Significance of Pulmonary Vascular Resistance and Diastolic Pressure Gradient on the New Definition of Combined Post-Capillary Pulmonary Hypertension

Koichi Sugimoto,1,2 MD, Akiomi Yoshihisa,1 MD, Kazuhiko Nakazato,1 MD, Tetsuro Yokokawa,1,2 MD, Tomofumi Misaka,1 MD, Masayoshi Oikawa,1 MD, Atsushi Kobayashi,1 MD, Takayoshi Yamaki,1 MD, Hiroyuki Kunii,1 MD, Takaufumi Ishida,1 MD and Yasuchika Takeishi,1 MD

Summary

Pulmonary hypertension (PH) caused by left-sided heart disease (LHD-PH) is classified into 2 types: isolated post-capillary PH (Ipc-PH) and combined pre- and post-capillary PH (Cpc-PH). However, the impact of pulmonary vascular resistance (PVR) or diastolic pressure gradient (DPG) on the prognosis of LHD-PH has varied among previous studies. Thus, we verified the significance of PVR or DPG on the prognosis of LHD-PH in our series.

We analyzed 243 consecutive LHD-PH patients. The patients were divided into 3 groups: Group A, patients with PVR ≤ 3 Wood unit (WU) and DPG < 7 mmHg; Group B, patients with either PVR > 3 WU or DPG ≥ 7 mmHg; and Group C, patients with PVR > 3 WU and DPG ≥ 7 mmHg.

The Kaplan-Meier curve demonstrated that Group B had lower cardiac death-free survival compared with Group A, whereas no significant differences were observed when compared with Group C. In the Cox hazard model, DPG was not associated with cardiac death in the LHD-PH patients. However, only in the ischemic heart disease group, patients with DPG ≥ 7 mmHg had worse prognosis compared with those with normal DPG.

The cardiac death-free rate of patients with either increased PVR or DPG was close to that of patients with both increased PVR and DPG. It seems reasonable to define Cpc-PH only by PVR in the new criteria. However, the significance of DPG in LHD-PH might be dependent on the underlying cause of LHD-PH.

Key words: Prognosis, Left heart disease, Hemodynamics, Etiology

Pulmonary hypertension due to left heart disease (LHD-PH) is the most common type of pulmonary hypertension. LHD-PH is defined by the 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) criteria as a mean pulmonary artery wedge pressure (PAWP) of > 15 mmHg and a mean pulmonary arterial pressure (PAP) of ≥ 25 mmHg at rest.1,2) Depending on its mechanism, LHD-PH is classified into 2 types. One type is isolated post-capillary pulmonary hypertension (Ipc-PH), which is caused by passive pressure propagation due to a rise in left ventricular (LV) filling pressure. The other is a combined pre- and post-capillary pulmonary hypertension (Cpc-PH), which is associated with stenotic lesions on the pulmonary arterial side in addition to a rise in left atrial pressure.1,2)

Previously, pulmonary vascular resistance (PVR) and transpulmonary gradient (TPG), the difference between mean PAP and mean PAWP, were used to detect vascular disease in the pulmonary arterial side in LHD-PH patients.3,5) In the 2015 ESC/ERS guidelines, Ipc-PH is defined as PVR < 3 Wood unit (WU) and/or diastolic pressure gradient (DPG), defined as diastolic PAP - mean PAWP, < 7 mmHg, and Cpc-PH is defined as PVR > 3 WU and/or DPG ≥ 7 mmHg since DPG is not easily affected by levels of PAWP or stroke volume (SV) compared with PVR and TPG.1,4) However, this classification has a problem in that the isolated elevations of PVR > 3 WU or DPG ≥ 7 mmHg are classified into both Ipc-PH and Cpc-PH.

