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Is Pulmonary Capillary Wedge Pressure a Reliable Indicator of Postcapillary Pulmonary Hypertension?

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Highlights

What is new?

- The peculiar hemodynamics of pulmonary hypertension (PH) needs right-sided pressures to be considered when interpreting left-sided filling pressures.
- A high pulmonary capillary wedge pressure (PCWP) alone may not necessarily indicate post-capillary PH.
- This diagnosis can be improved using LV transmural pressure difference (ΔP_{TM}).

What are the clinical implications?

- A new hemodynamic classification of PH based on ΔP_{TM} may better distinguish patients with accompanying “apparent” and “actual” left heart disease.
- This new classification may identify a subpopulation who are deprived of PH-specific treatments because of being labelled as having left heart disease but potentially benefit from PH-specific treatments.

Title page

Title: Is Pulmonary Capillary Wedge Pressure a Reliable Indicator of Postcapillary Pulmonary Hypertension?

Short title: PCWP- vs. ΔP_{TM}-based classification in PH

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Abbreviations

Cpc-PH, combined pre- and post-capillary pulmonary hypertension

HF, heart failure

Ipc-PH, isolated post-capillary pulmonary hypertension

LHD, left heart disease

LV, left ventricle

PH, pulmonary hypertension

PVR, pulmonary vascular resistance

PWCP, pulmonary capillary wedge pressure

RA, right atrium

RHC, right heart catheterization

SV, stroke volume

Abstract

Although current pulmonary hypertension (PH) guidelines recommend a pulmonary capillary wedge pressure (PCWP) above 15 mmHg for the detection of a post-capillary component, the rational of this recommendation may not be quite compatible with the peculiar hemodynamics of PH. We hypothesize that a high PCWP alone does not necessarily indicate left-sided disease and this diagnosis can be improved using LV transmural pressure difference (ΔP_{TM}). In this two-center, retrospective, observational study; we enrolled 1070 patients with PH who had undergone heart catheterization with the final study population comprising of 961 cases. ΔP_{TM} was calculated as PCWP minus right atrial pressure. The patients with group II PH had significantly higher ΔP_{TM} values (12.6 $\pm$ 6.6 mmHg) compared to the other groups (1.1 $\pm$ 4.8 in group I, 12.4 $\pm$ 6.6 in group II, 2.5 $\pm$ 6.4 in group III and 0.8 $\pm$ 8.0 in group IV, P<0.001) despite overlapping PCWP values. A ΔP_{TM} cut-off of 7 mmHg identifies left-heart disease when PCWP>15 (area under curve, 0.825; 95% confidence interval, 0.784 to. 0.866; P<0.001). Five-year mortality was significantly higher in patients with high ΔP_{TM} and PCWP subgroup compared to low ΔP_{TM} plus high PCWP (26.1% vs. 18.5%, P=0.027), and low ΔP_{TM} and PCWP subgroups (26.1% vs. 15.6%, P<0.001). ΔP_{TM} has supplementary discriminatory power in distinguishing patients with and without post-capillary PH. In conclusion, a new approach utilizing ΔP_{TM} may improve our understanding of PH pathophysiology and may identify a subpopulation who may potentially benefit from PH-specific treatments.

Keywords: heart failure, hemodynamics, pulmonary capillary wedge pressure, pulmonary vascular resistance, pulmonary hypertension

Introduction

European guidelines on pulmonary hypertension[1] (PH) defines pre-capillary PH as pulmonary vascular resistance (PVR) >2 Wood units, isolated post-capillary (Ipc-) PH as pulmonary capillary wedge pressure (PCWP) >15 mmHg, and the occurrence of both as combined pre- and post-capillary (Cpc-) PH. Despite these seemingly clear-cut definitions, it is challenging to classify patients with such precision in a real-world setting. In many patients, etiologic and hemodynamic profiles may not match as predicted and hemodynamic profile may show changes over time.[2-4] Importantly, adding the diagnosis of post-capillary to pre-capillary PH has important clinical implications.[5] Aside from being diagnosed with a serious comorbidity, these patients are also deprived of PH-specific treatments with the fear of aggravation of the left heart disease (LHD). In LHD, higher LV stretch is needed to maintain a normal stroke volume (SV) in accordance with the Frank-Starling law (Figure 1, A).[6, 7] LV stretch is governed by the LV transmural pressure difference (ΔP_{TM}), which is intracavitary pressure (LV end-diastolic pressure, LVEDP) minus pericardial pressure. Usually, pericardial pressure is low and therefore ignored so that LVEDP is used to characterize LHD.[8] As pericardial pressure is very close to right atrial (RA) pressure and PCWP is nearly equal to LVEDP, actual LV distending pressure can be approximated as ΔP_{TM} = PCWP - P_{RA}.[9-13] Therefore, in the setting of elevated pericardial pressure, LVEDP no longer accurately reflects ΔP_{TM}. This is potentially an important distinction in the setting of PH where right-sided pressures are often elevated (Figure 1, B). In these patients, LV is actually under-stretched and cannot use its full preload-induced contractile potential, but the high PCWP falsely suggests the otherwise. Accordingly, we hypothesize that ΔP_{TM}, rather than absolute PCWP may be a better estimate of LHD and post-capillary PH.

Methods

Hypothetical framework

Since a PCWP above 15 mmHg is the current standard for the diagnosis of LHD that cannot be compared against another gold standard, we proposed a series of sub-hypotheses to prove the additional value of ΔP_{TM}: (1) a fraction of the patients with a high PCWP have a low ΔP_{TM}, (2) the patients with a high PCWP but a low ΔP_{TM} will be more similar to the patients with pre-capillary PH with a low PCWP rather than patients with high PCWP and high ΔP_{TM} in terms of risk factors and clinical picture of LHD, (3) as high PCWP in patients without LHD is due to hypervolemia that aims to increase LV stretch (hence ΔP_{TM}), these patients will have higher RA pressures compared to the patients with LHD and there will be a correlation between ΔP_{TM} and SV in non-group II patients, (4) adding ΔP_{TM} may change the hemodynamic classification in a substantial number of patients, and (5) the patients with Cpc-PH but low ΔP_{TM} may have a lower mortality compared to the patients with Cpc-PH with high ΔP_{TM}.

