Tohoku J. Exp. Med., 2023, **260**, 87-92

Effects of Low-Dose Tadalafil in a Patient with Biventricular Heart Failure: A Case Report

Shoko Kono,[1] Jinya Takahashi,[1] Koutatsu Shimozono,[1] Jun Kumanomido,[1] Norikazu Inoguchi,[1] Shoichiro Nohara,[1] Naoki Itaya,[1] Takaharu Nakayoshi[1] and Yoshihiro Fukumoto[1]

[1]Division of Cardiovascular Medicine, Department of Internal Medicine, Kurume University School of Medicine, Kurume, Fukuoka, Japan

Phosphodiesterase type 5 (PDE5) inhibitors such as tadalafil, can improve cardiac output by increasing left ventricular preload; however, there are concerns that this can increase the risk of heart failure due to pulmonary congestion in patients with elevated left ventricular end-diastolic pressure. We encountered a case in which low dose tadalafil improved the hemodynamics of a 66-year-old male patient with dilated cardiomyopathy (DCM) with congestion and low cardiac output due to biventricular dysfunction. The patient received a cardiac resynchronization therapy defibrillator (CRT-D) and appropriate medical therapy for heart failure. During a hemodynamic evaluation after heart failure symptoms were alleviated, we attempted to increase the dose of renin-angiotensin-aldosterone system (RAAS) inhibitors, which contribute to low cardiac output, hypotension, and worsening of renal function. However, the administration of a low dose of tadalafil for the patient's benign prostatic hyperplasia allowed for the increase in the dose of RAAS inhibitors and markedly improved his subjective symptoms and hemodynamics. Because of the biventricular dysfunction in severe cases, we often experience further promotion of low cardiac output by standard treatments such as RAAS inhibitors, in which low doses of PDE5 inhibitors may be effective in maintaining biventricular linkage. PDE5 inhibitors may be effective in patients, who are not able to increase the dose of RAAS inhibitors due to low cardiac output.

Keywords: case report; heart failure; left ventricular dysfunction; pulmonary hypertension; tadalafil
Tohoku J. Exp. Med., 2023 May, **260** (1), 87-92.
doi: 10.1620/tjem.2023.J020

Introduction

The use of phosphodiesterase type 5 (PDE5) inhibitors in heart failure is controversial, and it remains unclear which clinical parameters are able to predict their efficacy. Recently, a soluble guanylate cyclase (sGC) stimulator, vericiguat, has been approved as a new treatment for heart failure (Armstrong et al. 2020). Both PDE5 inhibitors and sGC stimulators can increase cardiac output by increasing left ventricular preload (Hutchings et al. 2018), where pulmonary arterial blood flow is increased, pulmonary vascular resistance (PVR) is decreased, and right ventricular function should be improved; however, there are concerns that heart failure can worsen due to pulmonary congestion if the left ventricle is not able to tolerate the increased preload in patients with elevated left ventricular end-diastolic pressure. Here, we report a case wherein a low dose of PDE5 inhibitor, tadalafil, for prostatic hyperplasia was beneficial in a patient with biventricular dysfunction.

Case Presentation

A 66-year-old man was admitted to our hospital for decompensated heart failure and reduced left ventricular ejection fraction (LVEF). He was diagnosed with dilated cardiomyopathy (DCM) several years ago and treated with appropriate oral medication for left ventricular dysfunction. He received a cardiac resynchronization therapy defibrillator (CRT-D) implantation a month before his visit. His height was 170.6 cm, weight was 69.4 kg, blood pressure was 106/84 mmHg, heart rate was 88 beats per minute and regular, and arterial oxygen saturation (SpO_2) was 99% (in room air). The patient had jugular venous distention and