Also, the evaluation of DPG as a prognostic predictor for LHD-PH has been controversial. A previous report suggested that DPG ≥ 7 mmHg is a poor independent prognostic factor of LHD-PH,4,6) whereas several other studies have reported that DPG is not necessarily a poor prognostic factor, despite being a main specifying factor of LHD-PH.7,8) At the 6th World Symposium on PH in 2018, it was recommended that Ipc-PH should be distinguished from Cpc-PH using only PVR and that DPG should be excluded from the definition of Cpc-PH in the next revision of the guidelines.9,10)

From the 1Department of Cardiovascular Medicine, Fukushima Medical University, Fukushima, Japan and 2Department of Pulmonary Hypertension, Fukushima Medical University, Fukushima, Japan.

Address for correspondence: Koichi Sugimoto, MD, Department of Pulmonary Hypertension, Fukushima Medical University, 1 Hikarigaoka, Fukushima 960-1295, Japan. E-mail: ksugi@fmu.ac.jp

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It is still unclear whether there is a difference in the significance of Cpc-PH among etiologies of left heart disease, and several studies have reported that DPG does not reflect the prognosis of LHD-PH with non-ischemic cardiomyopathy.\textsuperscript{8,9} Tatebe, et al. have reported that the prognosis of reactive post-capillary PH (equivalent to the current Cpc-PH) has a significantly poorer prognosis than that of passive post-capillary PH (equivalent to the current Ipc-PH) regarding total mortality of ischemic heart disease patients, although those subjects were categorized according to the 2009 ESC guidelines.\textsuperscript{11} Thus, the significance of DPG or Cpc-PH on LHD-PH prognosis might be different due to the underlying diseases causing LV dysfunction.

In this study, we investigated the clinical characteristics and prognosis of the intermediate group, which was defined by isolated increased PVR or DPG to consider the validity of defining Cpc-PH with only PVR as upcoming new criteria. In addition, we examined the significance of PVR and DPG in the etiology of left heart disease.

**Methods**

**Study subjects:** The study subjects consisted of 243 consecutive LHD-PH patients who had been diagnosed using right heart catheterization between January 2007 and June 2015 at the Fukushima Medical University. We excluded cases of acute heart failure, acute coronary syndrome, idiopathic pulmonary arterial hypertension, connective tissue disease-associated PH, PH due to lung disease, and chronic thromboembolic PH. Figure 1 shows the enrollment criteria of the study subjects. Echocardiographic parameters and laboratory data were obtained from the patients' medical records, and written informed consent was obtained from all study subjects. The study protocol was approved by the ethics committee of the Fukushima Medical University, in compliance with the Declaration of Helsinki.

**Hemodynamics measurements:** All catheterizations were performed within 7 days after echocardiography in a resting supine position under fluoroscopic guidance. PAP, PAWP, mean right atrial pressure (RAP), and cardiac output were measured using a 7F Swan-Ganz catheter (Edwards Lifesciences, Irvine, CA, USA).\textsuperscript{12} We mainly used the thermodilution method for the measurement of cardiac output; however, for cases of advanced tricuspid regurgitation, we used the Fick method. The DPG was defined as the difference between the mean PAWP and diastolic PAP.\textsuperscript{1} The TPG was defined as the difference between the mean PAWP and mean PAP.\textsuperscript{2} The PVR was calculated using the conventional formula. The pulmonary arterial capacitance (PAC) was estimated as the ratio between the SV and the PAP, as described previously.\textsuperscript{4,13,14} The patients were classified into 3 groups according to previous literature, i.e., Group A, patients with PVR ≤ 3 WU and DPG < 7 mmHg; Group B, an intermediate group, which included those with isolated elevation PVR or DPG; and Group C, patients with PVR > 3 WU and DPG ≥ 7 mmHg.\textsuperscript{7} For the analysis of underlying diseases of LHD-PH, we further divided the patients into 4 groups: ischemic heart disease, valvular heart disease, non-
ischemic cardiomyopathy, and other etiologies groups. The end-point was defined as cardiac death. 

**Echocardiography:** Using standard techniques, transthoracic echocardiography was performed by an experienced echocardiographer. The left atrial dimension, interventricular septal thickness, LV end-diastolic diameter, LV end-systolic diameter, posterior wall thickness, LV end-diastolic volume, and LV ejection fraction (LVEF) were measured as echocardiographic parameters. All recordings were carried out on an ultrasound system (ACUSON Sequoia, Siemens Medical Solutions, Mountain View, CA, USA).