Study protocol

The study was undertaken at Marmara University, Pendik Training and Research Hospital and Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, both of which are tertiary centers for PH. An ethical committee approval was obtained (Marmara University Ethical Committee, No: 09.2022.1329). Two researchers (D.A. and Ö.Y.) screened electronic hospital records with an International Classification of Diseases, Tenth Revision code related to PH (I.27) between 2015 and 2022. Only patients with available right heart catheterization (RHC) performed by one of the researchers (D.A., E.A, H.A., or Ö.Y.) as the primary operator were included in the study. In patients with multiple RHC procedures, only the first one was included. The exclusion criteria were a mean

pulmonary arterial pressure equal to or >20 mmHg, early (<30 days) post-operative mortality after pulmonary endarterectomy operation and chronic kidney disease requiring dialysis.

In both institutions, all patients were routinely evaluated by a multidisciplinary PH team including a cardiologist, a thoracic surgeon, a pulmonologist, a rheumatologist, and a radiologist. The demographics and laboratory results were retrieved from electronic hospital records (D.A., M.Ö.). A 7F balloon-tipped Swan-Ganz catheter (Edwards Lifesciences, Irvine, USA) was used via the right jugular or femoral vein for RHC. Indirect Fick method was used for cardiac output estimation. Estimated resting $\dot{V}O_2$ was calculated as $\dot{V}O_2$ ($ml.min^{-1}$) = 125 x body surface area (m^2).[14, 15] All pressure tracings were evaluated by visual exploration for physiological accuracy and end-expiratory pressure values were taken. If PCWP pressure tracing was not satisfactory, a direct LV end-diastolic pressure measurement was performed using a pig-tail catheter via retrograde aortic approach.

The PH grouping adjudication was done by the consensus of the multidisciplinary team using all available clinical data including RHC results. A comprehensive approach was followed in accordance with the current guidelines,[1] with a slight modification of the interpretation of RHC results (Table 1). The patients who cannot be classified into one of the 4 isolated PH groups were excluded from the study. The LV transmural pressure difference (ΔP_{TM}) was calculated as PCWP minus right atrial pressure. All patients were managed according to the present-day PH guidelines.[1, 14] We checked the survival status of patients via the national electronic register system.

Statistical Analysis

The SPSS (version 26.0; SPSS Inc., Chicago, IL, US) statistics software was used for all statistical analyses. Continuous variables were expressed as mean ± standard deviation or median (interquartile range [IQR]), categorical variables were expressed in counts (percentages). The normality

of continuous variables was assessed using visual inspection of normal Q-Q plots. Inter-subgroup comparisons were executed using independent *t*-test, Mann-Whitney U test, one-way analysis of variance test and Kruskal-Wallis test, as appropriate. The diagnostic accuracy of ΔP_{TM} to predict the presence of LHD was analyzed using receiver operating characteristics curve analysis in the whole cohort and in the patients with a post-capillary PH component (PCWP >15 mmHg). The cut-off value of ΔP_{TM} for LHD was defined by Youden's J statistic. The correlation between PCWP, ΔP_{TM} and LV-SV was analyzed using Spearman's rank order correlation test. A Cohen's κ test was run to determine if there was agreement between PCWP- and ΔP_{TM}-based hemodynamic classification schemes. The predictive power of PCWP and ΔP_{TM} for 5-year mortality was also analyzed with receiver operating characteristics curve analysis in group II and non-group II PH patients. The cumulative all-cause mortality rates according to PCWP and ΔP_{TM} groups were displayed with Kaplan–Meier plots and compared using log-rank test. For all statistical analyses, a *P*-value <0.05 was considered significant.

Results

Patients

A total of 1070 cases were identified in our database; 92 patients were excluded due to a mean pulmonary arterial pressure equal to or >20 mmHg (n=79), early post-operative mortality after chronic thromboembolic pulmonary hypertension operation (n=8) and a history of chronic kidney disease requiring dialysis (n=5). A total of 17 patients were excluded due to unclear PH group adjudication. Therefore, the final study population comprised 961 cases. The distribution of the patients according to PH subgroups and the etiologic distribution of group I patients were presented in Figure 2. Among group II patients, 310 (75.7%) had HF with reduced ejection fraction, 82 (20.0%) had HF with preserved ejection fraction and 17 (4.2%) had valvular disease. In group IV patients, 156 (51.8%) had

been triaged for pulmonary endarterectomy operation, 36 (11.9%) had undergone pulmonary balloon angioplasty and 100 (33.2%) had been deemed as not candidates for either pulmonary endarterectomy or pulmonary balloon angioplasty. Baseline characteristics are summarized in Table 2. Echocardiographic and invasive hemodynamic parameters are presented in Table 3.

ΔP_{TM} and its distribution across PH groups

The mean ΔP_{TM} was 5.9 ± 8 mmHg in the whole cohort. ΔP_{TM} values were 1.1 ± 4.8 mmHg in group I, 12.6 ± 6.6 mmHg in group II, 2.5 ± 6.4 mmHg in group III and 0.8 ± 8.0 mmHg in group IV. The mean ΔP_{TM} in group II was significantly higher than the other groups (P<0.001). A receiver operating characteristics curve analysis revealed that the best cut-off of ΔP_{TM} to distinguish LHD (adjudicated group II PH) from other PH causes (non-group II PH) was 7 mmHg with a sensitivity of 77.5% and a specificity of 93.1% (area under curve [AUC], 0.924; 95% confidence interval [CI], 0.907 to. 0.941; P<0.001). The same cut-off retains its diagnostic accuracy when the analysis limited to the patients with a PCWP of 15 or above (sensitivity 77.5%, specificity 71.3%; AUC, 0.825; 95% CI, 0.784 to. 0.866; P=0.001).

Subgroups according to ΔP_{TM} and PCWP cut-offs

In the whole cohort, there was a significant correlation between ΔP_{TM} and PCWP (r_s=0.750, P<0.001). In dichotomous comparison with 15 mmHg and 7 mmHg cut-offs for PCWP and ΔP_{TM}, respectively, the agreement between two different classification schemes was good (κ=0.646, P<0.001). Nevertheless, 32.2% of the patients with a PCWP over 15 mmHg had a ΔP_{TM} equal to or lower than 7 mmHg, whereas only 2% of the patients with a low ΔP_{TM} had a high PCWP.