Received December 6, 2022; revised and accepted February 28, 2023; J-STAGE Advance online publication March 9, 2023
Correspondence: Jinya Takahashi, M.D., Ph.D., Division of Cardiovascular Medicine, Department of Internal Medicine, Kurume University School of Medicine, 67 Asahimachi, Kurume, Fukuoka 830-0011, Japan.
e-mail: takahashi_jinya@kurume-u.ac.jp
©2023 Tohoku University Medical Press. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (CC-BY-NC-ND 4.0). Anyone may download, reuse, copy, reprint, or distribute the article without modifications or adaptations for non-profit purposes if they cite the original authors and source properly.
https://creativecommons.org/licenses/by-nc-nd/4.0/

cold extremities. Chest X-ray findings showed a dilated heart and pulmonary congestion (Fig. 1A). An electrocardiogram (ECG) showed the pacemaker rhythm with atrial and ventricular pacing, and the heart rate was 80 beats per minute. Ultrasonic echocardiography showed severe biventricular dysfunction [LVEF of 17.3% and right ventricular functional area change (FAC) of 17%] and markedly reduced cardiac output with a left ventricular outflow tract velocity time integral (LVOT VTI) of 7.5 cm (Table 1, left). Blood tests showed renal and congestive hepatic dysfunc-

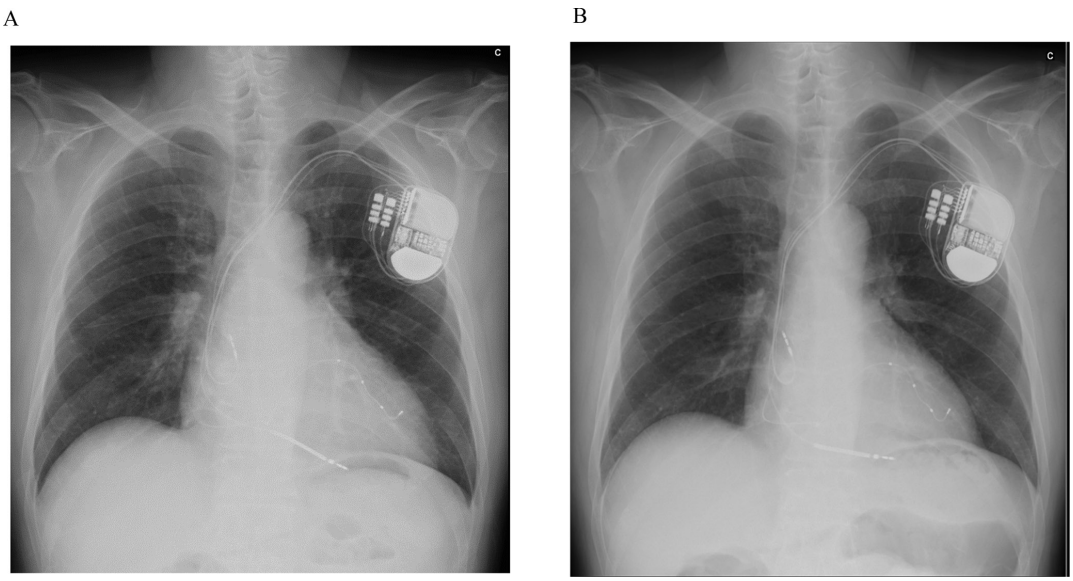

Fig. 1. Chest X-ray on admission (A), and after administration of tadalafil (B).

Table 1. The parameters of echocardiography before the administration of tadalafil and after discharge.

	Before the administration of tadalafil	After discharge	Normal range
LAVi (ml/m^2)	44	36	(10-38)
LVDd (mm)	64	65	(40-56)
LVDs (mm)	60	62	(13-21)
LVEF (Simpson %)	17.3	16	(54-74)
E/A	4.3	8.4	(≧ 2 in over 50 years)
E/e'	23.2	28.3	(< 14)
LVOT VTI (cm)	7.5	11.8	(> 8)
SVi (ml/m^2)	17	19.5	
CO (l/min)	2.5		
CI (l/min/m^2)	1.4		
TAPSE (mm)	13.1	14.3	(> 17)
TDIs' (cm/s)	9.2	9.8	(> 10)
FAC (%)	17	26	(> 35)
AR	none	none	
MR	moderate	mild	
PR	mild	trivial	
TR	moderate	mild	
TRPG (mmHg)	33	32	
IVC (Exp/Insp mm)	25.6/19.7	18.0/5.0	

LAVi, left atrial volume index; LVDd, left ventricular dimension at end diastole; LVDs, left ventricular dimension at end systole; LVEF, left ventricular ejection fraction; E/A, early diastolic LV filling velocity/peak atrial filling velocity ratio; E/e', early diastolic LV filling velocity/the average of septal and lateral early diastolic velocities; LVOT VTI, velocity time integral of the left ventricular outflow tract; SVi, stroke volume index; CO, cardiac output; CI, cardiac index; TAPSE, tricuspid annular plane systolic excursion; TDIs', tricuspid annular velocity; FAC, factional area change; AR, aortic regurgitation; MR, mitral regurgitation; PR, pulmonary valve regurgitation; TR, tricuspid regurgitation; TRPG, tricuspid regurgitation pressure gradient; IVC, inferior vena cava.

tion (Table 2, left).

