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Prognostic value and diagnostic properties of the diastolic pulmonary pressure gradient in patients with pulmonary hypertension and left heart disease

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ABSTRACT

Background: The use of the diastolic pressure gradient (DPG) for the diagnosis of combined post- and pre-capillary pulmonary hypertension (Cpc-PH) versus isolated post-capillary pulmonary hypertension (Ipc-PH) in patients with PH due to left heart disease (PH-LHD) remains controversial. We studied the incremental prognostic information provided by DPG and potential sources of disagreements between different hemodynamic criteria for Cpc-PH.

Methods: We studied 393 patients with PH-LHD who underwent right heart catheterization and were followed for hospitalizations and all-cause mortality for a median of 53 months. Patients were classified into Ipc-PH or Cpc-PH using DPG, pulmonary vascular resistance (PVR) or transpulmonary gradient (TPG)-based criteria.

Results: Classifying PH categories according to DPG alone was not associated with a significant difference in clinical outcomes between patients with Ipc-PH and Cpc-PH ($P = 0.17$). By contrast, PVR criteria alone were associated with a strong prognostic separation between Ipc-PH and Cpc-PH ($P = 0.005$). Adding DPG to the PVR-based classification contributed no additional prognostic information. Classifying PH using the cutoff of DPG >7 mmHg or TPG >15 mmHg, resulted in an almost perfect agreement (κ statistic 0.87; 93.4% agreement). However, in cases of disagreement, occurring with low or negative DPG values, the TPG-based classification was more likely to be correct.

Conclusion: The DPG does not add incremental prognostic information beyond PVR. Using DPG/PVR criteria to differentiate between Ipc-PH and Cpc-PH is equivalent to using TPG/PVR criteria with a TPG threshold >15 mmHg. However, the use of DPG for diagnostic purposes may lead to misclassification of PH when DPG is low or negative.

1. Introduction

Pulmonary hypertension (PH) is a common complication of left heart disease (LHD), often related to disease severity and clinical outcomes [1–4]. Passive backward transmission of filling pressures is the initial mechanism leading to PH. However, a considerable proportion of patients with LHD may develop another superimposed component, combining increased pulmonary vascular resistance (PVR) secondary to complex structural and functional abnormalities in the pulmonary vasculature [5–7]. This "reactive", "out of proportion" or combined pre-and post-capillary PH (Cpc-PH) [8,9] is associated with clinical deterioration and poorer prognosis [5,6,10].

Although accurate differentiation between pre- and post-capillary PH is clinically important, the best hemodynamic definition for pre-capillary PH in the setting of HF has been elusive. In some studies PVR was used to identify high-risk patients with reactive PH [6,11], while others used elevated trans-pulmonary gradient (TPG) [5,10]. These parameters have been criticized as being sensitive to changes in blood flow, stroke volume (SV) and filling pressures [12,13]. Recently, the diastolic pressure gradient (DPG) has been proposed as a better marker of changes in the pulmonary circulation in heart failure [3,13].

Gerges et al. first reported that DPG >7 mmHg was associated with a worse prognosis in a subgroup of patients with increased TPG >12 mmHg [14]. In other recent reports, however, DPG failed to predict mortality in patients with PH-LHD [15,16]. Furthermore, a recent hemodynamic study in patients with heart failure has shown that DPG is not less sensitive to changes in left atrial pressure and SV compared with TPG [17]. These results suggest that the respective value of the TPG

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and the DPG should be further explored, including their role in predicting outcome [3]. We studied the incremental prognostic information provided by DPG in patients with chronic heart failure. We also examined potential sources of disagreements between different hemodynamic criteria for these 2 methods that might lead to misclassification of Cpc-PH.

2. Methods

2.1. Patients

The study population included all consecutive patients diagnosed with HF and functional capacity NYHA ≥2, who were submitted for hemodynamic evaluation by right heart catheterization (RHC) between January 2004 and June 2018. Exclusion criteria consisted of age <18 and acute decompensated HF (evaluation performed when the patient was unstable hemodynamically). The study protocol was performed in conformity with the guidelines established in the Declaration of Helsinki and was approved by the institutional review board of Rambam Health Care Campus.

