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Authors

Tampakakis, Emmanouil
Leary, Peter J
Selby, Van N
et al.

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The Diastolic Pulmonary Gradient (DPG) does not Predict Survival in Patients with Pulmonary Hypertension due to Left Heart Disease (PH-LHD)

Emmanouil Tampakakis, MD[*], **Peter J Leary, MD MS**[†], **Van N Selby, MD**[‡], **Teresa A De Marco, MD**[‡], **Thomas P Cappola, MD ScM**[§], **Michael G Felker, MD MHS**[‖], **Stuart D. Russell, MD**[*], **Edward K. Kasper, MD**[*], and **Ryan J Tedford, MD**[*]

[*]Division of Cardiology, Department of Medicine Johns Hopkins Medical Institutions, Baltimore, Maryland [†]University of Washington, Division of Pulmonary and Critical Care, Seattle, Washington [‡]Division of Cardiology, University of California San Francisco, San Francisco, California [§]Penn Cardiovascular Institute, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania [‖]Division of Cardiology, Duke University Medical Center, Durham, North Carolina

Abstract

Objectives—To evaluate if diastolic pulmonary gradient (DPG) can predict survival in patients with pulmonary hypertension due to left heart disease (PH-LHD).

Background—Patients with combined post- and pre-capillary PH-LHD have worse prognosis than those with passive pulmonary hypertension. The transpulmonary gradient (TPG) and pulmonary vascular resistance (PVR) have commonly been used to identify high-risk patients. However, these parameters have significant shortcomings and do not always correlate with pulmonary vasculature remodeling. Recently, it has been suggested that DPG may be better marker, yet its prognostic ability in patients with cardiomyopathy has not been fully assessed.

Methods—A retrospective cohort of 1236 patients evaluated for unexplained cardiomyopathy at Johns Hopkins Hospital was studied. All patients underwent right heart catheterization and were followed until death, cardiac transplantation or the end of the study period (mean time 4.4 years). The relationships between DPG, TPG or PVR and survival in subjects with PH-LHD (n=469) were evaluated with Cox Proportional Hazards Regression and Kaplan Meier analyses.

Results—DPG was not significantly associated with mortality (HR 1.02; p=0.10) in PH-LHD whereas elevated TPG and PVR predicted death (HR 1.02, p=0.046 and HR 1.11, p=0.002,

Address for correspondence: Ryan J. Tedford, MD, Assistant Professor of Medicine, Division of Cardiology, Department of Medicine, Johns Hopkins Medical Institutions, 568 Carnegie; 600 North Wolfe Street, Baltimore, MD 21287, +1-410-955-7534, +1-410-955-3478 (fax), ryan.tedford@jhmi.edu.

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respectively). Similarly, DPG did not differentiate survivors from non-survivors at any selected cutpoints including a DPG of 7mmHg.

Conclusions—In this retrospective study of patients with cardiomyopathy and PH-LHD, an elevated DPG was not associated with worse survival.

Keywords

Diastolic pulmonary gradient; pulmonary hypertension; left heart disease; survival

Introduction

Patients with pulmonary hypertension (PH) due to left heart disease (defined as pulmonary capillary wedge pressure (PCWP) >15mmHg and mean pulmonary artery pressure (mPAP) ≥25mmHg) have worse prognosis compared to those without PH (1). Among those patients with PH, two phenotypes have been described: 1) a group of isolated post-capillary (IpcPH) or “passive” PH in which elevated pulmonary pressures are reversible and in proportion to increases in left atrial pressure, and 2) a group with “pre-capillary” component (combined post-capillary and pre-capillary PH) whose pulmonary hypertension is worse than can be fully explained by passive elevation secondary to elevated left atrial pressure. This latter group may have comorbid pulmonary vascular remodeling and therefore may demonstrate persistent PH after interventions to lower left sided filling pressures. The ability to accurately define and separate a high-risk subgroup has major implications in the management and outcomes of heart failure patients as those with combined post-capillary and pre-capillary PH (CpcPH) due to left heart disease (PH-LHD) have worse prognosis (1,2) and may not be suitable for cardiac transplantation (2).

