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RC time (resistance × compliance) is related to residual symptom after pulmonary endarterectomy in chronic thromboembolic pulmonary hypertension

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ABSTRACT

Background: Right ventricular (RV) afterload is widely assessed by pulmonary vascular resistance (PVR). However, RV afterload is underestimated because PVR does not account for the pulsatile load. The pulsatile load is often evaluated by pulmonary arterial compliance (PAC). The RC (resistance-compliance) time, which is calculated from the product of PVR and PAC, is considered to remain constant under medical therapy. However, little is known on how RC time is affected by invasive therapy in chronic thromboembolic pulmonary hypertension (CTEPH). This study aimed to evaluate change of RC time in patients underwent pulmonary endarterectomy (PEA). Furthermore, we investigated the clinical relevance of RC time.
Methods: We reviewed consecutive 50 patients except for death case underwent PEA. Baseline clinical parameters including RC time before performing PEA and follow-up were evaluated. Patients was classified as decrease or non-decrease according to change of RC time. Furthermore, we classified patients into a NYHA I group who had no symptom after treatment and a residual symptom group in order to investigate the relationship of RC time to residual symptoms.
Results: RC time was significantly decreased after PEA (0.54 ± 0.16 to 0.45 ± 0.12 sec, $p < 0.001$). Residual symptom after PEA of Decrease group were significantly better than that of Non-decrease group in RC time (12 patients, 40% vs. 11 patients, 78.6%, $p < 0.02$). Furthermore, multivariate analysis revealed that only RC time after PEA was independently associated with residual symptom (OR 1.026, 95% CI 1.005–1.048; $p = 0.017$).
Conclusions: RC time was decreased after PEA, and might be a possible indicator for predicting PEA success.

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by stenosis and obstruction of the pulmonary arteries due to an organized thrombus [1]. Without therapeutic intervention, the prognosis is so poor that a five-year survival rate in patients with a mean pulmonary artery pressure (mPAP) > 50 mmHg is 10% [2]. Pulmonary endarterectomy (PEA) is a gold standard therapy for patients with CTEPH [3 4].

Although pulmonary vascular resistance (PVR) is commonly used as right ventricular (RV) afterload, PVR accounts for only 75% of the RV afterload due to the underestimation of pulsatile load that accounts for the non-negligible 25% of the total RV afterload [5]. The pulsatile load of the pulmonary circulation is often evaluated by using pulmonary arterial compliance (PAC) [6]. Recently, there is growing evidence to show that pulmonary arterial compliance is also an important predictor

Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; PAC, pulmonary arterial compliance; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PEA, pulmonary endarterectomy; PVR, pulmonary vascular resistance; 95% CI, 95% confidence interval.

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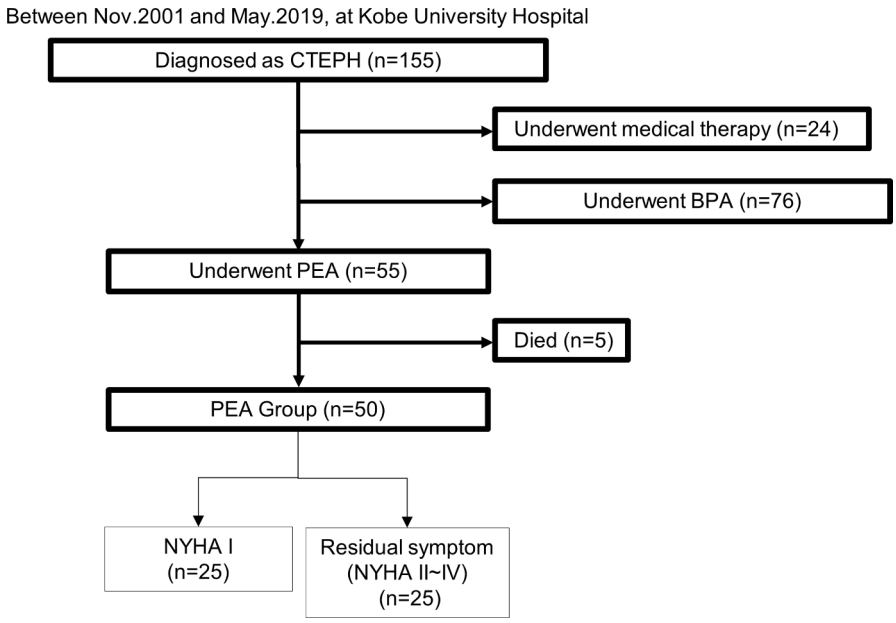