2.2. Hemodynamic evaluation

All catheterization measurements were performed in the supine position at rest using fluoroscopic guidance in accordance with conventional standard techniques. Pressures were measured using a 7F Swan-Ganz catheter. Cardiac output (CO) was evaluated using the Fick method. Pressure measurements were taken at end expiration. The transpulmonary gradient (TPG) was defined as the difference between the mean pulmonary artery pressure (mPAP) and the pulmonary arterial wedge pressure (PAWP). Diastolic pressure gradient (DPG) was defined as diastolic PAP – mean PAWP, with a value ≥7 mmHg considered elevated, according to recent guidelines [3]. Pulmonary vascular resistance (PVR) was calculated using standard formulas.

2.3. Hemodynamic definitions

Our primary goal was to compare various potential hemodynamic definitions for pre-capillary pulmonary hypertension. Based on the hemodynamic evaluation, the patients were classified into 3 groups as follows: (1) no PH (mPAP ≤25 mmHg), (2) Ipc-PH defined as DPG <7 mmHg and/or PVR ≤3 WU Post-capillary PH, (3) Cpc-PH was defined as PAWP >15 mmHg, DPG ≥7 mmHg and/or PVR >3 WU [9]. We also tested the older hemodynamic definitions of Ipc-PH/Cpc-PH as follows: (1) no PH (mPAP ≤25 mmHg), (2) post-capillary PH (mPAP >25 mmHg, PAWP >15 mmHg and TPG ≤12 mmHg), and (3) Combined post-capillary and pre-capillary PH (Cpc-PH) defined as mPAP >25 mmHg, PAWP >15 mmHg and TPG >12 mmHg [8,18].

2.4. Echocardiography

Right ventricular (RV) systolic function was assessed by echocardiography as previously described [4,19,20]. RV dysfunction was considered to be present if at least mild systolic dysfunction was observed.

2.5. Study endpoints

The primary endpoint was all-cause mortality and readmission for heart failure. Events were confirmed by manual review of patients' records and discharge summaries and review of the national death registry.

2.6. Statistical analysis

Continuous variables are presented as means ± SD or medians and 25th and 75th percentiles; categorical variables are presented as frequencies and percentages. Baseline characteristics of the groups were compared using analysis of variance (ANOVA) for continuous variables and by the χ^2 statistic for noncontinuous variables (or the Fisher exact test, where appropriate). When continuous data were not normally distributed or had unequal variance, groups were compared with the nonparametric one-way ANOVA (Kruskal-Wallis test).

Comparisons of hemodynamic measurements within patients were carried out with the Wilcoxon matched–paired rank–sum test. The relationship between 2 continuous variables was tested by Spearman rank correlation. Cohen kappa statistics were used to summarize the agreement between DPG and TPG-based definitions of Ipc-PH and Cpc-PH.

Event-free survival was estimated by the Kaplan–Meier method, and curves were compared with the log-rank test. Because of the declining numbers of patients at risk, cumulative-incidence plots have been truncated at 60 months. Univariate and multivariate Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for various hemodynamic definitions and variables.

Each variable was tested univariately and then retested after adjustments for other possible confounders in the Cox model. Variables perceived as clinically important and those with $P < 0.05$ in univariable analysis were included in the Cox multivariate model. The following parameters were considered as covariates in the final models: age, gender, estimated GFR (eGFR), hemoglobin level, left ventricular and right ventricular function, RAP, PAWP and type of PH. Backward selection was performed, with a value of $P < 0.2$ as the criterion to remain in the model. The proportional hazard assumption for the Cox Proportional hazards models was evaluated and satisfied by examining plots of Schoenfeld residuals.

In addition, comparison of non-nested models that included either PH categories or other hemodynamic variables was performed by calculating Akaike's information criterion (AIC) and the Bayesian information criterion (BIC), which are a statistical estimate of the trade-off between the likelihood of a model against its complexity, with a lower value indicating a better model [21,22].

Differences were considered statistically significant at the 2-sided $P < 0.05$ level. All statistical analyses were performed using the STATA software version 15.1 (College Station, TX).