In an effort to better characterize the two populations, several hemodynamic parameters have been used. A transpulmonary gradient (TPG: mPAP-PCWP) >12–15mmHg and a pulmonary vascular resistance (PVR: TPG/cardiac output) >2.5–3 Wood units (WU) have been used to describe patients with “out of proportion” or those with a pre-capillary component to PH (1). TPG however, is flow-dependent (3) and influenced by elevation in left atrial pressure (4), making it an unreliable marker of the pulmonary vascular contribution to PH-LHD. Although not without limitations, most favor PVR to identify high risk patients. Our group and others have shown that elevated PVR predicts outcomes in patients with PH-LHD better than TPG (5–7).

More recently diastolic pulmonary gradient (DPG: diastolic PAP minus PCWP) has been proposed to distinguish CpcPH from IpcPH (3,8). Elevated DPG (≥7mmHg) may be associated with pulmonary vascular remodeling and predict worse survival in individuals with elevated TPG and PH-LHD (9). We have previously shown, however, that DPG is not associated with death after heart transplant, which may call into question the assertion that DPG is a strong marker of intrinsic pulmonary vascular disease in PH-LHD (10). In this study, we sought to determine whether an elevated DPG predicted survival using a cohort of 1236 patients previously evaluated for unexplained cardiomyopathy (5).

Methods

Patients

Study subjects included inpatients and outpatients referred to the Johns Hopkins Hospital Cardiomyopathy Service for further evaluation of heart failure due to undiagnosed cardiomyopathy. All patients received treatment of their heart failure prior to undergoing right heart catheterization and biopsy. A total of 1236 patients were evaluated between December 1982 and December 1997 as previously described (11). All patients underwent extensive work up which included endomyocardial biopsy with right heart catheterization by a heart failure cardiologist and coronary angiography when indicated. After the evaluation, all patients were assigned a cause of cardiomyopathy. Age, gender, race, height and weight were recorded at the time of their initial evaluation. The patients were followed until death, cardiac transplantation or the end of the study period (January 1, 1998). Vital status was obtained from medical records and through a search of the Nation Death Index (12). The study was approved by the Joint Committee on Clinical Investigation at Johns Hopkins Hospital. All patients provided informed consent to use their data in the study.

Right heart catheterization

Patients underwent right heart catheterization by heart failure specialists at the Johns Hopkins catheterization laboratory with a balloon-tipped, flow-directed catheter placed into the right internal jugular vein. Hemodynamics were measured at the time of presentation before optimizing medical therapy. Cardiac output (CO) was determined as the mean of 3 to 5 separate measurements with the thermodilution method. Systemic arterial pressure was measured noninvasively. Mean right atrial pressure, systolic pulmonary artery pressure (sPAP), diastolic pulmonary artery pressure (dPAP), mean pulmonary artery pressure (mPAP), and pulmonary capillary wedge pressure (PCWP) were recorded at end expiration. Pulmonary vascular resistance (PVR) was calculated in Wood units as the difference between mPAP and PCWP divided by CO. Transpulmonary gradient (TPG) was calculated as the difference between mPAP and PCWP. Diastolic pulmonary gradient (DPG) was calculated as the difference between the dPAP and PCWP.

Statistical Analysis

Comparison of groups were performed with Mann-Whitney rank-sum test or, for multiple groups, by 1-way ANOVA. Categorical variables were compared with chi-squared test. Hazard ratios of death for DPG, TPG and PVR were estimated with Cox Proportional Hazards regression analysis in all patients with PH-LHD (PCWP >15mmHg and mPAP ≥25mmHg). The primary endpoint was death from all causes. Participants who underwent transplantation (n=36 of 469) were censored at the time of transplantation. Unadjusted and adjusted models for age, gender, race and body mass index were considered. For our sample size (n=469) and mortality rate (43%), we had adequate power (80%) to detect a 10% or smaller difference in the hazard of death for all of the evaluated hemodynamic parameters. While we might have been underpowered to detect smaller differences in the hazard of death, such small difference in mortality would argue against the use of these parameters to discriminate survivors. Survival was also estimated with the non-parametric methods of Kaplan and Meier and compared using the log-rank test. A *p*-value (two-tailed) of <0.05 was

considered significant. Medians are presented with interquartile range. Statistical analyses were performed using STATA version 12 (Stata Corp, Texas) and SigmaPlot version 11.0 (Systat Software Inc, San Jose, CA).