The patients with a high PCWP in groups I and IV had slightly higher ΔP_{TM} values compared to their isolated pre-capillary PH counterparts, but their ΔP_{TM} values were still significantly lower than those observed in group II patients (Figure 3). Furthermore, non-group II patients with a high PCWP but a low ΔP_{TM} show different baseline characteristics compared to group II patients with a high PCWP and ΔP_{TM}. Despite the patients in group II PH being younger (48 ± 12 vs. 63 ± 12, *P*<0.001), they had higher creatinine (1.1 ± 0.5 vs. 0.8 ± 0.3 $mg.dL^{-1}$, *P*<0.001) and lower glomerular filtration rates (84 ± 31 vs. 96 ± 39 $mL.min^{-1}.1.73m^{-2}$, *P*=0.018), were more likely to have hypertension (77.5% vs. 58.2%, *P*=0.002), hyperlipidemia (26.9% vs. %7.3, *P*=0.006), and coronary artery disease (43.5% vs. 20.0%, *P*<0.001) compared to the patients with non-group II PH with high PCWP. They also had lower ejection fractions (28 ± 15 vs. 58 ± 5, *P*<0.001), higher left ventricular mass indexes (157 ± 110 vs. 114 ± 45, *P*=0.003), higher left atrial volume indexes (44 ± 11 vs. 25 ± 13, *P*<0.001) and higher E/e' (0.15 ± 0.11 vs. 0.11 ± 0.05, *P*=0.026) on echocardiogram.

Pathophysiological insight

When the patients with a PCWP >15 compared according to their group II or non-group II classification, non-group II PH patients showed significantly lower ΔP_{TM} values (3.9 ± 6.3 vs. 12.6 ± 6.6 mmHg, *P*<0.001), higher RA pressures (15.5 ± 6.5 vs. 13.7 ± 6.1 mmHg, *P*=0.004), higher SVs (55 ± 17 vs. 45 ± 17 mL, *P*<0.001) and stroke indexes (29.3 ± 9.0 vs. 23.7 ± 8.6 $mL.m^{-2}$, *P*<0.001). In group II PH patients, there was a negative correlation between PCWP and SV (r_s= -0.315, *P*<0.001), and ΔP_{TM} (r_s= -0.155, *P*=0.003). On the contrary, there was no correlation between SV and PCWP (r_s= 0.194, *P*=0.052), but a weak, positive correlation between ΔP_{TM} and SV (r_s= 0.243, *P*=0.014) in non-group II PH patients.

Impact of ΔP_{TM}-based classification on hemodynamic profiles

When PH groups were subdivided according to their hemodynamic profiles, 18% of the patients (173/961) patients were reclassified into a new hemodynamic class, including 8.5% (20/234) of the patients in group I, 22.4% (92/409) of the patients in group II, 23.5% (4/17) of the patients in group III and 18.9% (57/301) of the patients in group IV (Figure 4).

Follow-up

The median follow-up duration was 511 (interquartile range, 752) days. A total of 192 patients died during 5-year follow-up (20.0%). The 5-year mortality rate was 13.7% (32/234) in group I, 25.4% (104/409) in group II, 11.8% (2/17) in group III and 17.9% (54/301) in group IV patients. After the patients were divided into subgroups according to the ΔP_{TM} cut-off of 7 mmHg and the conventional cut-off of 15 mmHg for PCWP, all-cause mortality rate was significantly higher in patients with both high PCWP and ΔP_{TM} subgroup compared to both low PCWP and ΔP_{TM} (26.1% vs. 15.7%, P<0.001) and high PCWP but low ΔP_{TM} subgroups (26.1% vs. 17.4%, P<0.001) (Figure 5).

Discussion

The distinction between isolated pre-capillary and combined pre- and post-capillary PH has important clinical, therapeutic and prognostic implications.[4, 16-18] Although a high PCWP is "the definition" of post-capillary PH and therefore it is very hard to prove its limitations, we believe that the totality of the evidence provided by the current study lends a strong support for our conceptual framework: (1) a substantial percentage of the patients with a high PCWP actually cannot fully use their preload-recruitable potential, as evidenced by low ΔP_{TM} values, (2) the patients with a high PCWP

but a low ΔP_{TM} are more similar to the patients with pre-capillary PH with a low PCWP rather than the patients with high PCWP and high ΔP_{TM} in terms of risk factors and clinical picture, (3) the former patient subset seems to have hypervolemic pre-capillary PH which aims to increase LV stretch to increase SV, as evidenced by higher RA pressures, and the correlation between ΔP_{TM} and SV, (4) adding ΔP_{TM} changes the hemodynamic classification in a substantial number of patients, and (5) the patients with Cpc-PH but low ΔP_{TM} have a lower mortality compared to the patients with Cpc-PH with high ΔP_{TM}.

These results have two important implications: (1) A considerable number of patients, who have been labelled as having LHD because of a high PCWP, actually may not have post-capillary PH and (2) some of the patients with PH and LHD, who are deprived of PH-specific therapies with the fear of aggravating left-sided HF, may potentially benefit from these therapies.

First, although right ventricular failure due to LHD is an established concept, the reverse, apparent LV failure due to right-sided HF, also seems possible. When right-sided pressures are increased, ΔP_{TM} decreases to a point that may limit LV stretch and contractility. The natural pathophysiologic response to this situation is volume sparing, which aims to increase ΔP_{TM} and thus SV. Hence, apparent Cpc-PH in these patients is actually an overvolemic version of precapillary PH. Our results revealed a significant correlation between higher PCWP with lower SVs (as an indication of lower LV contractility) and higher RA pressures (as an indication of hypervolemia) in non-group II PH patients. Correspondingly, this compensatory mechanism seems to reinstate higher ΔP_{TM} values, but did not result in as high ΔP_{TM} values as those seen in group II PH. On the other hand, in group II patients, who already exhausted their stretch-induced contractile reserve, the same compensatory mechanism seems to be insufficient to increase SV and resulted in very high ΔP_{TM} and PCWP levels. Thus, ΔP_{TM} provides additional diagnostic information over PCWP and may more accurately reflect

whether LV actually works at the upper limits of its contractile potential. It is also relatively insensitive to the volume status of the patient, as the opposing sides of the ΔP_{TM} equation are determined by the same volume status.