3. Results

Between January 1, 2004, and December 31, 2017, 696 patients with chronic LHF underwent RHC. Of these patients, 437 had an elevated PAWP above 15 mmHg. Pulmonary hypertension (mPAP ≥25 mmHg) consistent with PH-LHD was present in 393 (90.0%). Of the PH-LHD patients, 78 (20%) had increased DPG ≥7 mmHg, 173 (44%) had DPG between 0 and 6 mmHg and 142 (36%) had a negative DPG value.

The clinical characteristics and hemodynamics of patients with PH-LHD according to DPG levels are presented in Table 1. PAWP was higher in patients without elevated DPG. mPAP, PVR and TPR were markedly higher in patients with elevated DPG. Supplementary Fig. 1 shows that although there is an overall positive relationship between DPG and PVR, there were many patients with PVR >3 who were with DPG <7 and even with negative DPG.

3.1. Association between hemodynamic definitions of PH and clinical outcomes

The median follow-up time was 53 months (25th and 75th percentile, 49 and 65 months). During follow-up, there were 162 readmissions for heart failure and 176 patients died.

When PH category was classified according to DPG alone, there was no significant difference in readmission for HF and mortality between

Table 1
Clinical and hemodynamic characteristics in patients with elevated pulmonary artery pressure according to the diastolic pressure gradient.

Characteristic	DPG <7 mmHg (n = 315)	DPG ≥7 mmHg (n = 78)	*P* value
Age (years)	67 ± 12	63 ± 14	0.03
Female (%)	177 (56)	42 (54)	0.71
eGFR (ml/min/1.73m^2)	58 [42–76]	56 [37–81]	0.57
Hb (gr/dl)	11.7 ± 1.9	12.7 ± 2.0	0.0001
LVEF <45%	94 (30)	20 (26)	0.46
RV dysfunction	70 (22)	21 (27)	0.38
ICD/CRT	30 (10)	10 (13)	0.39
PAWP (mmHg)	25 ± 6	21 ± 6	<0.0001
mPAP (mmHg)	38 ± 9	48 ± 10	<0.0001
SV (ml)	63 ± 25	59 ± 23	0.18
CO (L/min)	4.5 ± 1.4	4.4 ± 1.5	0.68
Systolic PAP	57 ± 16	74 ± 17	<0.0001
Diastolic PAP	25 ± 6	35 ± 8	<0.0001
PP (mmHg)	32 ± 14	40 ± 16	0.001
PAC (ml/mmHg)	2.4 ± 1.3	1.7 ± 0.9	0.001
PVR (WU)	2.8 ± 1.7	6.0 ± 2.7	<0.0001
RAP (mmHg)	13 ± 6	15 ± 8	0.13
TPG (mmHg)	12 ± 6	27 ± 8	<0.0001
Medical therapy			
Beta blockers	227 (72)	55 (71)	0.79
ACEI/ARB	172 (55)	35 (45)	0.12
MRA	71 (23)	18 (23)	0.92
Diuretics	213 (68)	44 (56)	0.06

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; MRA, mineralocorticoid antagonist; mPAP, mean pulmonary arterial pressure; PAC, pulmonary arterial capacitance; PAWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PP, pulse pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SV, stroke volume; TPG, trans-pulmonary gradient; WU, Wood's unit.