Results

Study population

Among 1236 patients who were evaluated with a right heart catheterization for a new diagnosis of heart failure, 1174 had a complete set of hemodynamics. Most patients had diagnosis of a dilated cardiomyopathy. Of the 1174, 558 had an elevated PCWP >15mmHg. Of those, 469 had mPAP ≥25mmHg consistent with PH-LHD. 650 patients did not have PH (mPAP <25mmHg). Of the 1174 patients, 124 (10.6 %) had a DPG ≥7mmHg, and of those, 92 (74.2%) also had PH and 62 (50%) had PH-LHD. Therefore, 32 patients without PH (mPAP < 25mmHg) had a DPG ≥ 7 mmHg. In addition, 355 (30.2%) of all patients evaluated and 169 (36%) of the subjects with PH-LHD had a negative DPG value. The clinical characteristics and hemodynamics of those patients with a negative DPG are found in Supplemental table 1. On average, the negative DPG group had worse hemodynamics as evidenced by lower right and left ventricular stroke work index and higher PCWP.

The association between DPG, TPG, or PVR and death in PH-LHD

DPG was not significantly associated with mortality in unadjusted (HR 1.02; p=0.08) analysis or after adjusting for age, gender, race and body mass index (HR 1.02; p=0.10) (Table 1). TPG was associated with mortality in unadjusted (HR 1.02; p=0.03) and was borderline significant after adjustment (HR 1.02; p= 0.046). PVR predicted mortality in our cohort (unadjusted HR 1.13, p=0.002, adjusted HR: 1.11, p=0.002) (Table 1). Because DPG, TPG and PVR have different units, qualitative comparison of hazard ratios per unit change is difficult. Re-parameterization of markers by interquartile range allowed comparison between markers. The hazard of mortality appeared more similar in this context; however, the strength of association with re-parameterization is not changed and the association with mortality remained strongly significant for PVR, of borderline significance for TPG, and not significant for DPG.

Survival in patients with PH-LHD and elevated DPG

In keeping with the results of the Cox analysis, there was no statistical difference in mortality between high (defined as ≥1, ≥3, ≥5, ≥7, or ≥9mmHg) and low DPG groups (<1, <3, <5, <7, or <9mmHg) (Table 2). We further examined the cut-off of 7mmHg, which has previously been shown to be a surrogate marker for CpcPH (9) and has been proposed for clinical use (8). Demographic, diagnostic and hemodynamic data for those subjects (DPG<7 and DPG ≥ 7mmHg) as well as the 650 patients without PH are presented in Table 3. Demographic and heart failure diagnosis were similar between the high and low DPG groups. Compared with the lower DPG group (<7mmHg), patients with DPG ≥7mmHg had higher systemic and pulmonary artery pressures, higher right and left ventricular stroke work index and higher PVR. Patients with a lower DPG had a higher PCWP (26 vs. 22mmHg – p<0.001). No difference in survival between the two groups at a mean follow up time of 4.4 years was observed (Figure 1A).

Survival in patients with PH-LHD and elevated TPG or PVR

After exploring various TPG cut-off points (high defined as >6, >9, >12, or 15mmHg and low defined as ≤6, ≤9, ≤12, or ≤15mmHg), a TPG >9mmHg significantly differentiated survivors from non-survivors (Table 4). In a sub-cohort of patients with TPG >12 mmHg (n=151), higher DPG (≥7 mmHg) was not associated with increased mortality (Figure 1B).

All PVR cutpoints explored (low defined as <2, <2.5, <3, or < 3.5 and high defined as ≥2, ≥2.5, ≥3, or ≥3.5WU) predicted worse survival in the original cohort (Table 4). In exploratory models, PVR was considered as an effect modifier of the relationship between DPG or TPG and death. PVR did not significantly modify the association between TPG and death (p-interaction= 0.13). PVR did modify the association between DPG and death such that increasing DPG decreased the hazard of death at high levels of PVR (p-interaction=0.02; hazard ratio of the interaction term=0.98). Similarly, Figure 1C suggests that in subjects with PVR ≥3mmHg (n=179), those subjects with a low DPG (<7mmHg) trended towards worse survival compared with high DPG (≥7mmHg) (p=0.051). The number of participants at-risk in these exploratory subgroup analyses was relatively small and estimates of association may be unstable.

Removing patients with HIV diagnosis (who had an overall worse prognosis during this study period), those with an infiltrative disease (amyloid/sarcoid), and those with a diagnosis of restrictive cardiomyopathy left a cohort of 419 PH-LHD patients. DPG also did not predict survival in this cohort (Supplemental Table 2).