Second, the ultimate hemodynamic goal of PH-specific therapy is to increase cardiac output. However, according to our view, cardiac output in PH is limited by not only 1 but 2 bottlenecks. While the first and obvious one is the high PVR, the second and overlooked one is the LV, which cannot recruit its stretch-induced contractile reserve because of the external constraint created by the high right-sided pressures. Therefore, PH-specific therapies can only be beneficial in patients with a postcapillary component if (1) they decrease the increased PVR and (2) provide more preload to the under-stretched LV. To our knowledge, none of the studies on PH-specific drugs in patients with HF have focused on these 2 aspects, which may at least partly explain their predominantly negative and conflicting results. Apparently negative studies either did not enroll patients with high PVR[19, 20] or included patients with high baseline ΔP_{TM}.[21-23] The concern of increased risk of therapy-induced pulmonary congestion was further reinforced by a hemodynamic study by Huis In't Veld *et al.*,[24] in which the authors concluded that PH-specific treatment increased SV at the expense of increased PCWP similar to fluid loading. However, ΔP_{TM} and SV significantly increased after PH-specific treatment in this study, but the already high baseline ΔP_{TM} might have limited the benefit of any further increase in preload compared to the increase in PCWP. On the other hand, when baseline PVR was high and ΔP_{TM} was low, PH-specific therapy seems to cause a decrease in PVR, an increase in ΔP_{TM} and an associated increase in cardiac output without any further increase in PCWP.[25, 26] The post-hoc analyses of the AMBITION[27] and GRIPHON[28] trials also suggested that patients with cardiovascular risk factors may benefit from PH-specific combination therapies. Further studies are needed to explore

whether PH-specific therapies decrease mortality in this subgroup. Nevertheless, the drugs with fluid retention effects, such as endothelin receptor antagonists, may need additional caution.[23, 27]

Our study has several limitations. Since the current study was done in 2 tertiary PH centers, the distribution of PH etiology, as well as HF, may differ from the general PH population. We did not adjust for baseline characteristics in mortality prediction, as the power of the study was not adequate, and this could have led to overcorrection. We used indirect Fick method for cardiac output estimation, which may be inaccurate due to incorrect estimation of oxygen consumption, especially in the setting of pulmonary hypertension and heart failure.[30, 31] The close association between RA and pericardial pressures was supported in animal studies with open chest and limited human patients in operative settings[9-13] but has not been specifically studied in PH patients. The association in PH patients requires further mechanistic studies. PCWP sometimes may not reflect true LVEDP and give discrepant results in ΔP_{TM} estimation. Although we used direct LVEDP measurement when PCWP measurement was dubious, we were unable to compare these two approaches. This point must be elucidated in further studies. The ΔP_{TM} cut-off of 7 mmHg needs to be externally tested and validated. Because of the retrospective design of our study, pressure measurements were not done in a blinded fashion, which might have resulted in biased estimations. As a high PCWP with low ΔP_{TM} may indicate a stronger neurohormonal activation and worse right-sided cardiac function, it might have resulted in a similar mortality as seen in patients with LHD.

In conclusion, ΔP_{TM} shows the potential of having supplementary discriminatory power over PCWP to distinguish patients with and without LHD. Since ΔP_{TM} is easily obtainable during routine RHC, we believe that a new approach incorporating ΔP_{TM} into the hemodynamic classification of PH may have a utility in guiding treatment. This new approach may identify a subpopulation who are deprived of PH-specific treatments because of being labelled as having LHD but potentially benefit

from PH-specific treatments. Further studies are needed to explore the potential of ΔP_{TM}-based approach in PH management.

Conflict of interest

None

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Figure legends.

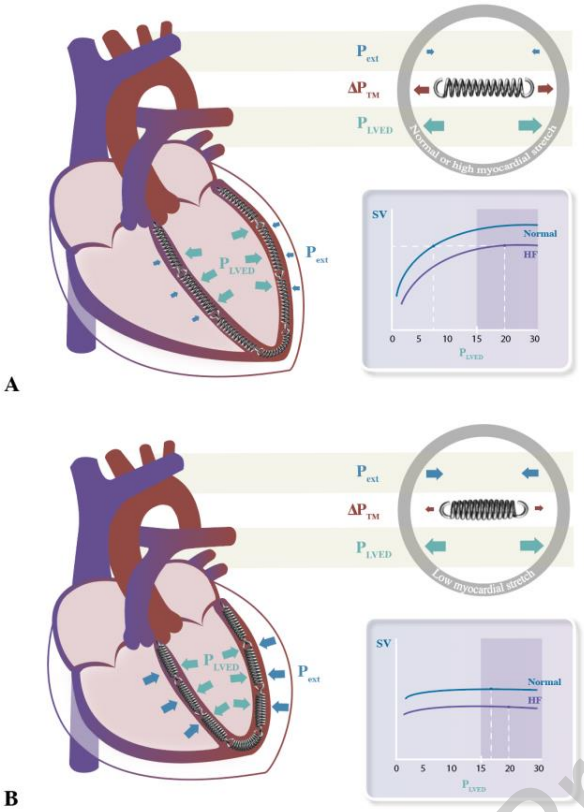


Figure 1. The relationship between left ventricular (LV) stretch, its determinants and stroke volume (SV). LV end-diastolic stretch is determined by the LV transmural pressure difference (ΔP_{TM}) which is the distending left ventricular end-diastolic pressure (P_{LVED}) minus constricting external pressure (P_{ext}), although only P_{LVED} is used as a surrogate for LV end-diastolic wall stretch for simplification in routine practice. **(A)** The Frank-Starling law dictates that LV-SV increases with increasing end-diastolic wall stretch (blue curve). With worsening LV contractility, the Frank-Starling curve becomes flattened (purple curve) and a higher end-diastolic wall stretch becomes necessary for the delivery of the same SV. **(B)** In situations where external pressure is increased, as in right-sided heart failure (HF) associated with pulmonary hypertension, end-diastolic ΔP_{TM} diminishes and LV becomes under-stretched, although PCWP appears to be high. In these situations, P_{LVED} does not represent the actual

Frank-Starling mechanism, therefore should not be used as the surrogate for LV end-diastolic wall stretch. HF, heart failure; P_{ext}, external pressure; P_{LVED}, left ventricular end-diastolic pressure; ΔP_{TM}, transmural pressure difference, SV, stroke volume.