Fig. 1. Study flowchart. BPA indicates balloon pulmonary angioplasty; CTEPH, chronic thromboembolic pulmonary hypertension; PEA, pulmonary endarterectomy.

in PH patients that is independent from PVR [7]. Furthermore, several studies have highlighted the relationship between resistance and compliance for evaluating pulmonary circulation. PVR and PAC exhibit an inverse hyperbolic relationship [8]. Consequently, the RC time, which is calculated as the product of PVR and PAC, is considered to remain constant regardless of disease severity and etiology [9] and also medical therapy [10]. Nevertheless, little is known on how RC time is changed after invasive therapy in CTEPH. In addition, the clinical significance of RC time is unclear.

Accordingly, we investigated the clinical relevance of RC time in CTEPH patients underwent PEA.

2. Methods

2.1. Study design

This observational retrospective study was conducted in all consecutive 155 patients who were diagnosed with CTEPH in Kobe University Hospital between November 2001 and May 2019. PEA was indicated based on conference between expert physicians, interventional cardiologists and PEA surgeons according to established clinical guidelines [4]. Inoperable patients not indicated for PEA had balloon pulmonary angioplasty (BPA) performed and/or medical therapy. Fifty-five patients underwent PEA and five died during the perioperative period. We enrolled 50 patients except for death cases in this study (Fig. 1). Further, the patients were divided into a NYHA I group and a residual symptom (NYHA II ~ IV) group after the treatment. The present study was approved by the Ethics Committee of Kobe University and conformed to the tenets of the Declaration of Helsinki, and written informed consent was waived because of the retrospective design.

2.2. Analyzed clinical parameters

We evaluated baseline clinical parameters before performing PEA and follow-up clinical parameters at three months after PEA. Hemodynamic parameters were assessed by right heart catheterization (RHC) at baseline and follow-up. Pulmonary vascular resistance (PVR) was represented as Wood units or mmHg·sec/mL, which was calculated from mean pulmonary artery pressure (mPAP), cardiac output (CO) and pulmonary capillary wedge pressure (PCWP). PAC was calculated by stroke volume divided by pulmonary arterial pulse pressure. Exercise tolerance was evaluated by six-minute walking distance (6MWD). Symptoms were classified based on New York Heart Association functional classification (NYHA). Oxygenation was examined by blood gas analysis at RHC. Brain natriuretic peptide (BNP) was also evaluated.

2.3. RC time

The classical definition of the RC time is that the resistance - capacitance time constant, also called tau, the time constant (in seconds) of an RC circuit, is equal to the product of the circuit resistance (in ohms) and the circuit capacitance (in farads). RC time (sec) was calculated as the product of PVR (mmHg·sec/mL) and PAC (ml/mmHg) from right heart catheter-measured parameters [8] in pulmonary circulation. Patients were classified into either a Decrease group a Non-decrease group according to change of RC time after PEA. The Decrease group was defined as having a decrease over 0.05 in RC time. The Non-decrease group was defines as a No-change group with a change < 0.05 and an Increase group with an increase over 0.05 in RC time.

2.4. PEA procedure

PEA was performed using principles similar to those established by the San Diego group [11]. Bilateral PEA was performed via median sternotomy with cardiopulmonary bypass. Distal endarterectomy was conducted with intermittent circulatory arrest for a period limited to 20 min in deep hypothermia, whereby the central temperature is cooled to 16 °C and maintained.

2.5. Statistical analysis

Quantitative values are presented as mean ± standard deviation, and differences in values were tested using the Student's *t*-test and analysis of variance. Categorical data were expressed as numbers and percentages and analyzed using the chi-squared test. Univariate and multivariate analyses based on the logistic regression model were used to investigate the associated factors for residual symptom after PEA. The differences in NYHA were tested by the Mann-Whitney test. A p-value < 0.05 was considered as statistically significant.

All statistical analyses were performed using SPSS Statistics 22.0 (SPSS Inc., Chicago, IL, USA).