Upon admission, the patient was treated with enalapril (an angiotensin-converting-enzyme inhibitor) 2.5 mg/day, bisoprolol (a selective type β1 adrenergic receptor blocker) 2.5 mg/day, spironolactone (a mineral corticoid receptor antagonist) 50 mg/day, tolvaptan (V2-receptor antagonists) 15 mg/day, azosemide (loop diuretic) 60 mg/day, and denopamine (adrenergic beta 1 receptor stimulator) 15 mg/day. Since heart failure exacerbation in a shortly after CRT-D implantation, the CRT-D was optimized using ultrasonic echocardiography. The optimal atrioventricular (AV) delay was defined as an AV delay associated with the largest average aortic Doppler VTI (Sawhney et al. 2004); we decided on DDD 80-110 ppm and AV intervals of 160 ms (130 ms); LV-RV 0 ms that the pre-hospitalization setting was most appropriate. On day 5, his symptoms improved to New York Heart Association class II, and we performed right heart catheterization. This revealed a mean pulmonary capillary wedge pressure of 21 mmHg, mean pulmonary artery pressure (PA) of 27 mmHg, mean right atrial pressure of 5 mmHg, cardiac index of 1.87 L/min/m², and mixed venous oxygen saturation of 59.0% (Table 3, left). The patient had pulmonary hypertension due to a low cardiac output caused by left heart disease. Therefore, we increased the dose of enalapril (from 2.5 mg/day to 3.75 mg/day) on day 6 to reduce the left ventricular afterload pressure, while monitoring his blood pressure. However, enalapril was reduced on day 9 due to progressed low output state, hypotension, worsening renal function, and decreased blood sodium level and pulse pressure (Table 2, middle; Fig. 2). We determined that the left ventricular preload could not be adequately maintained due to the right cardiac dysfunction.

Simultaneously, the patient suffered from benign prostatic hyperplasia and tadalafil (5 mg/day) was prescribed on day 11. Although we did not perform any intervention after enalapril reduction, his blood pressure improved, and his fatigue lessened even after tadalafil administration was initiated. His blood pressure, pulse rate, and respiratory status remained stable; thus, we were able to increase the dose of enalapril (from 2.5 mg/day to 3.75 mg/day) on day 12. Subsequently, his peripheral cold sensation improved, and he was able to maintain his blood pressure and renal function. On day 18, right heart catheterization showed almost complete normalization (Table 3, right). Combined with cardiac rehabilitation, his heart failure symptoms and chest X-ray findings improved (Fig. 1B). The left atrial volume decreased, mitral regurgitation was reduced from moderate to mild, cardiac output with a left ventricular outflow tract velocity time integral (LVOT VTI) increased, and right heart function showed an improvement on echocardiography (fractional area change, FAC: from 17% to 26%) (Table 1, right). Blood tests showed that N-terminal pro-brain natriuretic peptide (NT-proBNP) levels decreased from 10,679 pg/mL to 3,696 pg/mL at the time of patient discharge, on day 20 (Table 2, right).

Table 2. Laboratory data.