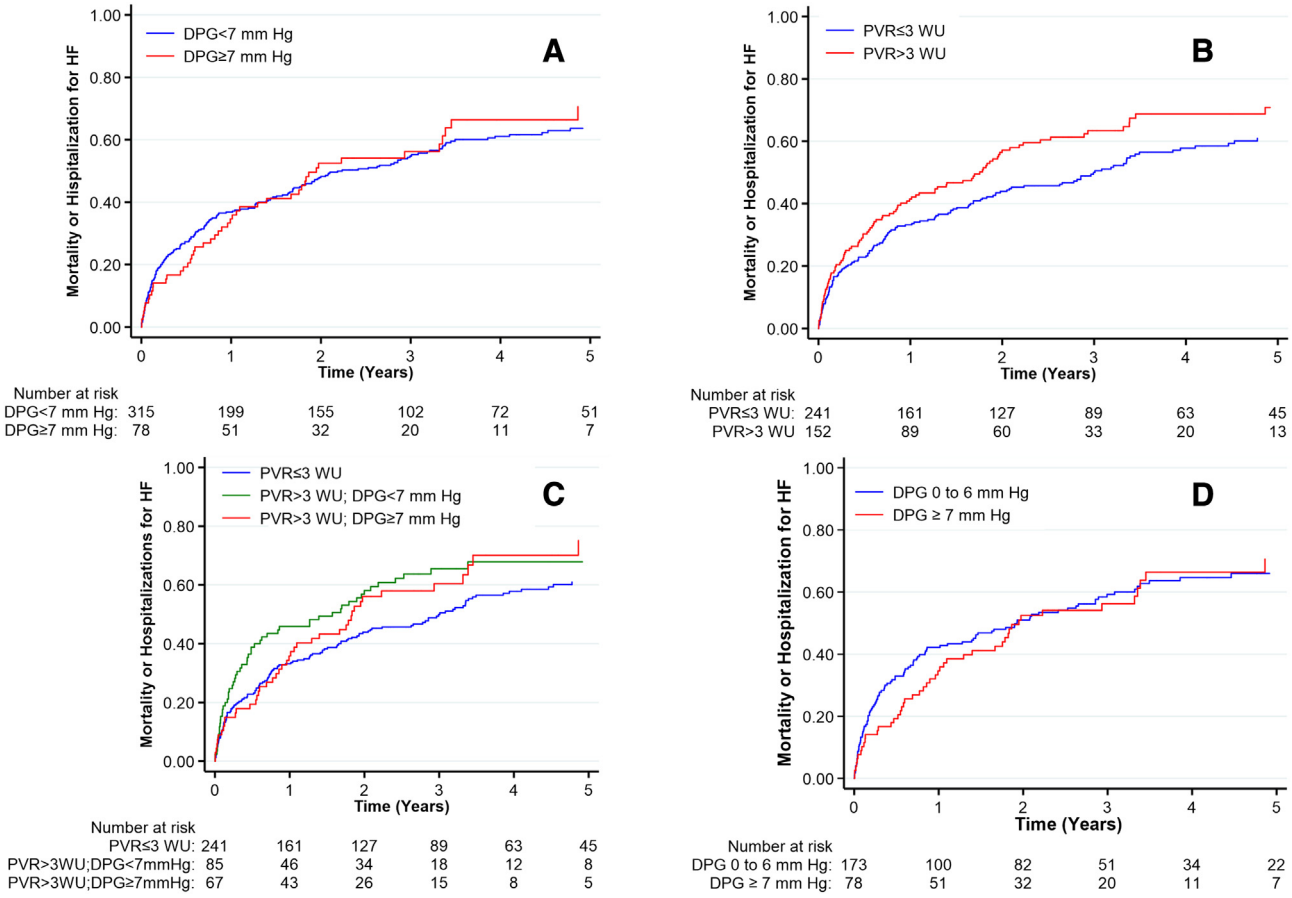

Fig. 1. Kaplan-Meier plot for admission for heart failure or mortality using various classifications of PH in LHD. (A) PH classified according to DPG alone (B) PH classified based on PVR criteria (C) PH classified based on PVR criteria with patients with PVR >3 WU further divided based on DPG above or below 7 mmHg (D) PH classified according to DPG with the exclusion of patients with negative DPG.

patients with Ipc-PH and Cpc-PH (Log-rank $P = 0.39$; Fig. 1A; Table 2, Model 1). By contrast, when PH categories were determined based on PVR criteria alone, patients with Cpc-PH had a worse outcome than patients with Ipc-PH (Log-rank $P = 0.008$; Fig. 1B, Model 2).

Dividing patients with PVR >3 WU based on DPG above or below 7 mmHg contributed no additional prognostic information (Fig. 1C; Table 2, Model 3), indicating that elevated DPG is not associated with worse clinical outcome in PH-LHD patients with elevated PVR.

We also tested the possibility that negative DPG values affect the prognostic information contributed by DPG. After excluding the 142 patients with PH-LHD and negative DPG (i.e., excluded from the DPG <7 mmHg group), there was still no significant difference in clinical outcomes between patients with and without elevated DPG (Fig. 1D; HR 1.02; 95% CI 0.73–1.44; $P = 0.90$ for the comparison between DPG above and below 7 mmHg). Finally, PH classification based on TPG alone showed prognostic differences between Ipc and Cpc in both on univariable and multivariable analyses (Table 2, Model 4). Overall, the model based on PVR criteria alone was most straightforward to differentiate Ipc-PH from Cpc-PH, and had the best model fit as indicated by the lowest AIC and BIC values (AIC and BIC 2603.4 and 2635.2 vs.

