n_2 = 29$$

where the type I error or α as 5% giving Z_α (alfa standard deviation) as 1.96; the type II error (β) we took was 10% providing Z_β (beta standard deviation) as 1.28. The total standard deviation (S) was calculated from the equation in the reference study[9]; and X_1-X_2 = differences between significant minimal mean in 2 groups.

Right heart catheterization was carried out by a cardiologist based on the standard operational procedure in Dr. Sardjito General Hospital, Yogyakarta. The measurement of PVR/SVR ratio was conducted by comparing PVR over SVR with the Fick equation. The calculation of PVR, SVR, and Fick equation are explained below:

PVR = (mPAP – PAWP) / CO[10]
SVR = (MAP – RAP) / CO[11]
CO (by Fick equation) = VO2 (ml/min) / A-V O^2 difference[12]

where mPAP is mean pulmonary artery pressure; PAWP is pulmonary arterial wedge pressure; CO is cardiac output; SVR is systemic vascular resistance; MAP is mean arterial pressure; RAP is right atrium pressure; VO2 is oxygen consumption, A-V O^2 difference is oxygen saturation difference between the pulmonary artery and venous.

The PVR/SVR ratio baseline was obtained from the first RHC followed by RHC evaluation >1 year after taking oral sildenafil. The primary outcome was the changes in PVR/SVR ratio from baseline to evaluated RHC. All subjects in this study had been informed and given their consent to this study. This study was approved by the Medical and Health Research Ethic Committee, Faculty of Medicine, Public Health and Nursing/Dr. Sardjito General Hospital (ref. no. with Ethical KE/FK/0738/EC July 7, 2020).

Statistical Analysis

Data were expressed in mean ± SD (standard of deviation). The data normality was tested with the Shapiro Wilk test (p>0.05 means normal distribution). The PVR/SVR ratio changes were analyzed with paired t-test or Wilcoxon test.

RESULT

Primary outcome

A total of 72 subjects with CHD shunt were identified from the COHARD-PH registry in Dr. Sardjito General Hospital, who underwent twice RHC from March 2014-May 2020. Hoever, only 30 subjects were enrolled in this study (FIGURE 1). The subject enrollment was stopped afterward because the minimal sample size was achieved. The baseline characteristics of the subjects are shown in TABLE 1.

TABLE 1. The baseline characteristic of the subjects

Variable (n=30)	Value
Age [med (min-max) year]	35.13 (22-65)
Female [n (%)]	28 (93.33)
Hypertension [n (%)]	1 (3.33)
Other drugs	
• CCB [n (%)]	1 (3.33)
• ACEi/ARB [n (%)]	0
Peripheral oxygen saturation (%)	94.17± 4.62
6MWD (m)	337 ±79.09
WHO class functional (m)	1.8 ± 0.61
NT-proBNP [ng/L]	1226.86± 1017.52
Eisenmenger syndrome [n (%)]	12 (40)
PAH-specific therapy	
• Sildenafil monotherapy [n (%)]	14 (46.67)
• Combination therapy [n (%)]	16 (53.33)
Sildenafil dosage	
• < 120 mg/day [n (%)]	22 (73.33)
• ≥ 120 mg/day [n (%)]	8 (26.67)
Mean time baseline – evaluation RHC (mo)	23.3 (12-64)
Pre-tricuspid shunt [n (%)]	25 (83.33)
Right atrium diameter [mm]	45.90 ± 7.36
Right ventricle diameter [mm]	41.73 ± 9.88
TAPSE [mm]	21.40 ± 5.49
TR Vmax [m/s]	4.5 ± 0.73
Probability PH	
• Low [n (%)]	0
• Intermediate [n (%)]	4 (13.33)
• High [n (%)]	26 (86.67)
mPAP (mmHg)	58.07 ± 16.03
PVR (WU)	15.98 ± 10.67
SVR (WU)	36.65 ± 13.99
PVR/SVR (ratio)	0.48 ± 0.32