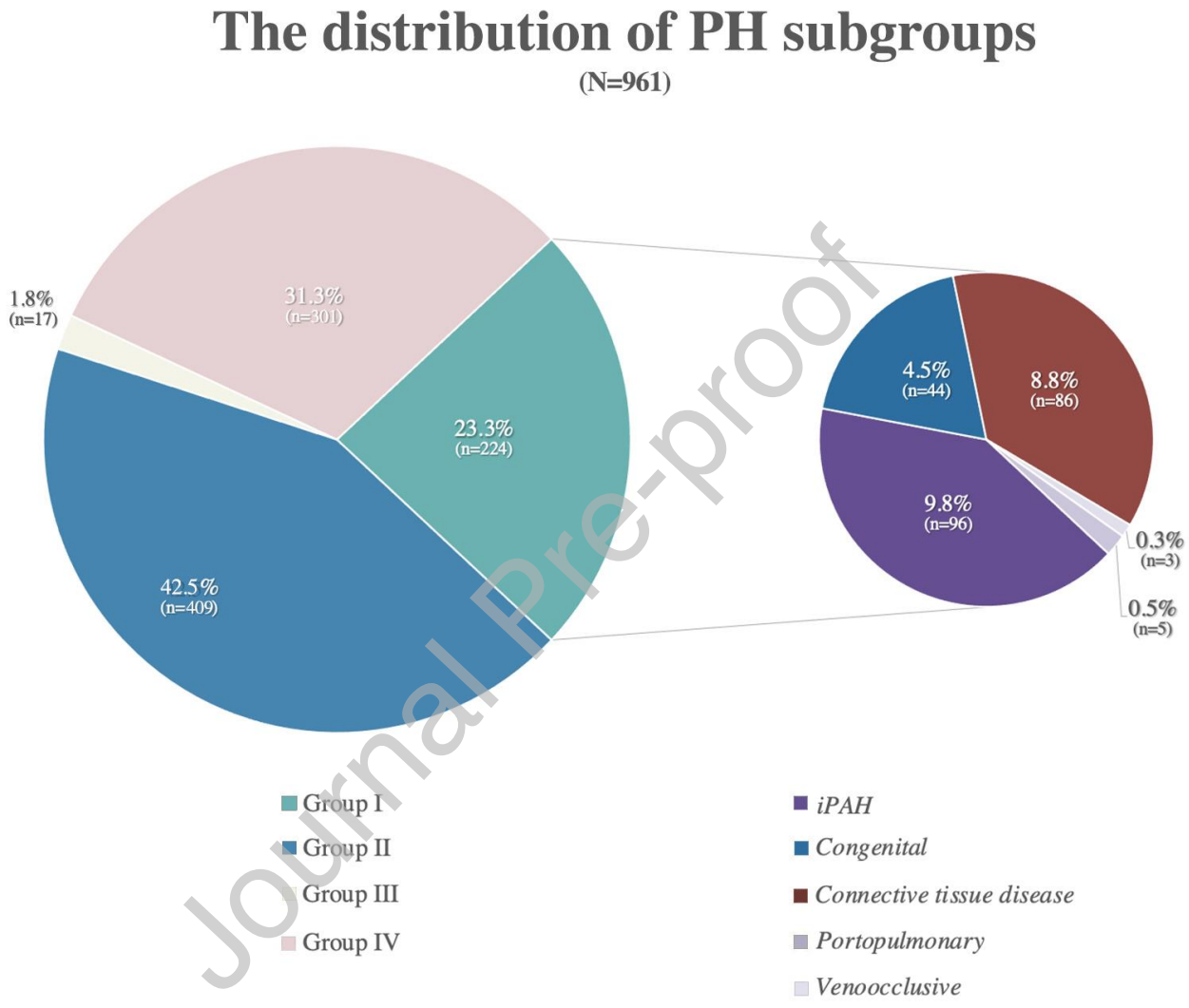
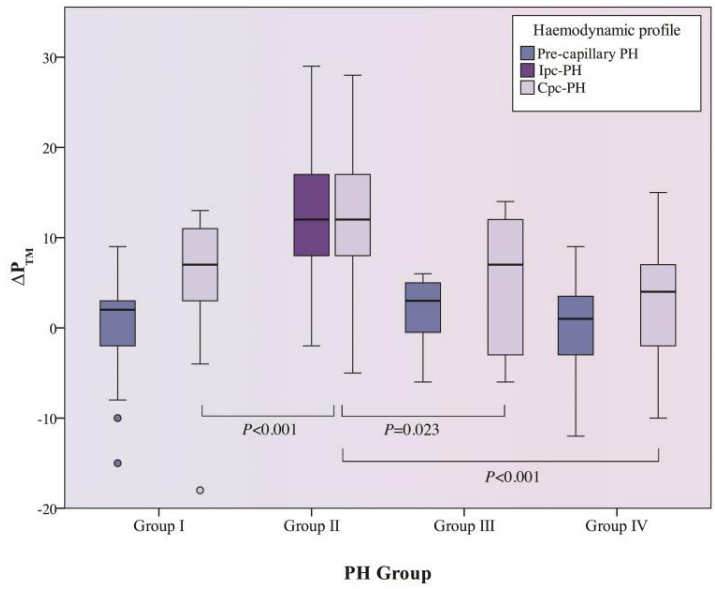


Figure 2. The distribution of pulmonary hypertension subgroups. iPAH, idiopathic pulmonary arterial hypertension; PH, pulmonary hypertension.



ΔP_{TM} (mmHg)

	Pre-capillary PH	Ipc-PH	Cpc-PH	*P*-value
Group I	2 (6)	-	7 (9)	<0.001
Group II	-	12 (9)	12 (9)	0.856
Group III	2 (6)	-	7 (20)	<0.001
Group IV	1 (7)	-	4 (10)	<0.001

Figure 3. Left ventricular transmural pressure difference (ΔP_{TM}) values according to hemodynamic profiles and pulmonary hypertension (PH) groups. Although ΔP_{TM} values in non-group II PH patients with combined pre- and post-capillary PH were higher compared to their isolated pre-capillary PH counterparts, these values were still significantly less than those observed in group II PH patients. ΔP_{TM}, left ventricular transmural pressure difference; Cpc-PH, combined pre- and post-capillary pulmonary hypertension; Ipc-PH, isolated post-capillary pulmonary hypertension; PH, pulmonary hypertension.