Table 2
Unadjusted and Adjusted Proportional Hazards Model for All-Cause Mortality and rehospitalization for heart failure.

Model	Unadjusted		Adjusted	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Model 1: DPG-based PH classification[a]				
Cpc-PH vs. Ipc-PH	1.06 (0.77–1.45)	0.73	1.25 (0.91–1.73)	0.17
Model 2: PVR-based PH classification[b]				
Cpc-PH vs. Ipc-PH	1.38 (1.06–1.78)	0.015	1.46 (1.12–1.87)	0.005
Model 3: PVR and DPG-based PH classification[c]				
Cpc-PH with normal DPG vs. Ipc-PH	1.44 (1.07–1.96)	0.02	1.35 (0.99–1.85)	0.054
Cpc-PH with elevated DPG vs. Ipc-PH	1.29 (0.92–1.82)	0.14	1.65 (1.13–2.25)	0.009
Cpc-PH with elevated DPG vs. Cpc-PH with normal DPG	0.90 (0.61–1.33)	0.58	1.18 (0.78–1.76)	0.43
Model 4: TPG-based PH classification[d]				
Cpc-PH vs. Ipc-PH	1.59 (1.20–2.03)	0.001	1.45 (1.11–1.89)	0.006

[a] Ipc-PH – mPAP ≥25 and DPG <7 mmHg; Cpc-PH – mPAP ≥25 and DPG ≥7 mmHg.
[b] Ipc-PH – mPAP ≥25 and PVR <3 WU; Cpc-PH – mPAP ≥25 and PVR ≥3 WU.
[c] Ipc-PH – mPAP ≥25 and PVR <3 WU; Cpc-PH with normal DPG – mPAP ≥25 and PVR ≥3 WU and DPG <7 mmHg; Cpc-PH with elevated DPG – mPAP ≥25 and PVR ≥3 WU and DPG ≥7 mmHg.
[d] Ipc-PH – mPAP ≥25 and TPG ≤12 mmHg; Cpc-PH – mPAP ≥25 and TPG ≥12 mmHg.

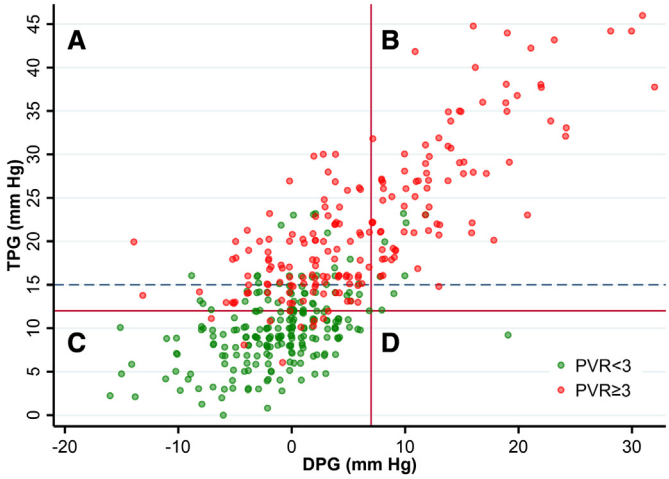

Fig. 2. Plot of the agreement between DPG- and TPG-based classification of Ipc-PH/Cpc-PH categories. Areas B and C show agreement between the 2 sets of criteria. Area A includes patients classified as Cpc-PH by TPG and Ipc-PH by DPG. Area D includes patients classified as Cpc-PH by DPG and Ipc-PH by TPG, green circles indicate PVR<3 WU; red circles indicate PVR> = 3 WU.

2599.6 and 2611.6, respectively for the DPG-based model and PVR-based model). Analyzing only the endpoint of mortality yielded similar results (Supplementary Fig. 2).