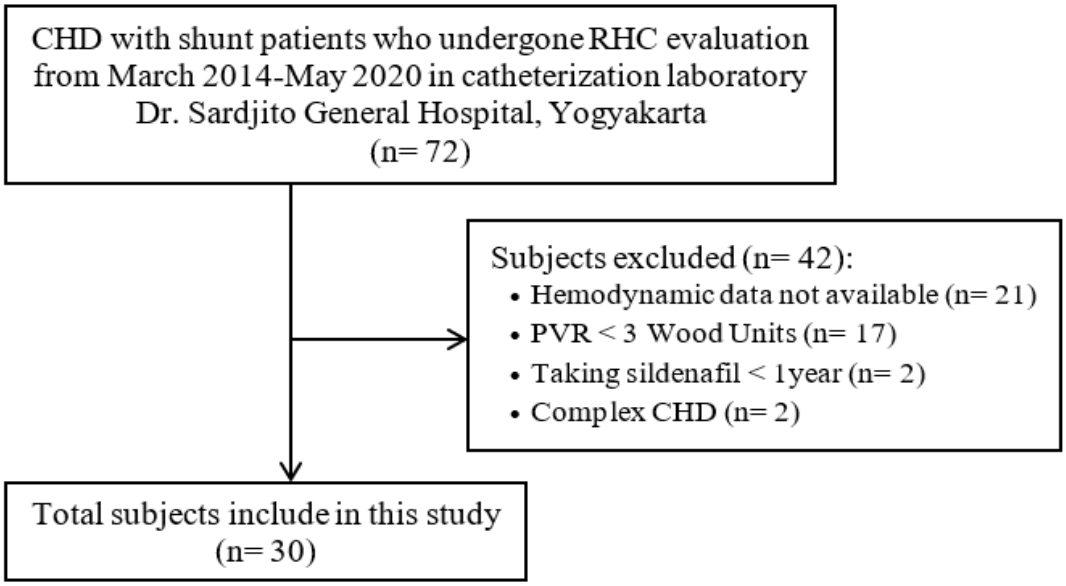

FIGURE 1. Subjects recruitment

Right heart catheterization evaluation was then performed to investigate hemodynamic parameters in subjects who received sildenafil for a minimal 1-year. Although we found changes in the mixed vein saturation and aortic saturation before and after sildenafil therapy, it was not statistically significant different (p>0.05). No significantly changes in the flow ratio, PVR and SVR were also observed (p>0.05), although there was a tendency toward decreasing in mPAP (TABLE 2). Furthermore, as much as 15 subjects (50%) were experiencing PVR/SVR ratio decreasing, even though they did not show any significantly difference before and after sildenafil therapy (0.48 ±0.32 to 0.49 ±0.36 p=0.882), as shown in TABLE 2 and FIGURE 2.

TABLE 2. Sildenafil effect in hemodynamic parameter (by RHC) before and after sildenafil therapy

Variable	Δ	p
Mixed vein saturation (%)	-1.6	0.288
Aortic saturation (%)	-0.73	0.777
Flow ratio	0.13	0.579
mPAP (mmHg)	-0.7	0.672
PVR (WU)	2.4	0.206
SVR (WU)	2.69	0.262
PVR/SVR ratio	0.01	0.882