**Statistical analysis:** Normally distributed variables were presented as the mean ± SD, and non-normally distributed variables were presented as the median (interquartile range). Categorical variables were expressed as numbers and percentages. The baseline characteristics of the groups were compared using the analysis of variance for the continuous variables. A χ² test for the non-continuous variables. The proportional-hazard assumption were violated in the Cox hazard model, the NYHA classification, CI, SV index, and PAC of Group C were significantly lower than those of Group A. Heart rate, systolic PAP, diastolic PAP, mean PAP, pulmonary arterial pressure, PVR, DPG, and TPG were significantly higher in Group C. The patients in Group B had almost intermediate values between Group A and Group C in heart rate, CI, SV index, systolic PAP, diastolic PAP, mean PAP, PVR, PAC, DPG, and TPG. There were no significant differences in the levels of mean RAP, mean PAWP, systolic arterial pressure (AoP), diastolic AoP, or mean AoP among the 3 groups. In the echocardiographic data, there were no significant differences in left atrial diameter, LV end-diastolic volume index or LVEF. There was no difference in the medical treatment for heart failure.

**Results**

In total, 244 patients were diagnosed with LHD-PH via right heart catheterization, 243 of whom were followed up (Figure 1). The median follow-up period was 1,021 days, with cardiac death occurring in 21 patients (8.6%). Forty-nine patients (20.2%) with isolated elevation of PVR or DPG were classified into Group B (Table I).

Table II shows the clinical characteristics, hemodynamic data, echocardiographic parameters, and laboratory data of each group. There were no significant differences in age, sex, complication rates of atrial fibrillation and hemodialysis, etiology of heart failure, or the NYHA classification among the 3 groups. As for the hemodynamic indices, the CI, SV index, and PAC of Group C were significantly lower than those of Group A. Heart rate, systolic PAP, diastolic PAP, mean PAP, pulmonary arterial pressure, PVR, DPG, and TPG were significantly higher in Group C. The patients in Group B had almost intermediate values between Group A and Group C in heart rate, CI, SV index, systolic PAP, diastolic PAP, mean PAP, PVR, PAC, DPG, and TPG. There were no significant differences in the levels of mean RAP, mean PAWP, systolic arterial pressure (AoP), diastolic AoP, or mean AoP among the 3 groups. In the echocardiographic data, there were no significant differences in left atrial diameter, LV end-diastolic volume index or LVEF. There was no difference in the medical treatment for heart failure.

**Table I** Classification of LHD-PH Patients by PVR and DPG

| PVR ≤ 3 WU | PVR > 3 WU |
|------------|------------|
| DPG < 7 mmHg | 177 (72.8%) | 46 (18.9%) |
| DPG ≥ 7 mmHg | 3 (1.2%)   | 17 (7%)    |

χ² P < 0.0001. DPG indicates diastolic pressure gradient, and PVR, pulmonary vascular resistance.

Even though we used the new criteria for Cpc-PH, which classified the LHD-PH patients by only PVR, those with PVR > 3 WU had a lower survival rate compared with those with PVR ≤ 3 WU (Figure 3A), whereas no significant difference in cardiac death between the DPG ≥ 7 mmHg and DPG < 7 mmHg was observed in our case series (Figure 3B).

In the Cox hazard model, the NYHA classification, CI, SV index, mean RAP, PVR, PAC, log BNP, eGFR, and hemoglobin levels were significantly associated with cardiac death in the LHD-PH patients (Table III).