Table 1
Baseline and post-procedural results in patients underwent PEA.

Variables	PEA (n = 50)		
	Pre	Post	p-value
NYHA (I/II/III/IV), n	0/13/31/6	25/15/9/1	<0.001
6MWD, m (n)	340 ± 118 (32)	357 ± 135 (29)	0.50
RAP, mmHg	7.2 ± 6.6	5.4 ± 3.4	0.14
sPAP, mmHg	76.0 ± 17.4	37.4 ± 14.3	<0.001
mPAP, mmHg	43.0 ± 9.9	22.7 ± 7.8	<0.001
dPAP, mmHg	24.8 ± 9.0	13.8 ± 5.1	<0.001
PCWP, mmHg	9.7 ± 5.1	9.1 ± 3.6	0.86
PVR, Wood units	11.0 ± 4.7	3.8 ± 2.4	<0.001
PVR, mmHg sec/mL	0.66 ± 0.28	0.23 ± 0.14	<0.001
Cardiac index, L/min/m^2	2.0 ± 0.6	2.6 ± 0.8	<0.001
Stroke volume, ml	44.2 ± 17.3	54.8 ± 24.0	0.005
Heart rate, /min	75.1 ± 14.0	79.8 ± 14.4	0.08
PAC, ml/mmHg	0.97 ± 0.58	2.63 ± 1.55	<0.001
RC time, sec	0.54 ± 0.16	0.45 ± 0.12	<0.001
SaO_2, %	91.4 ± 4.5	94.9 ± 3.2	<0.001
SvO_2, %	61.1 ± 9.2	66.5 ± 6.4	<0.001
BNP, pg/ml (n)	377 ± 431 (43)	136 ± 151 (41)	0.001
PH targeted therapy, n (%)	28 (56)	16(32)	0.02
Warfarin, n (%)	50 (100)	50 (100)	1
HOT, n (%)	19 (38)	9 (18)	0.03

Values are mean ± standard deviation or n (%) except as noted. 6MWD indicates 6-minute walking distance; BNP, brain natriuretic peptide; dPAP, diastolic pulmonary arterial pressure; HOT, home oxygen therapy; mPAP, mean pulmonary arterial pressure; NYHA, New York Heart Association functional classification; PAC, pulmonary arterial compliance; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SaO_2, arterial oxygen saturation; SvO_2, mixed venous oxygen saturation; sPAP, systolic pulmonary arterial pressure;

3. Results

3.1. Baseline characteristics and efficacy of PEA

The baseline characteristics before PEA and the hemodynamic and clinical data after PEA are shown in Table 1. PEA dramatically improved all hemodynamics and clinical status except for 6MWD at three months after PEA. RC time was significantly decreased by PEA (0.54 ± 0.16 to 0.45 ± 0.12 sec, $p < 0.001$).

3.2. Parameters related to changes in RC time

Comparison of parameters between Decrease group and Non-decrease group on RC time is shown in Table 2. NYHA and residual symptom after PEA of Decrease group were significantly better than that of Non-decrease group (NYHA: 18/7/4/1 vs. 3/7/4/0, $p = 0.04$, Residual symptom: 12 patients, 40% vs. 11 patients, 78.6%, $p < 0.02$, respectively). However, there were not significant difference between both groups in hemodynamic parameters after PEA included PAP and CI.

3.3. Residual symptom related factors after PEA

Because residual symptoms might be related to RC time, the difference of clinical parameters between the NHYA I group and the residual symptom group in PEA were evaluated (Table 3). Twenty-five patients (50% of patients underwent PEA) had no symptom after PEA. The residual symptom group was significantly older than the NYHA I group at baseline (54.5 ± 13.4 vs. 62.3 ± 12.6 y, $p = 0.04$). For post-procedural results, the residual symptom group were significantly more severe than the NYHA I group in mPAP, CI, and PVR after PEA (19.3 ± 5.8 vs. 26.2 ± 8.3 mmHg, $p = 0.001$, 2.9 ± 0.9 vs. 2.4 ± 0.6 L/min/m^2, $p = 0.014$, 2.6 ± 1.3 vs. 5.0 ± 2.6 Wood units, $p < 0.001$, respectively). The RC time of the NYHA I group was significantly lower than that of the residual symptom group after PEA (0.38 ± 0.07 vs. 0.52 ± 0.12 sec, $p < 0.001$). Table 4 presents the results of the logistic regression analysis of variables relating residual symptom after PEA. In univariate analysis, age, mPAP, CI, PVR and RC time after PEA were related with residual symptom after PEA. Then, in multivariate analysis, only RC time after PEA was independently associated with residual symptom after PEA (OR 1.026, 95% CI 1.005–1.048; $p = 0.017$). Based on the receiver operating characteristic curve analysis, the optimal cut-off value of RC time for the presence of residual symptom was 0.428 s, with a sensitivity of 83.3% and a specificity of 81.8% (area under the curve, 0.886; 95% CI, 0.790–0.982; Fig. 2).