	At admission	Enalapril dose up	After tadalafil & enalapril dose up	Normal range
White blood cell count (μL)	6.6×10^3	6.8×10^3	6.2×10^3	($3.3\text{-}8.6 \times 10^3$)
Hemoglobin (g/dL)	14.7	15.6	13.1	(11.6-14.8)
Platelet (μL)	253×10^3	240×10^3	184×10^3	($158\text{-}348 \times 10^3$)
C-reactive protein (mg/dL)	1.46	-	-	(< 0.14 mg)
Aspartate aminotransferase (U/L)	49	38	31	(13-30)
Alanine aminotransferase (U/L)	40	37	33	(7-30)
Lactate dehydrogenase (U/L)	307	254	233	(124-222)
Alkaline phosphatase (U/L)	472	-	314	(106-322)
Creatine phosphokinase (U/L)	48	-	-	(41-153)
Blood nitrogen urea (mg/dL)	33	36	28	(8-20)
Creatinine (mg/dL)	1.48	1.68	1.14	(0.46-0.79)
eGFR (ml/min/1.73 m^2)	38	33	50.5	
Sodium (mmol/L)	133	129	130	(138-145)
Potassium (mmol/L)	4.9	5.5	4.4	(3.6-4.8)
LDL cholesterol (mg/dL)	70	88	-	(65-139)
HDL cholesterol (mg/dL)	60	-	-	(40-103)
Triglyceride (mg/dL)	112	-	-	(30-149)
Glucose (mg/dL)	164	-	-	(73-109)
HbA1c (%)	6.8	-	-	(4.9-6.0)
NT-proBNP (pg/mL)	10,679	-	3,696	(< 54.5)

eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, hemoglobin A1c; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Table 3. Cardiac catheterization before the administration of tadalafil and at discharge.

	Before the administration of tadalafil	At discharge
HR (bpm)	80	80
PCW (mmHg)	a = 26 v = 34 m = 21	a = 8 v = 8 m = 6
PA (mmHg)	39/19 m = 27	20/6 m = 13
RV (mmHg)	38/5	20/5
RA (mmHg)	a = 8 v = 5 m = 5	a = 2 v = 1 m = 1
Ao (mmHg)	103/63 m = 76	96/57 m = 70
C.O. (l/min)	3.36	4.15
CI (l/min/m^2)	1.87	2.29
SvO_2 (%)	59	65.9
PVR (dynes・sec・cm^{-5})	95.2	134
SVR (dynes・sec・cm^{-5})	1,690	1,330

PCW, pulmonary capillary wedge pressure; PA, pulmonary artery pressure; RV, right ventricular pressure; RA, right atrial pressure; Ao, aorta; C.O., cardiac output; CI, cardiac index; SvO_2, mixed venous oxygen saturation; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance index; a, atrial systolic pressure; v, atrial diastolic vein filling pressure; m, mean pressure.