Figure 4 shows the results of the Kaplan-Meier curves in each etiology of LHD-PH. In the LHD-PH due to ischemic heart disease, the patients with PVR > 3 WU had a significantly higher rate of cardiac death. In the group with non-ischemic cardiomyopathy, the rate of cardiac death in the patients with increased PVR tended to be higher than that of the normal PVR group, but no statistically significant difference was observed in this study. In the valvular heart disease group, non-ischemic cardiomyopathy group and other etiologies group, there was no significant difference in cardiac death between the PVR > 3 WU, and the PVR ≤ 3 WU. DPG ≥ 7 mmHg affected the occurrence of cardiac death only in ischemic heart disease patients. The rate of cardiac death was not affected.

In total, 244 patients were diagnosed with LHD-PH via right heart catheterization, 243 of whom were followed up (Figure 1). The median follow-up period was 1,021 days, with cardiac death occurring in 21 patients (8.6%). Forty-nine patients (20.2%) with isolated elevation of PVR or DPG were classified into Group B (Table I).
Table II. Comparison of LHD-PH Patient Characteristics of Each Group

| Characteristics                      | Group A (n = 177) | Group B (n = 49) | Group C (n = 17) | P-value |
|--------------------------------------|------------------|-----------------|-----------------|---------|
| Age (years)                          | 64.3 ± 14.1      | 63.3 ± 15.7     | 59.1 ± 17.0     | 0.368   |
| Male (n, %)                          | 105 (59.3)       | 21 (42.9)       | 11 (64.7)       | 0.093   |
| Af (n, %)                            | 89 (50.3)        | 31 (63.3)       | 10 (58.8)       | 0.246   |
| HD (n, %)                            | 21 (11.9)        | 6 (12.2)        | 1 (5.9)         | 0.750   |
| Etiology of heart failure (n, %)     |                  |                 |                 |         |
| Valvular heart disease               | 48 (27.1)        | 19 (38.8)       | 5 (29.4)        | 0.286   |
| Ischemic heart disease               | 54 (30.5)        | 9 (18.4)        | 3 (17.6)        | 0.158   |
| Non-ischemic cardiomyopathy         | 24 (13.6)        | 11 (22.4)       | 3 (17.6)        | 0.308   |
| Others                               | 51 (28.8)        | 10 (20.4)       | 6 (35.3)        | 0.386   |
| NYHA classification (n) (I/II/III/IV)| (37/63/71/6)     | (5/14/28/2)     | (2/5/8/2)       | 0.191   |

Hemodynamic variables

| HR (b.p.m.)                          | 71.5 ± 17.4      | 73.0 ± 18.6     | 82.7 ± 13.4*    | 0.043   |
| CI (L/minute/m²²)                    | 2.7 ± 0.8        | 2.2 ± 0.6**     | 2.2 ± 0.5*      | <0.001  |
| SVI (mL/m²)                          | 40.1 ± 13.1      | 30.8 ± 10.0**   | 27.8 ± 8.8**    | <0.001  |
| Mean RAP (mmHg)                      | 10.4 ± 4.6       | 10.1 ± 5.0      | 12.1 ± 4.4      | 0.291   |
| Systolic PAP (mmHg)                  | 44.1 ± 9.0       | 55.2 ± 11.3**   | 60.5 ± 16.0**   | <0.001  |
| Diastolic PAP (mmHg)                 | 21.1 ± 5.0       | 25.2 ± 6.4**    | 31.7 ± 6.3**    | <0.001  |
| Mean PAP (mmHg)                      | 30.2 ± 5.7       | 37.9 ± 10.0**   | 41.2 ± 9.5**    | <0.001  |
| Mean PAWP (mmHg)                     | 22.6 ± 5.6       | 23.5 ± 6.0      | 22.9 ± 5.8      | 0.567   |
| PP (mmHg)                            | 23.0 ± 7.0       | 30.0 ± 10.1**   | 28.8 ± 11.9*    | <0.001  |
| PVR (Wood unit)                      | 1.7 ± 0.6        | 4.3 ± 1.9**     | 5.2 ± 2.1*      | <0.001  |
| PAC (mL/mmHg)                        | 3.1 ± 1.3        | 1.9 ± 1.6**     | 1.9 ± 1.0*      | <0.001  |
| DPG (mmHg)                           | –1.4 ± 3.5       | 1.6 ± 3.9**     | 8.7 ± 2.0**††   | <0.001  |
| TPG (mmHg)                           | 7.6 ± 3.1        | 14.4 ± 8.2**    | 18.3 ± 5.5**‡†   | <0.001  |
| Systolic AoP (mmHg)                  | 134.2 ± 31.3     | 123.2 ± 28.7    | 126.8 ± 31.5    | 0.144   |
| Diastolic AoP (mmHg)                 | 70.6 ± 13.5      | 70.3 ± 15.6     | 70.8 ± 13.0     | 0.988   |
| Mean AoP (mmHg)                      | 94.8 ± 17.8      | 89.2 ± 20.4     | 93.5 ± 14.5     | 0.267   |