4. Discussion

The present study showed the clinical relevance of RC time in CTEPH patients underwent PEA. PEA decreased RC time, and furthermore, RC

Table 2
Comparison of parameters between Decrease group and Non-decrease group on RC time.

Variables	Pre			Post		
	Decrease group (n = 30)	Non-decrease group (n = 14)	p-value	Decrease group (n = 30)	Non-decrease group (n = 14)	p-value
Proximal lesion type, n (%)	25 (83.3)	13 (92.9)	0.39			
Jamieson classification (I/II/III/IV), n	1/24/5/0	3/10/1/0	0.08			
NYHA (I/II/III/IV), n	0/8/18/4	0/4/9/1	0.70	18/7/4/1	3/7/4/0	0.04
Residual symptom, n (%)	–	–	–	12 (40)	11 (78.6)	0.02
6MWD, m (n)	341.3 ± 136.6 (21)	326.0 ± 70.1 (9)	0.75	375.6 ± 161.3 (17)	322.0 ± 92.9 (10)	0.35
RAP, mmHg	7.1 ± 7.4	6.6 ± 5.1	0.82	5.9 ± 3.7	4.9 ± 2.5	0.31
sPAP, mmHg	74.5 ± 16.7	82.9 ± 13.2	0.10	38.1 ± 11.8	41.6 ± 18.1	0.45
mPAP, mmHg	43.2 ± 10.3	44.7 ± 8.0	0.62	23.3 ± 7.1	24.6 ± 8.6	0.62
dPAP, mmHg	26.1 ± 8.7	23.4 ± 9.8	0.37	14.4 ± 5.4	14.5 ± 4.3	0.94
PCWP, mmHg	8.7 ± 4.0	11.2 ± 7.2	0.15	9.8 ± 3.6	8.3 ± 3.1	0.17
PVR, Wood units	11.8 ± 4.9	10.2 ± 3.8	0.29	3.5 ± 2.0	4.5 ± 3.2	0.21
Cardiac index, L/min/m^2	2.0 ± 0.6	2.0 ± 0.5	0.89	2.7 ± 0.9	2.5 ± 0.6	0.28
Stroke volume, ml	46.4 ± 17.0	40.6 ± 11.0	0.25	56.4 ± 27.4	54.1 ± 17.3	0.77
Heart rate, /min	70.8 ± 13.1	80.8 ± 12.7	0.02	81.1 ± 15.0	74.3 ± 11.8	0.14
PAC, ml/mmHg	1.00 ± 0.39	0.69 ± 0.18	0.001	2.74 ± 1.81	2.40 ± 1.05	0.52
RC time, sec	0.62 ± 0.14	0.40 ± 0.94	<0.001	0.42 ± 0.10	0.50 ± 0.15	0.046
SaO_2, %	90.7 ± 4.6	93.2 ± 4.1	0.09	95.5 ± 2.9	93.5 ± 3.9	0.06
SvO_2, %	59.8 ± 10.2	62.7 ± 7.3	0.34	66.4 ± 7.1	66.1 ± 5.6	0.86
BNP, pg/ml (n)	406.9 ± 479.5 (28)	344.4 ± 357.3 (12)	0.69	148.5 ± 171.0 (26)	131.9 ± 123.2 (12)	0.77

Values are mean ± standard deviation or n (%) except as noted. Abbreviations are defined in Table 1.

Table 3
Baseline and post-procedural results between patients with NHYA I and residual symptom after PEA.