3.2. Agreement between DPG and TPG-based definitions of PH

We tested the agreement between PVR/DPG- and PVR/TPG-based definitions of PH categories. Using the DPG ≥7 mmHg and TPG >12 mmHg cutoffs, the κ statistic was 0.70 (95% CI 0.63–0.76) indicating substantial agreement (84.5%) between the 2 definitions of PH subgroups [23]. Disagreement occurred mainly in 59 patients who were classified as Ipc-PH by PVR/DPG criteria and as Cpc-PH by the PVR/TPG criteria (Supplementary Table 1).

Supplementary Fig. 3 shows that the outcome of the disagreement group (patients classified as Ipc-PH by the DPG/PVR criteria and as Cpc-PH by the TPG/PVR criteria) was identical to that of patients with Cpc-PH (rather than Ipc-PH) by both sets of criteria, suggesting that the TPG/PVR-based criteria were the correct classification.

When the cutoff for elevated TPG was increased to >15 mmHg, the κ statistic increased to 0.87 (95% CI 0.82–0.92) indicating an almost perfect agreement (93.4%) [23]. The disagreement in patients classified as Ipc-PH by PVR/DPG criteria and as Cpc-PH by the PVR/TPG criteria decreased from 59 to 24 patients (Supplementary Table 1).

Fig. 2 shows the agreement between individual DPG and TPG measurements in the context of PVR values. In area B (Cpc-PH) and C (Ipc-PH), using DPG or TPG leads to the same PH classification. There was 1 case in which a high DPG suggesting Cpc-PH was associated with a low TPG (Fig. 2, Area D). Therefore, disagreement between the DPG and TPG occurred predominantly with cases where TPG values were high, suggesting Cpc-PH, but DPG values were low or even negative (Fig. 2, Area A). In the majority of these cases (and especially when the TPG cutoff is >15), the PVR was ≥3 WU (Fig. 2, Area A, red dots), indicating that the TPG-based classification was more likely to be correct.

4. Discussion

The current classification of PH-LHD favors the use of DPG/PVR criteria to differentiate Ipc-PH from Cpc-PH [9] over the classical assessment using TPG/PVR criteria [8]. This transition was based on a small number of studies, [14] as well as on theoretical considerations, favoring DPG to identify the presence or absence of pulmonary vascular disease (PVD) in patients with PH-LHD [13].

We studied the sources of disagreement between these 2 methods as well as the incremental prognostic information provided by DPG over PVR in patients with chronic heart failure. With regard to the association with clinical outcome, PVR was the primary hemodynamic determinant of clinical outcome in patients with PH-LHD. DPG alone or in addition to PVR provided no additional prognostic information. In addition, the classification of patients into Ipc–PH or Cpc–PH based on the PVR/DPG or PVR/TPG criteria was almost identical when elevated TPG was defined as >15 mmHg. Furthermore, misclassification of PH category may occur in a subset of patients when the DPG is low or negative (suggesting Ipc-PH) and PVR is elevated. The likely diagnosis, in this case, is Cpc-PH (rather than Ipc-PH) and the TPG remains elevated.

4.1. DPG and clinical outcomes in LHD

Although recommended by recent guidelines for the differentiation of Ipc-PH and Cpc-PH [9], and supported by several studies [14,24], the diagnostic and prognostic value of DPG remains controversial given the conflicting results on the relationships between DPG and clinical outcomes. The lack of prognostic value of elevated DPG in the present study is consistent with several recent reports [6,15,16,25–27]. Tampakakis et al. showed in a large sample of patients with PH-LHD that the DPG did not discriminate survivors from nonsurvivors [15]. Tedford and colleagues demonstrated that an elevated DPG had no effect on post-transplant survival in patients with PH and an elevated TPG and PVR [16]. More recently, Assad et al. reported similar mortality in Cpc-PH and Ipc-PH when defined by using DPG but increased mortality in Cpc-PH defined according to PVR alone [25]. Vanderpool et al. found that PVR >3 WU carried a higher risk for mortality compared with TPG >12 mmHg and DPG ≥7 mmHg. In addition, DPG ≥7 mmHg was not associated with cardiac hospitalizations [28]. Finally, Al-Naamani et al. reported in patients with HFpEF, that elevated DPG was associated with a similar outcome as normal DPG [26]. ROC analysis demonstrated that the area under the curve for DPG was 0.50, implying that there was no DPG cutoff that predicts clinical outcome.