Laboratory data

| log BNP (pg/dL)                      | 2.5 ± 0.5        | 2.8 ± 0.5*      | 2.7 ± 0.7       | 0.008   |
| eGFR (mL/minute/1.73 cm²)           | 53.7 ± 28.0      | 50.0 ± 25.5     | 53.5 ± 33.9     | 0.706   |
| UA (mg/dL)                           | 6.8 ± 2.0        | 6.9 ± 2.4       | 7.4 ± 2.2       | 0.432   |
| Hemoglobin (g/dL)                   | 12.5 ± 2.5       | 12.8 ± 2.4      | 12.6 ± 2.5      | 0.710   |

Echocardiographic data

| LAD (mm)                             | 46.8 ± 10.3      | 43.2 ± 10.6     | 43.8 ± 8.5      | 0.074   |
| LVEDVI (mL/m²)                       | 78.0 ± 42.3      | 73.6 ± 29.8     | 68.7 ± 27.0     | 0.555   |
| LVEF (%)                             | 46.9 ± 17.2      | 47.6 ± 16.7     | 56.2 ± 15.7     | 0.103   |
| Preserved EF (> 45%) (n, %)          | 102 (59.0)       | 17 (34.7)       | 9 (52.9)        | 0.011   |

Medical therapy

| β-blockers                           | 130 (73.4)       | 37 (75.5)       | 14 (82.4)       | 0.711   |
| ACE-inhibitor/ARB                    | 145 (81.9)       | 41 (83.7)       | 15 (88.2)       | 0.116   |
| Diuretics                            | 102 (57.6)       | 33 (67.3)       | 13 (76.5)       | 0.184   |
| Digitalis                            | 18 (10.2)        | 9 (18.4)        | 1 (5.9)         | 0.212   |
| Inotropic agents                     | 16 (9.0)         | 14 (28.6)       | 4 (23.5)        | 0.001   |

Values are shown as mean ± SD or n (%). ACE-inhibitor indicates angiotensin-converting enzyme-inhibitor; Af, atrial fibrillation; AoP, arterial pressure; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CI, cardiac index; DPG, diastolic pressure gradient; eGFR, estimated glomerular filtration rate; HD, hemodialysis; HR, heart rate; LAD, left atrial diameter; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAC, pulmonary arterial capacitance; PAP, pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; PP, pulmonary arterial pulse pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SVI, stroke volume index; TPG, transpulmonary pressure gradient; and UA, uric acid. *P < 0.05 and **P < 0.01 versus group A. †P < 0.05 and ††P < 0.01 versus Group B.

by DPG ≥ 7 mmHg or DPG < 7 mmHg in the valvular heart disease group, non-ischemic cardiomyopathy group, or other etiologies group.

Discussion

In the present study, we revealed that the hemodynamics of Group B (patients with isolated increased PVR or DPG) were almost intermediate of that of Group A (patients with both normal PVR and DPG) and Group C (patients with both increased PVR and DPG). The risk of cardiac death in Group B was nearly equivalent to that in Group C. Although IpC-PH and Cpc-PH were defined only by PVR according to the upcoming criteria, the risk
of cardiac death in patients with Cpc-PH was worse than that in patients with Ipc-PH, whereas there was no difference between the increased DPG and normal DPG groups. Also, Cox hazard analysis revealed that DPG was not a predictive factor of cardiac death in LHD-PH patients in our series. However, in patients with LHD-PH due to ischemic heart disease, the risk of cardiac death was significantly increased by PVR > 3 WU or DPG ≥ 7 mmHg.