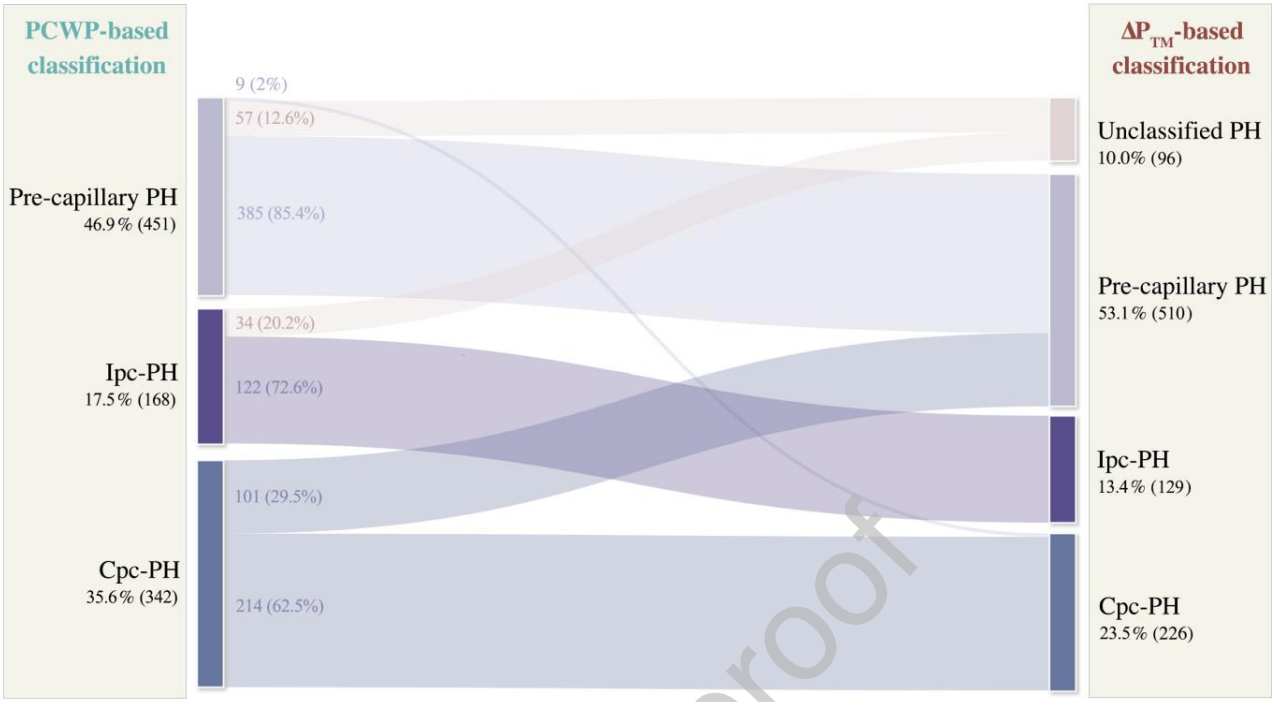
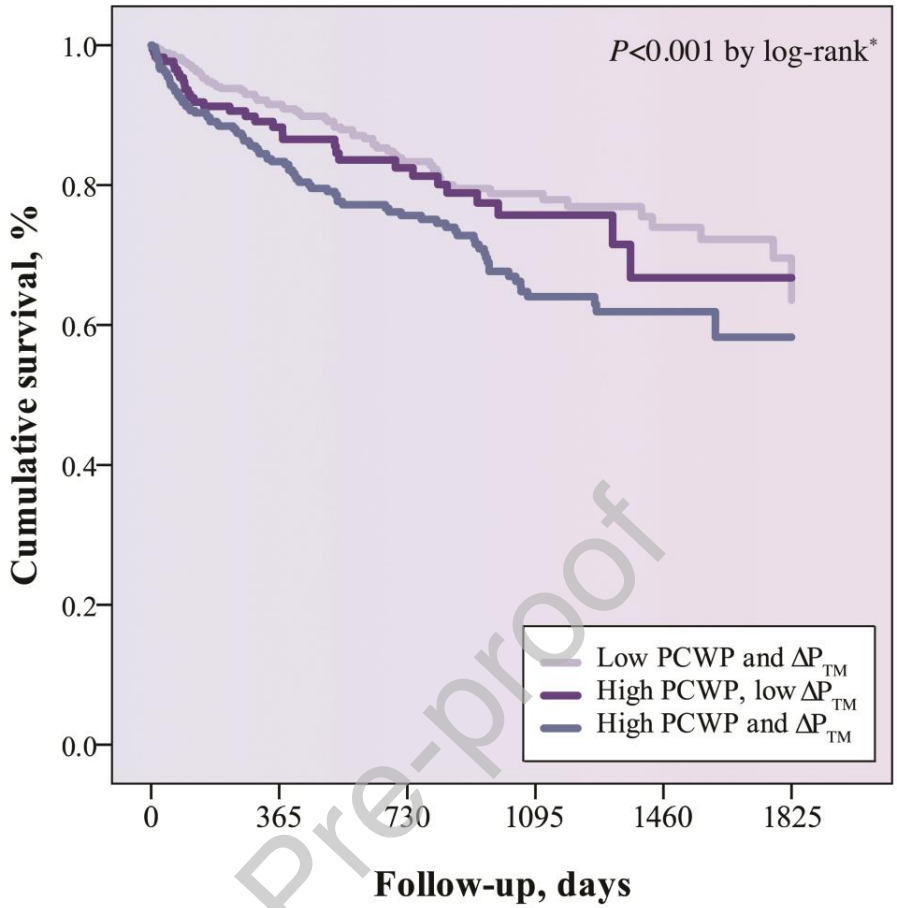


Figure 4. The difference in hemodynamic profile distribution according to pulmonary capillary wedge pressure- (PCWP) and left ventricular transmural pressure difference (ΔP_{TM})-based classifications. Values are median (interquartile range). ΔP_{TM}, left ventricular transmural pressure difference; Cpc-PH, combined pre- and post-capillary pulmonary hypertension; Ipc-PH, isolated post-capillary pulmonary hypertension; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension.