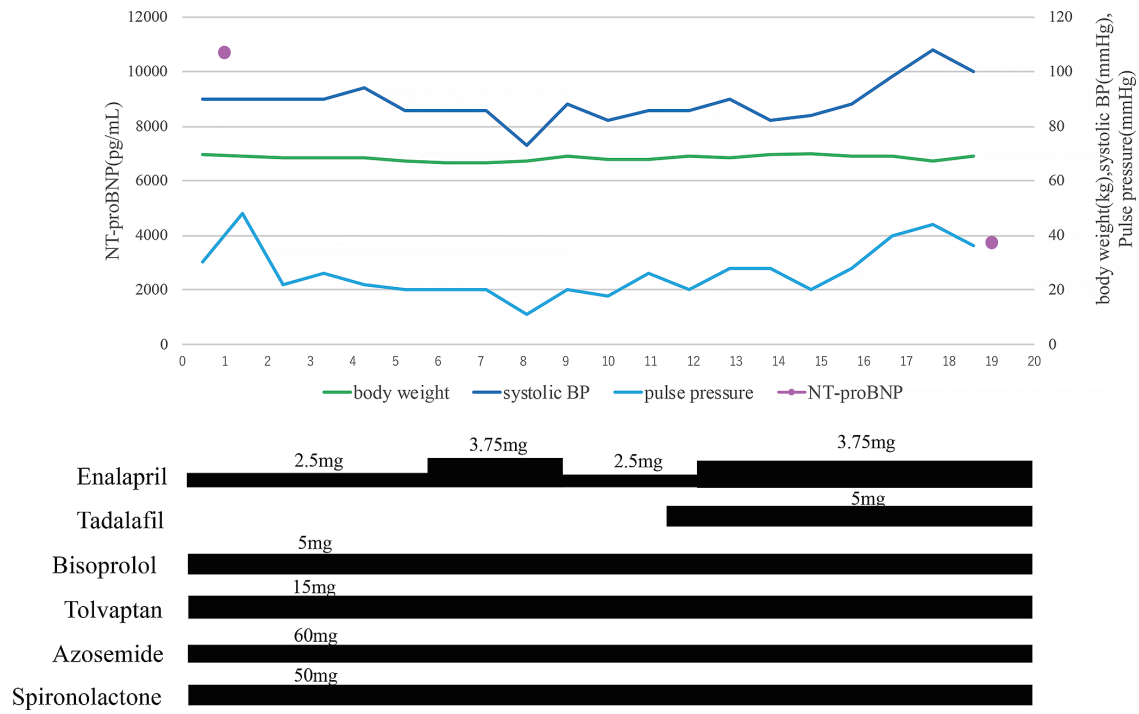

Fig. 2. Clinical time-course.
Pulse pressure decreased with increasing doses of enalapril. Pulse pressure improved at the start of tadalafil administration. BP, blood pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Discussion

Here, we report a case in which low dose tadalafil for prostatic hyperplasia improved cardiac output (CO) in a patient with severe biventricular dysfunction. After the administration of tadalafil and an increased dose of renin-angiotensin-aldosterone system (RAAS) inhibitors, his peripheral cold sensation and hemodynamics improved without changes in body weight or diuretic dose. Moreover, no changes in blood pressure, heart rate, or oxygenation were observed. Although the patient's condition dramatically improved after tadalafil administration, it remains unclear whether a low dose of tadalafil directly affects cardiac and vascular function (Förstermann and Sessa 2012; Santos et al. 2014). The precise mechanism needs to be clarified in future studies.

In this case, the administration of tadalafil and an increased dose of RAAS inhibitors decreased mean right atrial pressure, left atrial pressure, and mean pulmonary artery pressure and increased CO. As a result, PVR was

increased at discharge in this patient; however, we expect that PVR would be decreased in chronic phase. The use of RAAS inhibitors for chronic right ventricular dysfunction often decreases CO and induces central volume reduction (Konstam et al. 2018) (Fig. 3B). Prior to tadalafil administration, we were unable to increase the dose of RAAS inhibitors due to the progression of low output syndrome (LOS), probably because right ventricular dysfunction decreased left ventricular preload (Fig. 3B'). However, after tadalafil administration, we were able to increase the dose of RAAS inhibitors. In general, tadalafil increases CO by decreasing PVR. In this case, the increase in PVR at discharge could have been caused by a marked decrease in the pulmonary capillary wedge pressure.

Regarding pulmonary vasodilators for heart failure, both prostacyclin derivatives and endothelin receptor antagonists are associated with heart failure and worse prognosis. Hwang et al. (2017) reported that the use of PDE5 inhibitors in patients with heart failure with reduced ejection fraction improved exercise capacity, cardiac performance, and pulmonary hemodynamics. The potential benefits of PDE5 inhibitors in heart failure have been suggested in animal studies; PDE5 inhibitors prevent myocardial dysfunction by anti-remodeling, anti-apoptotic, and anti-inflammatory effects in various disease models of heart failure (Nagayama et al. 2009; Kim et al. 2012, 2015). In addition, with regard to the composite endpoint of death or hospitalization, there was a significant protective effect of PDE5 inhibitors on patients with heart failure with reduced ejection fraction (De Vecchis et al. 2017).

Based on the above, it might be effective to use a low dose of a PDE5 inhibitor in patients with severe heart failure who have pulmonary hypertension associated with the left and right ventricular dysfunction, as in the present case. However, high dose tadalafil may over-dilate pulmonary artery, increase pulmonary artery blood flow too much for left ventricular reserve, increase left ventricular end-diastolic pressure, and can cause pulmonary congestion (Fig. 3C). Due to the presence of severe right ventricular dysfunction, we often experience LOS caused by standard treatments such as RAAS inhibitors, in which low doses of PDE5 inhibitors may be effective in maintaining biventricular linkage (Fig. 3D).