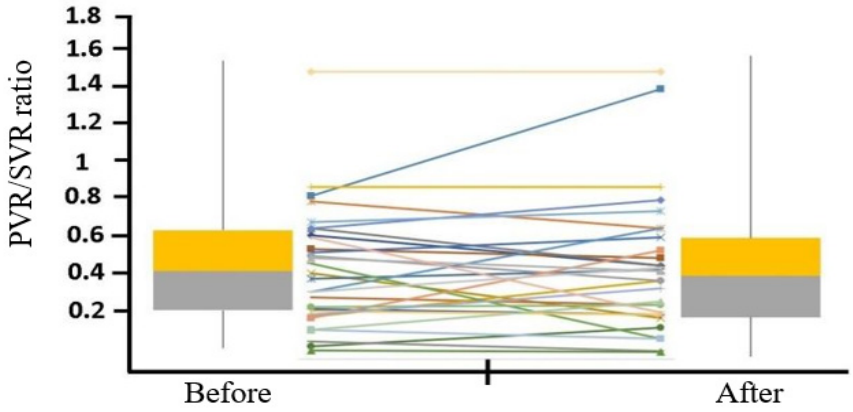

FIGURE 2. PVR/SVR ratio changes before and after sildenafil therapy

Secondary outcome

A further analysis was also performed to investigate the characteristics of subjects who showed decreased PVR and PVR/SVR ratios. The subjects were divided into 5 subgroups based on their clinical appearance (Eisenmenger syndrome vs. non-Eisenmenger syndrome), type of lesion (pre-tricuspid vs. post-tricuspid), baseline PVR (PVR < 8 WU *vs.* PVR > 8 WU), therapy (sildenafil monotherapy vs. combination therapy with beraprost 30 mcg twice to three times daily), and baseline NT-proBNP (NT-proBNP <1400 ng/L vs. NT-proBNP >1400 ng/L).

In the increased/unchanged and decreased PVR group, there was no significantly difference in the mean age (34.75 ± 9.83 and 36.29 ± 12.74 respectively; p=0.847). From the decreased PVR group, the proportion of non-Eisenmenger syndrome was higher than the proportion in Eisenmenger syndrome (64.3% vs. 35.7%; p=0.722), although it was not statistically significant. We found a higher proportion in pre-tricuspid shunt, PVR >8 WU, combination therapy, and NT-proBNP level < 1400 ng/L as well, however, the difference was not statistically significant (TABLE 3).

TABLE 3. Subgroups analysis in PVR changes and PVR/SVR ratio changes

Variable	Increased/ unchanged PVR [n (%)]	Decreased PVR [n (%)]	p	Increased/ unchanged PVR/ SVR ratio [n (%)]	Decreased PVR/SVR ratio [n (%)]	p
Age (mean ±SD years)	34.75 ±9.83	36.29 ±12.74	0.847	35.85 ±9.25	36.12 ±12.9	0.587
Eisenmenger syndrome						
• Yes	7 (43.7)	5 (35.7)	0.722	6 (40)	6 (40)	1.000
• No	9 (56.3)	9 (64.3)		9 (60)	9 (60)	
Shunt						
• Pre- tricuspid	13 (81.3)	12 (85.7)	1.000	13 (86.7)	12 (80)	1.000
• Post- tricuspid	3 (18.7)	2 (14.3)		2 (13.3)	3 (20)	
PVR						
• > 8 WU	14 (87.5)	10 (71.4)	0.378	13 (86.7)	11 (73.3)	0.651
• < 8 WU	2 (12.5)	4 (28.6)		2 (13.3)	4 (26.7)	
Therapy						
• Combination	8 (50)	8 (57.1)	0.730	10 (66.7)	6 (40)	0.272
• Mono-therapy	8 (50)	6 (42.9)		5 (33.3)	9 (60)	
NT-proBNP						
• > 1400 ng/L	7 (43.7)	4 (28.6)	0.466	8 (53.3)	3 (20)	0.128
• < 1400 ng/L	9 (56.3)	10 (71.4)		7 (46.7)	12 (80)	

In the increased/unchanged and decreased PVR/SVR ratio group, there was no significantly difference in the mean age (35.85 ±9.25 and 36.12 ±12.9; p=0.587). Although in the decreased PVR/SVR ratio group, the proportion of the non-Eisenmenger syndrome group was higher than the-Eisenmenger syndrome (60% *vs.* 40%; p=1.000), there was no significantly difference (p>0.05). Although the proportion in pre-tricuspid shunt, PVR >8WU, sildenafil monotherapy, and NT-proBNP level <1400 ng/L showed an increase, there was no significantly difference (p>0.05) (TABLE 3).