No. at risk

Low PCWP and ΔPTM	483	447	426	417	402	395
High PCWP, low ΔPTM	147	119	115	111	111	110
High PCWP and ΔPTM	336	283	266	249	248	247

Figure 5. Kaplan-Meier mortality curves for 5-year mortality according to pulmonary capillary wedge pressure (PCWP) and left ventricular transmural pressure difference (ΔP_{TM}) cut-offs. ΔP_{TM}, left ventricular transmural pressure difference; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension.

*Mortality was significantly higher in pairwise comparisons of high PCWP and high ΔP_{TM} subgroup with high PCWP and low ΔP_{TM} subgroup (P<0.001) and with low PCWP and low ΔP_{TM} subgroup (P=0.025).

Tables.

Table 1. Pulmonary hypertension group adjudication.*

	Group 1	Group 2	Group 3	Group 4
Clinical features	Demographics, risk factors, symptoms, and/or signs compatible with PAH	Demographics, risk factors, symptoms, and/or signs compatible with PH and LHD	Demographics, risk factors, symptoms, and/or signs compatible with PH and pulmonary disease	Demographics, risk factors, symptoms, and/or signs compatible with PH and CTEPH
Pulse oximetry	Baseline SpO_2>92% in the absence of Eisenmenger syndrome or PVOD	Baseline SpO_2 >92%	Baseline SpO_2 ≤92%	Baseline SpO_2 >92%
PFT	Normal or mildly impaired	Normal or mildly impaired	Severely abnormal	Normal or mildly impaired
DL_{CO}	Normal or mild-to-moderately reduced	Normal or mild-to-moderately reduced	Severely low	Normal or mild-to-moderately reduced
Imaging	Evidence of diffuse periph-	Signs of predominant con-	Imaging evidence of pulmo-	Non-matched defects at V/Q

	eral pruning of peripheral vessels *and/or* Evidence of congenital heart defects with shunt, portal hypertension or PVOD	gestion *and/or* LVEF ≤40% *or* LAVI> 34 mL/m^2 LVMI>149 (men)/122 (women) g/m^2 *or* Severe left-sided valvular disease	nary parenchymal disease	scan *and/or* Evidence of intraluminal pulmonary arterial obstruction on pulmonary CT angiogram after at least 3 months of anticoagulation *and/or* Signs of pulmonary infarction
RHC	PVR>2		PVR>2	PVR>2
	If PCWP>15, should *not* fulfil the imaging criteria for	If PCWP<15 should fulfil the imaging criteria for group 2 without fulfilling	If PCWP>15, should *not* fulfil the imaging criteria for group 2	If PCWP>15, should *not* fulfil the imaging criteria for group 2

	group 2	criteria for other groups

CT, computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; DL_{CO}, carbon monoxide diffusion capacity; LAVI, left atrial volume index; LHD, left heart disease; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PFT, pulmonary function tests; PH, pulmonary hypertension; PVOD, pulmonary venous occlusive disease; PVR, pulmonary vascular resistance; RHC, right heart catheterization; SpO_2, pulse oximeter arterial saturation; V/Q, ventilation-perfusion.

*Adapted from the European Society of Cardiology and European Respiratory Society 2022 guidelines on pulmonary hypertension.[1]

Table 2. Baseline characteristics*

	All (N=961)	Group I (n=224)	Group II (n=409)	Group III (n=17)	Group IV (n=301)
Demographics					
Age, years	52.3 ± 14.9	48.7 ± 15.3	49.3 ± 13.4	61.2 ± 7.9	52.3 ± 14.9
Female, %	438 (45.6)	150 (66.9)	100 (24.4)	9 (52.9)	179 (59.4)
BMI, kg.m^{-2}	28.2 ± 5.9	26.8 ± 5.9	27.9 ± 5.6	28.0 ± 6.5	29.6 ± 5.7
Heart rate, beats.min^{-1}	83 ± 16	82 ± 16	84 ± 18	93 ± 21	81 ± 15
SBP, mmHg	128 ± 26	131 ± 22	122 ± 26	137 ± 23	134 ± 26
Comorbidities					
Hypertension, n (%)	377 (39.2)	61 (27.2)	158 (38.6)	9 (52.9)	150 (49.8)
Diabetes, n (%)	184 (19.1)	20 (8.9)	117 (28.6)	6 (35.3)	41 (13.6)
Dyslipidemia, n (%)	168 (17.5)	17 (7.6)	104 (25.4)	4 (23.5)	43 (14.2)
CAD, n (%)	253 (26.3)	24 (10.7)	175 (42.8)	4 (23.5)	50 (16.6)
CKD, n (%)	86 (8.9)	9 (4.0)	41 (10.0)	1 (5.9)	35 (11.6)
Thyroid disorder, n (%)	113 (11.8)	42 (18.7)	22 (5.4)	3 (17.6)	46 (15.2)
Laboratory parameters					
GFR, mL.min^{-1}.m^{2}	93 ± 42	102 ± 38	84 ± 31	80 ± 21	101 ± 55
Hemoglobin, g.dL^{-1}	13.1 ± 2.0	13.6 ± 1.9	13.0 ± 2.2	13.9 ± 2.8	12.9 ± 1.8
hs-cTnT, ng.L^{-1}	11.6 ± 12.4	11.3 ± 11.9	9.2 ± 10.4	7.0 ± 9	12.6 ± 13.3
NT-proBNP, ng.L^{-1}	757	319	1278	801	422

	(2151)	(1699)	(2356)	(1133)	(1759)
Functional class					
WHO class I, n (%)	163 (17.0)	74 (33.0)	29 (7.1)	1 (5.9)	59 (19.6)
WHO class II, n (%)	410 (42.7)	103 (45.9)	161 (39.6)	6 (35.3)	140 (46.5)
WHO class III, n (%)	316 (32.9)	49 (21.9)	167 (41.0)	9 (52.9)	91 (30.2)
WHO class IV, n (%)	70 (7.3)	8 (3.6)	50 (12.3)	1 (5.9)	11 (3.6)
6MWT, m	329 ± 121	357 ± 122	303 ± 111	184 ± 126	321 ± 117
Treatment					
Supportive therapies					
Anticoagulants, n (%)	535 (55.7)	78 (34.8)	165 (40.3)	5 (29.4)	287 (95.3)
Diuretics, n (%)	733 (76.3)	147 (65.6)	386 (94.4)	8 (47.0)	192 (63.7)
Beta blockers, n (%)	554 (57.6)	89 (39.7)	380 (92.9)	6 (35.3)	79 (26.2)
ACEI/ARBs, n (%)	525 (54.6)	61 (27.2)	356 (87.0)	6 (375.3)	102 (33.8)
Statins, n (%)	167 (17.4)	19 (8.5)	107 (26.2)	1 (5.9)	40 (13.2)
PH-specific therapy					
PDE5i only, n (%)	37 (3.9)	23 (10.3)	6 (1.5)	3 (17.6)	5 (1.6)
ERA only, n (%)	74 (7.7)	73 (32.6)	0 (0)	0 (0)	1 (0.3)
Riociguat, n (%)	258 (26.8)	10 (4.5)	0 (0)	0 (0)	248 (82.3)
ERA + PDE5i or riociguat, n (%)	77 (8.0)	63 (28.1)	0 (0)	0 (0)	14 (4.6)