In the current study, the number of patients in Group A was higher and that of Group B were lower compared with those reported by Palazzini, et al., whose sample size was similar to that in the current study. Although there were slight differences in the composition of the subjects and the end-point definitions, our results were similar to theirs regarding the clinical features and prognosis of Group B. Moreover, most of the patients in the current Group B were those with isolated increased PVR, similar to that in Palazzini’s study. Cumulatively, these results support distinguishing Cpc-PH from Ipc-PH with PVR alone in the upcoming guidelines.

DPG is affected by many factors including lung disease, sepsis, hypoxia, acidosis, and coronary artery bypass surgery. Furthermore, it is known that DPG in usual practice is easily underestimated under conditions of elevated v wave of PAWP (e.g., mitral regurgitation). Therefore, in such cases, the new criteria might be more useful and accurate than the 2015 ESC/ERS guidelines.

Conversely, Gerges, et al. reported that the rate of Group B, which was unclassified as per the 2015 ESC/ERS guidelines, was up to 30%, and they proposed defining Ipc-PH as PH-LHD with a DPG of < 7 mmHg and/or PVR of ≤ 3 WU, and Cpc-PH as PH-LHD with a DPG of ≥ 7 mmHg and PVR of > 3 WU. The authors also demonstrated that DPG reflected pulmonary vascular remodeling, although the pulmonary artery samples they used were obtained from patients with extremely high DPG (> 15-20) and extremely elevated PVR, which is rare in LHD-PH. Therefore, it cannot be said that DPG is an inappropriate factor for distinguishing between Ipc-PH and Cpc-PH only because DPG itself is not associated with prognosis. Further research is necessary to investigate this issue.

Vanderpool, et al. revealed that TPG, PVR, and DPG are all associated with mortality and cardiac hospitalizations in a large number of heart failure patients with preserved EF. The differences between our results and their results can be attributed to how the data in our respective studies were obtained; they obtained data by using only preserved EF patients, whereas we obtained our data from both preserved EF and reduced EF patients.

Tampakakis, et al. analyzed several LHD-PH patients...
Table III. Predictors of Cardiac Death by Cox Proportional Hazards Model

| Variables        | β coefficient | Univariate HR (95% CI) | P-value  |
|------------------|---------------|------------------------|----------|
| Age              | 0.004         | 1.005 (0.974-1.005)    | 0.774    |
| Male             | 0.066         | 1.068 (0.425-2.681)    | 0.889    |
| Af               | 0.211         | 1.234 (0.707-2.156)    | 0.460    |
| NYHA classification | 1.531     | 4.625 (2.242-9.542)    | < 0.001  |
| HR               | 0.021         | 1.022 (0.999-1.044)    | 0.056    |
| CI               | −0.787        | 0.455 (0.227-0.911)    | 0.026    |
| SVI              | −0.063        | 0.939 (0.902-0.977)    | 0.002    |
| Mean RAP         | 0.117         | 1.124 (1.037-1.219)    | 0.005    |
| Systolic PAP      | 0.031         | 1.032 (0.999-1.066)    | 0.060    |
| Diastolic PAP     | 0.051         | 1.053 (0.988-1.122)    | 0.111    |
| Mean PAP          | 0.024         | 1.024 (0.983-1.066)    | 0.259    |
| Mean PAWP         | 0.032         | 1.032 (0.965-1.104)    | 0.360    |
| PP               | 0.034         | 1.034 (0.987-1.084)    | 0.157    |
| PVR              | 0.155         | 1.168 (1.000-1.364)    | 0.049    |
| PAC              | −0.853        | 0.426 (0.256-0.710)    | 0.001    |
| DPG              | 0.045         | 1.046 (0.951-1.151)    | 0.356    |
| TPG              | 0.017         | 1.017 (0.964-1.072)    | 0.538    |
| LVEF             | 0.000         | 1.000 (0.975-1.025)    | 0.987    |
| log BNP          | 1.839         | 6.290 (2.538-15.586)   | < 0.001  |
| eGFR             | −0.030        | 0.971 (0.954-0.971)    | 0.001    |
| UA               | 0.102         | 1.108 (0.911-1.347)    | 0.305    |
| Hemoglobin       | −0.291        | 0.748 (0.632-0.884)    | 0.001    |