DISCUSSION

The PVR/SVR ratio has been known for a long time as a valuable parameter in CHD-associated PAH. This parameter could predict the surgical outcome in CHD-associated PAH. In this study, we found no changes in PVR/SVR ratio after minimal 1-year sildenafil therapy in CHD-associated PAH with the shunt. Sildenafil is a drug of choice for PAH. According to the SUPER-1 study, various doses of sildenafil could reduce mPAP, as well as improve clinical parameters such as exercise capacity and WHO functional class.[7] This study also revealed a decrease in mPAP as well, although it was no statistical significance (p>0.05). Moreover, there was no report on PVR/SVR ratio changes in the SUPER-1 study.

The discrepancy found in our study and previously published studies on sildenafil therapy might be due to the difference in the clinical condition of the subjects. In the SUPER-1 study, most study subjects were idiopathic PAH (IPAH) followed by connective tissue disease (CTD)-associated PAH, while CHD-associated PAH subjects were only less than 10% of all study subjects. In this study, all of the subjects were CHD-associated PAH; therefore, the subject response toward sildenafil therapy could be different.

The difference in the proportion of PAH patients was also described in other studies. This difference may be associated with PAH epidemiology in each country or region. In Western countries, IPAH is the most common type of PAH (30-50%), followed by CTD-associated PAH (15-30%), CHD-associated PAH (10-23%), and portopulmonary hypertension (5-10%). Meanwhile, in non-Western countries such as China, CHD-associated PAH is the most common PAH that contributes to 43% of all PAH cases.[13] A recent study in Sardjito General Hospital, Indonesia, demonstrated that the most common type of PAH is CHD-associated PAH. Most of these patients were undetected in earlier years, and 66.9% of them developed PAH later in life.[3]

Our secondary analysis in this study displayed characteristics of subjects with decreased PVR or PVR/SVR ratio after sildenafil therapy in specific sub-groups, including the presence of Eisenmenger syndrome, tricuspid lesion, the specific cut-off of PVR value, multi/monotherapy, and a certain NT-proBNP level. This study found that the proportion of non-Eisenmenger syndrome subjects was higher than Eisenmenger syndrome in decreasing PVR and PVR/SVR, although the difference was not statistically significant (p>0.05).

In the pathogenesis of PAH, there are 3 major processes of pulmonary artery constriction. First is vasoconstriction which is caused by a vasodilator/vasoconstrictor agent imbalanced in pulmonary circulation, followed by pulmonary vascular remodeling due to smooth muscle cells and endothelial cells proliferation. The coagulation abnormality results in thrombosis in situ, leading to an increase in PVR. The early stage of this process is known to be reversible.[14] However, the advanced stage is progressive, leading to obliteration of the pulmonary vascular bed (irreversible stage).[15] Progressive increased PVR could drive shunt reversal in CHD-associated PAH patients, from

the initial left-to-right shunt to right-to-left shunt, referred to as Eisenmenger syndrome. Most people perceived this syndrome as irreversible, although it is believed that not all Eisenmenger syndromes were irreversible PAH. A previous study showed that not all PAH with a negative oxygen response was irreversible PAH.[14] The same result was also reflected in our study in which we found Eisenmenger syndrome subjects with increased PVR, but the PVR/SVR ratio was decreased to the grey zone (0.3-0.5).

The characteristic of the tricuspid lesion in our study showed a higher proportion of pre-tricuspid lesion group in decreased PVR or decreased PVR/SVR ratio than the post-tricuspid lesion group, although the result was not statistically significant. This study result is consistent with Hascoët *et al.*[16] which showed no differences in Eisenmenger syndrome caused by pre-tricuspid shunt and post-tricuspid shunt in increasing PVR. This recent study revealed that 2 post-tricuspid shunt subjects with increased PVR/SVR ratio were Eisenmenger syndrome, while 3 post-tricuspid shunts with decreased PVR/SVR ratio were non-Eisenmenger syndrome.