ERA + PDE5i + PCA, n (%)	26 (2.7)	26 (11.6)	0 (0)	0 (0)	0 (0)
Follow-up					
Days, median (IQR)	514 (774)	529 (837)	511 (840)	175 (257)	533 (706)

* Values are mean ± standard deviation, median (IQR) or number (percentage).

6MWT, six-minute walk test; ACEI/ARB, angiotensinogen converting enzyme inhibitors or angiotensin II receptor blockers; BMI, body-mass index; CAD, coronary artery disease; CCB, calcium channel blockers; CKD, chronic kidney disease; CRP, C-reactive protein; ERA, endothelin receptor antagonists; GFR, glomerular filtration rate; hs-cTnT, high-sensitivity cardiac troponin T; IQR, interquartile range; NT-proBNP, N-terminal pro-brain natriuretic peptide; PCA, prostacyclin analogues; PDE5i, phosphodiesterase-5 inhibitors; PH, pulmonary hypertension; RVEF, right ventricular energy failure; SBP, systolic blood pressure, WHO, World Health Organization.

Table 3. Echocardiographic and hemodynamic parameters*

	All (N=961)	Group I (n=224)	Group II (n=409)	Group III (n=17)	Group IV (n=301)
Echocardiographic parameters					
LVEF, %	60 (5)	60 (5)	50 (10)	65 (0)	60 (0)
LAVI, mL.m^{-2}	16 (8)	16 (9)	22 (6)	18 (6)	15 (6)
RAVI, mL.m^{-2}	21 (8)	24 (10)	17 (5)	23 (3)	21 (7)
LVMI, g.m^{-2}	107 (61)	98 (55)	143 (73)	105 (26)	107(56)
TR V_{max}, m.sec^{-1}	3.9 (0.9)	4.1 (1.1)	3.5 (0.7)	3.9 (1.0)	3.9 (0.9)
sPAP, mmHg	65 (35)	70 (45)	54 (20)	60 (41.5)	70 (35)
TAPSE, mm	18 (7)	17 (8)	21 (4.8)	23 (5.5)	18 (7)
TAPSE/sPAP, mm.mmHg^{-1}	0.28 (0.26)	0.25 (0.29)	0.40 (0.19)	0.42 (0.35)	0.26 (0.24)
RV MPI	0.32 (0.13)	0.31 (0.11)	0.36 (0.07)	0.35 (0.06)	0.31(0.08)
RV TDI S-velocity, cm.sec^{-1}	11 (4)	12 (5)	13 (2)	13 (2.3)	11 (4)
Pulmonary acceleration time, msec	109 (55)	109 (59)	134.5 (45)	143 (10)	109 (55)
Pericardial effusion, n (%)	190 (19.7)	59 (26.3)	45 (11.0)	0 (0)	86 (28.5)
Invasive hemodynamic parameters					
PA systolic pressure, mmHg	60 (32)	60 (46)	55 (27)	57 (22)	66 (37)
PA diastolic pressure, mmHg	25 (15)	25 (19)	27 (15)	29 (17)	25 (14)
PA mean pressure, mmHg	39 (20)	39 (28)	37 (17)	38 (16)	41 (21)
Ao systolic pressure, mmHg	125 (35)	128 (30)	117 (36)	128 (40)	130 (35)
Ao diastolic pressure, mmHg	75 (19)	76 (17)	70 (18)	80 (22)	79 (19)

Ao mean pressure, mmHg	92 (22)	93 (16)	87 (21)	91 (27)	98 (22)
RA mean pressure, mmHg	11 (8)	10 (7)	13 (9)	9 (9)	10 (7)
PCWP, mmHg	15 (15)	10 (5)	25 (10)	14 (12)	11 (4)
PVR, Woods	4.0 (5.5)	5.0 (7.2)	3.0 (3.6)	4.5 (4.2)	6.0 (5.7)
SVR, Woods	19.8 (9.2)	18.5 (7.6)	21.0 (10.4)	19.9 (9.5)	18.4 (9.2)
PVR/SVR	0.2 (0.3)	0.3 (0.4)	0.1 (0.1)	0.4 (0.2)	0.3 (0.3)
SaO_2, %	96 (6)	96 (5)	97 (3)	94 (11)	93 (7)
MvO_2, %	62 (14)	68 (12)	57 (16)	65 (19)	63 (13)
CO, $L.min^{-1}$	4.0 (1.8)	4.5 (1.7)	3.5 (1.7)	3.9 (1.3)	4.5 (1.9)
CI, $L.min^{-1}.m^{-2}$	2.2 (1.0)	2.6 (1.1)	1.8 (0.7)	2.2 (0.7)	2.4 (1.0)
SV, mL	51 (25)	57 (27)	43 (21)	47 (20)	55 (26)
SI, $mL.m^{-2}$	27 (14)	32 (15)	22 (12)	27 (11)	30 (15)

* Values are median (interquartile range) or number (percentage).

Ao, aortic; CI, cardiac index; CO, cardiac output; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MPI, myocardial performance index; MvO_2, mixed venous oxygen saturation; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RA, right atrium; RAVI, right atrial volume index; RV, right ventricular; RVEF, right ventricular energy failure; SaO_2, systemic oxygen saturation; sPAP, estimated systolic pulmonary artery pressure; SI, stroke index; SV, stroke volume; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; TDI, tissue Doppler imaging; TR, tricuspid regurgitation; V_{max}, maximum velocity.

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