In the treatment of heart failure, beta-blockers, RAAS inhibitors, mineral corticoid receptor antagonists and sodium glucose co-transporter-2 inhibitors should be used at doses as high as possible. PDE5 inhibitors may be effective in treating patients in whom the dose of RAAS inhibitors cannot be increased due to low CO. In such cases, excessive intravascular dehydration should be avoided. Further, if left ventricular function is impaired, we should be careful of pulmonary congestion due to rapid left ventricular loading by using pulmonary vasodilators.

PDE5 inhibitors increase cyclic guanylyl monophosphate (GMP) levels only in the presence of nitric oxide (NO), while a sGC stimulator, vericiguat, is a good option

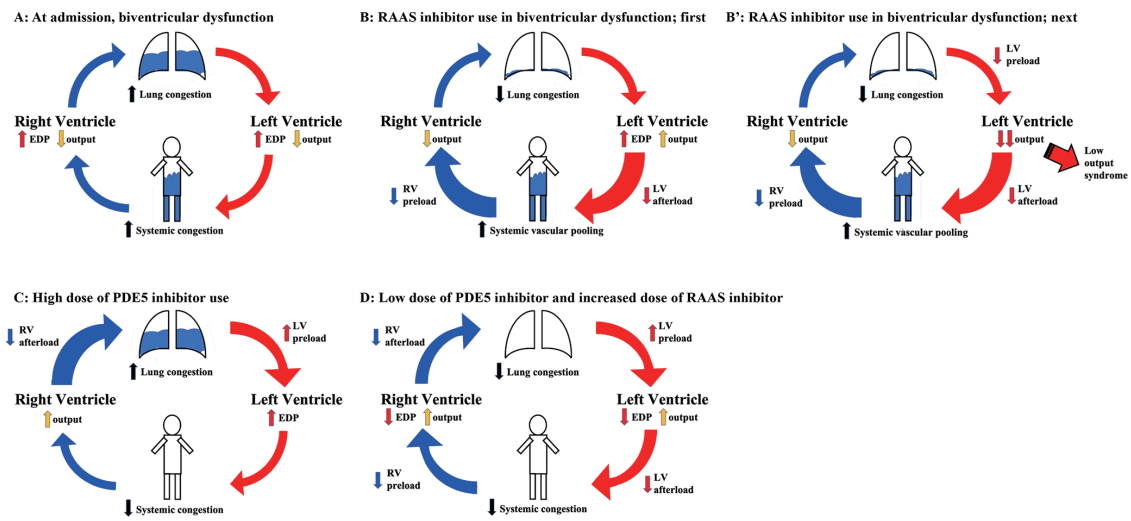

Fig. 3. Potential mechanism of low dose PDE5 inhibitor in heart failure with biventricular dysfunction.
(A) At admission, the patient had pulmonary and systemic congestion due to biventricular dysfunction. EDP, end-diastolic pressure. (B) What occurs first in the use of renin-angiotensin-aldosterone system (RAAS) inhibitor in biventricular dysfunction. When heart failure patients with biventricular dysfunction are treated by RAAS inhibitors, left ventricular (LV) afterload decreases, and LV output can be increased. (B') What occurs next in the use of RAAS inhibitor in biventricular dysfunction. The simultaneous increase in systemic vascular pooling, coupled with hypotension, can decrease right ventricular (RV) preload and RV output. Then, LV preload is decreased, and finally causes low output syndrome. (C) High dose of PDE5 inhibitor may decrease RV afterload and increase LV preload too much. In severe LV dysfunction, the increased preload can cause pulmonary congestion. (D) Low dose of PDE5 inhibitor may moderately decrease RV afterload and improve RV output. The appropriate amount of LV preload is maintained, and hemodynamics will be stabilized. Then, RAAS inhibitor is able to be increased. Arrows indicate vessels and the width shows vessel sizes, including vasodilation or vasoconstriction.

in the treatment of heart failure with reduced ejection fraction (HFrEF), which is able to increase GMP in the absence of NO; however, vericiguat was not available at the time of this case. The beneficial effects on pulmonary hemodynamics of vericiguat in HFrEF patients should be established in near future. Also, phosphodiesterase type 3 (PDE3) inhibitor, milrinone, can be used in the intravenous administration in the acute phase; however, oral administration is required in chronic phase. In the present case, long-term evaluation is required to clarify the efficacy and adverse effects of tadalafil on biventricular heart failure.