Variables	PEA (n = 50)					
	Pre			Post		
	NHYA I (n = 25)	Residual symptom (n = 25)	p-value	NHYA I (n = 25)	Residual symptom (n = 25)	p-value
Age, y	54.5 ± 13.4	62.3 ± 12.6	0.04			
Female, n (%)	13 (52)	17 (68)	0.25			
Proximal lesion type, n (%)	20 (80)	24 (96)	0.08			
6MWD, m (n)	379 ± 167 (13)	313 ± 65 (19)	0.20	446 ± 94.2 (8)	324 ± 138 (21)	0.03
RAP, mmHg	8.7 ± 8.1	5.8 ± 4.6	0.14	5.5 ± 3.4	5.3 ± 3.5	0.81
sPAP, mmHg	76.0 ± 18.6	76.0 ± 16.5	1.00	32.1 ± 10.9	43.0 ± 15.5	0.006
mPAP, mmHg	43.8 ± 11.4	42.2 ± 8.5	0.58	19.3 ± 5.8	26.2 ± 8.3	0.001
dPAP, mmHg	25.4 ± 9.8	24.2 ± 8.3	0.64	11.2 ± 3.2	16.4 ± 5.5	<0.001
PCWP, mmHg	11.1 ± 5.6	8.4 ± 4.3	0.08	9.2 ± 3.7	9.0 ± 3.6	0.90
PVR, Wood units	10.6 ± 4.7	11.3 ± 4.8	0.61	2.6 ± 1.3	5.0 ± 2.6	<0.001
PVR, mmHg·sec/mL	0.64 ± 0.28	0.68 ± 0.29	0.61	0.15 ± 0.08	0.30 ± 0.16	<0.001
Cardiac index, L/min/m^2	2.1 ± 0.7	1.9 ± 0.5	0.44	2.9 ± 0.9	2.4 ± 0.6	0.01
Stroke volume, ml	44.2 ± 21.6	44.2 ± 12.4	0.99	59.8 ± 29.3	50.2 ± 18.0	0.18
Heart rate, /min	77.7 ± 13.5	72.4 ± 14.6	0.19	82.4 ± 15.5	77.1 ± 13.3	0.21
PAC, ml/mmHg	1.06 ± 0.75	0.88 ± 0.35	0.30	3.05 ± 1.64	2.24 ± 1.41	0.08
RC time, sec	0.53 ± 0.15	0.55 ± 0.18	0.74	0.38 ± 0.07	0.52 ± 0.12	<0.001
SaO_2, %	91.8 ± 4.5	91.0 ± 4.7	0.59	95.6 ± 2.9	94.4 ± 3.4	0.19
SvO_2, %	61.2 ± 10.4	61.0 ± 8.3	0.93	67.7 ± 5.8	65.5 ± 7.0	0.26
BNP, pg/ml (n)	352.4 ± 397.2 (19)	395.9 ± 472.7 (24)	0.75	68.3 ± 40.6 (16)	179.7 ± 180.8 (25)	0.02

Values are mean ± standard deviation or n (%) except as noted. Abbreviations are defined in Table 1.

Table 4
Univariate and multivariate logistic regression analysis of residual symptom related factors after PEA.

Variables	PEA					
	Univariate			Multivariate		
	OR	95 %CI	p-value	OR	95% CI	p-value
Age, y	1.048	1.001 – 1.098	0.047			
PAC, ml/mmHg	0.676	0.425 – 1.074	0.098			
mPAP, mmHg	1.159	1.045 – 1.286	0.005			
Cardiac index, L/min/m^2	0.315	0.112 – 0.890	0.029			
PVR, Wood units	2.206	1.343 – 3.623	0.002			
RC time, msec	1.024	1.010 – 1.039	0.001	1.026	1.005–1.048	0.017
SaO_2, %	0.876	0.718 – 1.070	0.195			
BNP, pg/ml	1.012	1.000 – 1.023	0.042			

CI indicates confidence interval; OR, odds ratio. Other abbreviations are shown in Table1.