The same result was also found in the PVR group. There was a higher proportion of the group with PVR > 8 WU compared to the group with PVR < 8 WU, although it was not statistically significant. European Society of Cardiology guideline for adult congenital heart disease management showed that CHD with shunt patients whose PVR ≥5 WU rarely improved the hemodynamic parameter. Therefore, these patients need PAH-specific therapy before undergoing RHC evaluation to get a prompt decision for the defect correction.[17]

In our study, although we could not find a significant difference in terms of therapy used by the subjects with a decreased PVR or PVR/SRV ratio, more than half of the subjects (57.1%) in this study with a decrease in PVR were in the combination therapy group. On the contrary, a higher proportion of the monotherapy group has been found in the decreased PVR/SVR ratio. This finding might be caused by the combination therapy used in this study. According to ESC guideline 2015, the recommendation for initial combination therapy is the PDE-5 inhibitor and Endothelin receptor antagonist (ERA). ERA plays role in decreasing pulmonary arterial vasoconstriction, which is the basic pathomechanism of PAH. However, due to the unavailability of ERA in our hospital, PDE-5 inhibitor and beraprost were used in our study. The previous study demonstrated that this combination therapy could improve functional capacity without affecting hemodynamic parameters, albeit using the PDE-5 inhibitor and prostacyclin analog combination was not recommended in ESC guideline 2015.[1]

In ALPHABHET study, beraprost initially improved 6MWD and WHO functional class, but the extended follow-up showed that the improvement was not sustained. Beraprost has been approved in some South-East Asian countries, including Indonesia that uses beraprost for treating PAH patients in WHO functional class III.[18] But unfortunately, in this study, we did not evaluate further clinical improvement, since we focused on hemodynamic improvement instead of clinical improvement.

The level of NT-proBNP cut-off used in this study referred to ESC guideline 2015, where NT-proBNP level >1400 ng/L is considered a high-risk feature of PH with more than 10% 1-year mortality estimation.[1] In our study, the proportion of subjects with NTproBNP level <1400 ng/L was higher than those with NTproBNP level > 1400 ng/L in both decreased PVR and decreased PVR/SVR ratio groups. Although the result was not statistically significant, this result was in contrast to a previous study showing that the degree of severity in PAH is proportional to the increased NT-

proBNP level.[19] However, another study suggested that the serial examination of NT-proBNP was superior to a single baseline examination.[20]

However, this study has several limitations. Our study design was an observational study with an abnormal distribution of subjects, namely in the pre-tricuspid lesion *vs.* post-tricuspid lesion, as well as in PVR <8 WU vs. PVR >8 WU. In addition, beraprost, a prostacyclin analog used in the combination therapy could enhance the vasodilatation effect in the pulmonary artery; however, there were no drug acts in decreasing pulmonary artery vasoconstriction. We believe the combination of sildenafil and ERA could carry a better result since ERA is one of the PAH-specific therapy that plays a direct role in the endothelin pathway to decrease vasoconstriction in the pulmonary artery.

CONCLUSION

This study does not find any significantly change in PVR/SVR ratio after ≥1-year sildenafil therapy in the adult with uncorrectable CHD-associated PAH. There is a tendency toward decreasing in PVR or PVR/SVR ratio occurred in subjects without Eisenmenger syndrome, pre-tricuspid shunt, and baseline NT-proBNP < 1400 ng/L.

ACKNOWLEDGEMENTS

This study was funded by Dana Masyarakat Research Grant 2019 under the contract number 1510/UN-1/FK-KMK/PP/PT/2019.

REFERENCES

1. Galiè N, Chairperson ESC, Humbert M, Chairperson ERS, Vachiery J, Gibbs S, *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 Respir J 2015; 46(4):903-75. https://doi.org/10.1183/13993003.01032-2015
2. McLaughlin VV, Davis M, Cornwell W. Pulmonary arterial hypertension. Curr Probl Cardiol 2011; 36(12):461-517. https://doi.org/10.1016/j.cpcardiol.2011.08.002
3. Dinarti LK, Hartopo AB, Kusuma AD, Satwiko MG, Hadwiono MR, Pradana AD, *et al*. 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. https://doi.org/10.1186/s12872-020-01434-z
4. Schwerzmann M, Pfammatter JP. Approaching atrial septal defects in pulmonary hypertension. Expert Rev Cardiovasc Ther 2015; 13(6):693-701. https://doi.org/10.1586/14779072.2015.1047763
5. Myers PO, Tissot C, Beghetti M. Assessment of operability of patients with pulmonary arterial hypertension associated with congenital heart disease. Circ J 2014; 78(1):4-11. https://doi.org/10.1253/circj.cj-13-1263
6. Palma G, Giordano R, Russolillo V, Cioffi S, Palumbo S, Mucerino M, *et al*. Sildenafil therapy for pulmonary hypertension before and after pediatric congenital heart surgery. Texas Hear Inst J 2011; 38(3):238-42.