In conclusion, we encountered a case in which low dose tadalafil was effective in a patient with severe biventricular dysfunction. We were able to increase the dose of RAAS inhibitors to achieve almost normalized hemodynamics during right heart catheterization.

Acknowledgments

The authors thank Kurume University Diversity and the Inclusion Promotion Office.

Conflict of Interest

The authors declare no conflict of interest.

References

Armstrong, P.W., Pieske, B., Anstrom, K.J., Ezekowitz, J., Hernandez, A.F., Butler, J., Lam, C.S.P., Ponikowski, P., Voors, A.A., Jia, G., McNulty, S.E., Patel, M.J., Roessig, L., Koglin, J., O'Connor, C.M., et al. (2020) Vericiguat in patients with heart failure and reduced ejection fraction. *N. Engl. J. Med.*, **382**, 1883-1893.

De Vecchis, R., Cesaro, A., Ariano, C., Giasi, A. & Cioppa, C. (2017) Phosphodiesterase-5 inhibitors improve clinical outcomes, exercise capacity and pulmonary hemodynamics in patients with heart failure with reduced left ventricular ejection fraction: a meta-analysis. *J. Clin. Med. Res.*, **9**, 488-498.

Förstermann, U. & Sessa, W.C. (2012) Nitric oxide synthases: regulation and function. *Eur. Heart J.*, **33**, 829-837, 837a-837d.

Hutchings, D.C., Anderson, S.G., Caldwell, J.L. & Trafford, A.W. (2018) Phosphodiesterase-5 inhibitors and the heart: compound cardioprotection? *Heart*, **104**, 1244-1250.

Hwang, I.C., Kim, Y.J., Park, J.B., Yoon, Y.E., Lee, S.P., Kim, H.K., Cho, G.Y. & Sohn, D.W. (2017) Pulmonary hemodynamics and effects of phosphodiesterase type 5 inhibition in heart failure: a meta-analysis of randomized trials. *BMC Cardiovasc. Disord.*, **17**, 150.

Kim, H.L., Kim, Y.J., Kim, K.H., Lee, S.P., Kim, H.K., Sohn, D.W., Oh, B.H. & Park, Y.B. (2015) Therapeutic effects of udenafil on pressure-overload cardiac hypertrophy. *Hypertens. Res.*, **38**, 597-604.

Kim, K.H., Kim, Y.J., Ohn, J.H., Yang, J., Lee, S.E., Lee, S.W., Kim, H.K., Seo, J.W. & Sohn, D.W. (2012) Long-term effects of sildenafil in a rat model of chronic mitral regurgitation: benefits of ventricular remodeling and exercise capacity. *Circulation*, **125**, 1390-1401.

Konstam, M.A., Kiernan, M.S., Bernstein, D., Bozkurt, B., Jacob, M., Kapur, N.K., Kociol, R.D., Lewis, E.F., Mehra, M.R., Pagani, F.D., Raval, A.N. & Ward, C.; American Heart Association Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular Surgery and Anesthesia (2018) Evaluation and management of right-sided heart failure: a scientific statement from the American Heart Association. *Circulation*, **137**, e578-e622.

Nagayama, T., Hsu, S., Zhang, M., Koitabashi, N., Bedja, D., Gabrielson, K.L., Takimoto, E. & Kass, D.A. (2009) Sildenafil stops progressive chamber, cellular, and molecular remodeling and improves calcium handling and function in hearts with pre-existing advanced hypertrophy caused by pressure overload. *J. Am. Coll. Cardiol.*, **53**, 207-215.

Santos, R.C., de Faria, A.P., Barbaro, N.R., Modolo, R., Ferreira-Melo, S.E., Matos-Souza, J.R., Coelho, O.R., Yugar-Toledo, J.C., Fontana, V., Calhoun, D. & Moreno, H. (2014) Tadalafil-induced improvement in left ventricular diastolic function in resistant hypertension. *Eur. J. Clin. Pharmacol.*, **70**, 147-154.

Sawhney, N.S., Waggoner, A.D., Garhwal, S., Chawla, M.K., Osborn, J. & Faddis, M.N. (2004) Randomized prospective trial of atrioventricular delay programming for cardiac resynchronization therapy. *Heart Rhythm*, **1**, 562-567.