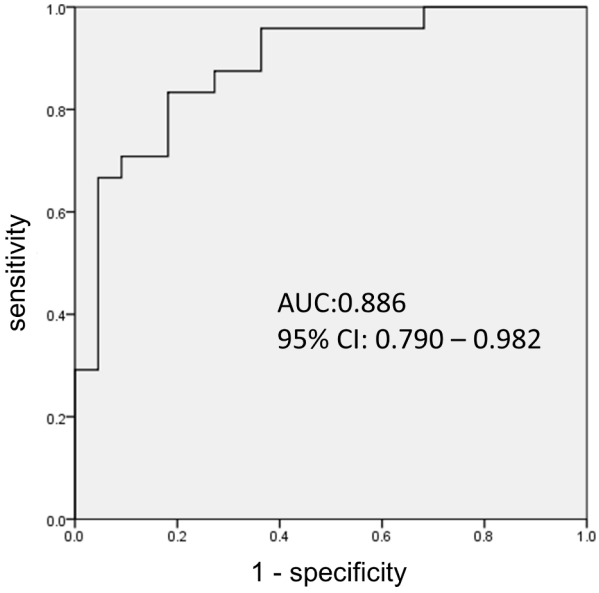

Fig. 2. Receiver operating characteristic curve of the association between RC time and residual symptom. AUC indicates area under the curve.

time after PEA was independently associated with residual symptom.

RC time was previously reported to be fairly constant over a wide range of disease severity and etiology in PH patients [9 10]. However, several studies subsequently pointed out that RC time is not always constant. For patients with left heart failure, low RC time values of 0.33–0.35 sec were observed when PCWP was elevated to 26–21 mmHg [12 13]. In contrast, higher values of RC time in PH patients without left heart failure have been reported by several studies. Previous reports showed an RC time of 0.56–0.65 sec from four studies [10 13 14 15] of idiopathic pulmonary arterial hypertension and 0.49–0.55 sec from two CTEPH studies [10 15]. In addition, the RC time of patients with normal pulmonary hemodynamics has been reported as 0.47 ± 0.13 sec [14]. From a systematic review, the RC time of healthy volunteers was calculated to be 0.39 ± 0.34 sec [14 16], which was remarkably lower than that of pH patients. Furthermore, Robert V et al reported a decrease in RC time from 0.49 ± 0.11 to 0.38 ± 0.11 sec after PEA in CTEPH [15]. In the present study as well, PEA significantly reduced RC time. Meanwhile, Lankhaar JW demonstrated that medical treatment did not change RC time in PH [10]. In this study, we showed for the first time the possibility that RC time after PEA was independently associated with residual symptom.

Although the pathophysiological significance of decreased RC time by PEA is still unclear, the decrease in RC time towards normal levels could be due to a structural change in the proximal pulmonary artery through the removal of lesions with thickened intima and organized thrombus. Furthermore, it was speculated that an explanation for change of RC time was that the removal at PEA of tunica intima and part of tunica media of the pulmonary artery with subsequent healing might

not leave the arterial wall with the same compliance properties as the normal pulmonary artery [15]. Because we didn't quantify the felicity of each operation, we don't have the direct data which proves our speculation. However, we believe that removing the intimal thrombus by PEA reduces RC time. Namely, our result suggesting an independent association of residual symptom and RC time might suggest that a sufficient decrease in RC time after PEA could be utilized as a therapeutic indicator to represent a successful PEA.

4.1. Limitation

This is a retrospective single center observational study and the number of patients was small. Therefore, the occurrence of missing values was unavoidable and might have influenced the result in the multivariate regression model. Furthermore, the possibility that an unknown confounding factor exists cannot be denied.

5. Conclusion

PEA reduced RC time which is the product of PVR and PAC. Furthermore, RC time after PEA was independently associated with residual symptom. Therefore, RC time might be an optimal indicator to predict the success of PEA.

Conflict of interest statement: Dr Nakayama reports a research grant in the field of pulmonary hypertension from Janssen Pharmaceutical K.K., Nippon Shinyaku Ltd, and Bayer Ltd. Dr Taniguchi reports a research grant in the field of pulmonary hypertension from Actelion Pharmaceuticals Ltd, and Nippon Shinyaku Ltd. Dr Emoto reports a research grant in the field of pulmonary hypertension from Bayer Ltd, Actelion Pharmaceuticals Ltd, and Nippon Shinyaku Ltd. Dr Hirata reports a research grant in the field of pulmonary hypertension from Actelion Pharmaceuticals Ltd, and Nippon Shinyaku Ltd. The other authors have no conflicts of interest to declare.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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