7. Galie N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, *et al*. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med 2005; 353(20):2148-57. https://doi.org/10.1056/NEJMoa050010
8. Galie N, McLaughlin VV, Rubin LJ, Simonneau G. An overview of the 6th World Symposium on Pulmonary Hypertension. Eur Respir J 2019; 53(1):1802148. https://doi.org/10.1183/13993003.02148-2018
9. Garg N, Sharma MK, Sinha N. Role of oral sildenafil in severe pulmonary arterial hypertension: clinical efficacy and dose response relationship. Int J Cardiol 2007; 120(3):306-13. https://doi.org/10.1016/j.ijcard.2006.10.017
10. Abbas AE, Fortuin FD, Schiller NB, Appleton CP, Moreno CA, Lester SJ. A simple method for noninvasive estimation of pulmonary vascular resistance. J Am Coll Cardiol 2003; 41(6):1021-7. https://doi.org/10.1016/s0735-1097(02)02973-x
11. Stefadouros MA, Dougherty MJ, Grossman W, Craige E. Determination of systemic vascular resistance by a noninvasive technic. Circulation 1973; 47(1):101-7. https://doi.org/10.1161/01.cir.47.1.101
12. Davies GG, Jebson PJ, Glasgow BM, Hess DR. Continuous Fick cardiac output compared to thermodilution cardiac output. Crit Care Med 1986; 14(10):881-5. https://doi.org/10.1097/00003246-198610000-00010
13. Lau EMT, Giannoulatou E, Celermajer DS, Humbert M. Epidemiology and treatment of pulmonary arterial hypertension. Nat Rev Cardiol 2017; 14(10):603-14. https://doi.org/10.1038/nrcardio.2017.84
14. Huang JB, Liang J, Zhou LY. Eisenmenger syndrome: not always inoperable. Respir Care 2012; 57(9):1488-95. https://doi.org/10.4187/respcare.01418
15. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, *et al*. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. Circulation 2010; 122(2):156-63. https://doi.org/10.1161/CIRCULATIONAHA.109.911818
16. Hascoët S, Baruteau AE, Humbert M, Simonneau G, Jais X, Petit J, *et al*. Long-term outcomes of pulmonary arterial hypertension under specific drug therapy in Eisenmenger syndrome. J Hear Lung Transplant 2017; 36(4):386-98. https://doi.org/10.1016/j.healun.2016.10.006
17. Baumgartner H, De Backer J, Babu-Narayan SV, Budts W, Chessa M, Diller GP, *et al*. 2020 ESC Guidelines for the management of adult congenital heart disease. Eur Hear J 2020;42(6):563-645. https://doi.org/10.1093/eurheartj/ehaa554
18. Humbert M, Ghofrani HA. The molecular targets of approved treatments for pulmonary arterial hypertension. Thorax 2016; 71(1):73-83. https://doi.org/10.1136/thoraxjnl-2015-207170
19. Souza R, Jardim C, Fernandes CJC, Lapa MS, Rabelo R, Humbert M. NT-proBNP as a tool to stratify disease severity in pulmonary arterial hypertension. Respir Med 2007; 101(1):69-75. https://doi.org/10.1016/j.rmed.2006.04.014
20. Wolfson AM, Maitland ML, Thomeas V, Glassner C, Gomberg-Maitland M. A serial NT-proBNP model to improve prognostication in patients with pulmonary arterial hypertension. J Clin Exp Cardiol 2017; 8(11):1000555. https://doi.org/10.4172/2155-9880.1000555