Wright et al. investigated the effect of QRS-gated PAWP measurement within late diastole (at the onset of the QRS) on DPG calculation. With this approach, which minimizes the influence of systolic V waves, the average DPG was higher, a larger proportion of patients were diagnosed as having Cpc–PH, and fewer patients had negative DPG values [29]. However, mortality was not different during 1-year follow-up based on the reclassification categories.

4.2. DPG as a diagnostic indicator of pulmonary vascular remodeling

It has been argued that the value of the DPG is mainly diagnostic of the presence of PVD (rather than prognostic) [30]. In a hemodynamic study in patients with heart failure, we have recently shown similar responses of DPG and TPG to changes in filing pressures and SV [17]. The DPG does not directly reflect the hemodynamic stress on the RV or its ability to adapt to pressure overload. However, if elevated DPG indicates the presence of PVD, it should be associated with poor outcome, because pulmonary vascular remodeling affects both the resistive and pulsatile load on the right ventricle [10]. Other indicators of PVD such as PAC strongly predict outcome in PH-LHD [10,26]. Indeed, any measure of Cpc-PH is expected to be associated with poorer outcome, [5].

The 5th World Symposium on Pulmonary Hypertension proposed that a DPG ≥7 mmHg alone should define Cpc-PH [3]. In the current European guidelines, Cpc-PH may be diagnosed when either PVR or DPG are elevated [9]. These definitions may lead to ambiguous conclusions. For example, a patient with PVR 2.5 WU and DPG of 8 mmHg may be classified as Ipc-PH based on PVR value and as Cpc-PH based on DPG values.

Our results demonstrate that in terms of the diagnostic value of DPG in differentiating Ipc-PH from Cpc-PH, the transition from TPG/PVR criteria [31] to the current DPG/PVR criteria [9] was equivalent to increasing the

TPG threshold for Cpc-PH to 15 mmHg, a threshold previously used to define "mixed" or "out-of-proportion" PH due to LHD [32,33].

Our data suggest that misclassification of PH category may occur in a subset of patients when the DPG is low or negative, suggesting Ipc-PH. If PVR is concomitantly elevated, the clinical outcome is similar to that of patients with Cpc-PH (rather than Ipc-PH) by both sets of criteria. Furthermore, given that many of these patients had negative DPG values, it is likely that these patients would be correctly classified as Cpc-PH by TPG/PVR or by PVR alone. In some of these cases, misclassification may arise by overestimation of PAWP (and hence lower DPG) with standard practice [29]. Finally, these results are consistent with the most recent recommendations outlined in the Proceedings of the 6th World Symposium on Pulmonary Hypertension, namely to relay on PVR ≥3 WU for the diagnosis of Cpc-PH [34].

4.3. Study limitations

Our study has some limitations that merit emphasis. First, the present analysis is retrospective and thus the results must be regarded as hypothesis generating and exploratory and require validation in other studies. Some negative DPG may have been the result of measurement errors [35], shifting patients from a high to low DPG. However, negative DPG values are also common when based on left ventricular end diastolic pressure measurements [36], and direct left atrial pressure measurements yield only slightly higher calculated DPG values than PAWP [37].

Our study lacks any dynamic hemodynamic measurements which might shed light on some perceived advantages of DPG over TPG. For example, by dynamically changing the cardiac output, may allow determining whether TPG is more sensitive to changes in stroke volume and filling pressures then DPG [13,14].

Finally, during the writing of this manuscript, the definitions of Ipc-PH and Cpc-PH were changed, with a reduction of the mPAP threshold for diagnosis of PH to >20 mmHg [34]. Analysis of 47 patients with mPAP between 21 and 25 mmHg and PAWP>15 mmHg demonstrated that these patients had low PVR and other hemodynamic characteristics of Ipc-PH by both DPG and TRG criteria. Therefore, the inclusion of these patients would not have changed the study conclusions.

4.4. Conclusions

We found no evidence for any incremental prognostic information provided by DPG. Using the conventional DPG >7 mmHg for the diagnosis of Cpc-PH is similar to using TPG >15 mmHg. However, the use of DPG for the diagnostic purposes may lead to misclassification of PH when DPG is low or negative. PVR-based criteria were the best prognostic discriminators between Ipc-PH and Cpc-PH.

Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.05.016.

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