Af indicates atrial fibrillation; BNP, B-type natriuretic peptide; CI, cardiac index; DPG, diastolic pressure gradient; eGFR, estimated glomerular filtration rate; HR, heart rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAC, pulmonary arterial capacitance; PAP, pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; PP, pulmonary arterial pulse pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SVI, stroke volume index; TPG, transpulmonary pressure gradient; and UA, uric acid.

Figure 4. Kaplan-Meier curves for survival from cardiac death in LHD-PH patients in each etiology. DPG indicates diastolic pressure gradient, and PVR, pulmonary vascular resistance.

and reported that DPG was not associated with prognosis. However, all of their patients were cardiomyopathy patients, whereas in the present study, patients with all etiologies of LHD were included. It is undeniable that the significance of DPG or Cpc-PH on the prognosis of LHD-PH may differ due to the underlying diseases that induce LV dysfunction.

In the current study, in the ischemic heart disease group only, high DPG significantly increased cardiac death compared with low DPG, despite there not being any significant difference in overall LHD-PH patients. Although the statistical power in our study was low due to the small sample size, it is highly possible that the importance of DPG in the prognosis of LHD-PH differs depending on the underlying disease. Furthermore, in this study, PAC was significantly lower in patients with DPG ≥ 7 mmHg than in those with DPG < 7 mmHg in the ischemic heart disease group, whereas it was comparable in the other groups (Supplemental Table). PAC may affect the difference of prognosis of patients with ischemic heart disease whose DPG is ≥ 7 or < 7 mmHg.

The 2015 ESC/ERS guidelines and the recent World Symposium on Pulmonary Hypertension classify LHD-PH as a subgroup of heart failure with reduced ejection fraction, heart failure with preserved ejection fraction, valvular heart disease, and obstruction of the pulmonary vein according to pathophysiology. If possible, further classification for each disease, such as ischemic heart disease, valvular heart disease, non-ischemic cardiomyopathy, and other etiologies, are required in the future.

Since the definitions of Ipc-PH and Cpc-PH in the 2009 ESC/ERS guidelines were changed just a few years after their establishment, and there is a report that PVR is not a prognostic factor for LHD-PH, it is apparent that the debate regarding the definition of Cpc-PH will con-
continue even after the next criteria is applied, which warrants extensive research to investigate and clarify this issue in detail. The difference between Cpc-PH and Ipc-PH may affect the treatment strategy of LHD-PH, and a better index is required to distinguish these phenotypes.

The present study has some limitations. First, the study involved a relatively small number of samples from a single institution. Second, the cardiac output was measured by both the thermodilution method and Fick’s method, which raises the issue of a possible variability in data interpretation due to the inherent differences between these methods. However, we used the thermodilution method in the standard manner, and the number of patients for whom Fick’s method was used was small.

Conclusions

We here showed that the prognosis of the intermediate group, which was defined by isolated increased PVR or DPG, was worse than that of patients with both normal PVR and DPG. The number of patients with isolated increased DPG was small, and it seems reasonable to define Cpc-PH only by PVR in the upcoming new criteria. The significance of DPG in LHD-PH remains controversial, and the analysis of each underlying disease of LHD-PH needs to be examined in larger study populations.

Disclosure

Conflicts of interest: Koichi Sugimoto and Tetsuro Yokokawa belong to an endowed department sponsored by Astereion Pharmaceuticals Japan. The funders had no role in the study design, data collection, and analysis, decision to publish, or preparation of the manuscript. All other authors declare that no competing interest exists.

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