Discussion

In the present study, we used a well characterized, large cohort of patients previously evaluated by the cardiomyopathy service at Johns Hopkins Hospital with right heart catheterization and cardiac biopsy (5), to assess the ability of DPG to predict mortality. DPG used independently or in combination with elevated TPG or PVR and in either unadjusted or adjusted analyses, failed to predict mortality in patients with PH-LHD. Conversely, PVR was associated with decreased survival in all analyses in subjects with PH-LHD, similar to prior analyses (6,7,13).

In PH due to left heart disease, elevated left heart filling pressures are transmitted to the pulmonary veins and lead to increased diastolic PAP. Persistent pulmonary venous congestion results in endothelial dysfunction with decreased nitric oxide production, increase production of vasoactive factors (endothelin 1, angiotensin II etc) favoring vasoconstriction and may ultimately lead to irreversible remodeling of the pulmonary vasculature (8,14). Elevation in left atrial pressure also leads to increased vascular stiffness (decreased compliance). This results in an increased systolic PAP, and therefore mPAP, leading to elevation of TPG as well as PVR (4, 14). Both of these factors depend on the flow (cardiac output) (3). The diastolic PAP however is less sensitive to these effects, and therefore DPG (diastolic PAP minus PCWP) has been recommended as an alternative and more reliable marker of PH-LHD with a pre-capillary component (8).

The prognostic capability of DPG in patients with CpcPH was recently evaluated in a cohort of 1094 patients with PH-LHD. In this study by Gerges et al., participants with a TPG >12mmHg and a DPG ≥7mmHg had worse survival compared to those with a TPG ≤12mmHG and a DPG <7mmHg. In 18 of these participants, lung tissue was evaluated and participants with elevated DPG had advanced remodeling of the pulmonary vasculature (9). This study coupled with sound physiologic reasoning has led to the recent recommendations from the Fifth World Symposium on Pulmonary Hypertension that DPG be the sole discriminator of pre- and post-capillary PH in those with left heart disease (8). Our heart failure cohort was significantly different from the study population of Gerges et al. as it had relatively lower incidence of PH (44% vs. 91%) Our patients were also younger and were less likely to have an ischemic cardiomyopathy. When considering only the PH-LHD patients, the distribution of CpcPH (TPG > 12mmHg) was relatively similar (32 vs. 45%).

Using the United Network of Organ Sharing (UNOS) database, we recently demonstrated that elevated pre-transplant DPG had no association with post-transplant survival (10). These findings argued against DPG as a marker of clinically significant irreversible pulmonary vascular remodeling, although they did not necessarily exclude the possibility that DPG could predict outcomes in a heart failure population that did not undergo transplant. Unfortunately, the findings of our current study do not support the use of DPG in this regard. DPG was not associated with survival in any analysis and high DPG may have even been a marker of better prognosis in an exploratory subgroup of CpcPH with high PVR. The lack of association or even inverse association with mortality may be related to the important observation in our cohort that low DPG may have identified a sicker group of patients with a higher PCWP and lower systemic blood pressure. This was true in both the entire cohort of 1174 patients as well as those only with PH-LHD.

Despite its promise, the use of DPG has significant shortcomings and limitations. The DPG may be particularly susceptible to technical errors. Measurement of diastolic PAP, particularly when using fluid filled catheters, is subject to error from catheter motion artifacts. This likely accounts for the negative DPG values observed in our study as well as others. In a study of critically ill patients by Wilson and colleagues, the DPG was negative in 18.5% of the readings (15). Similar results have been reported after coronary artery bypass surgery (16). Moreover, in a classic investigation by Harvey et al., patients with left heart disease had a mean DPG of −2mmHg (17). Even small errors in the measurement of diastolic PAP or PCWP will have a major impact on the DPG given its relatively low absolute value. As previously highlighted by Ryan et al., the use of computerized mean PCWP pressures averaged throughout the respiratory cycle rather than end-expiratory measurements leads to an underestimation of the true PCWP, particularly in patients with higher intrathoracic pressures (18). In addition, inaccurate wedging of the pulmonary artery catheter can overestimate PCWP leading to falsely low DPG. Finally, DPG itself accounts for only a small proportion of total right ventricular load in patients with PH-LHD and therefore may not be necessarily associated with significant RV dysfunction. Right ventricular function is a well known prognosticator of outcomes in heart failure, and therefore, PVR may be a superior prognosticator because it includes flow assessment (19). However, even in patients with an elevated PVR, an elevated DPG was not associated with worse prognosis.

The use of DPG in PH is not new and it was extensively studied in previous decades (15, 20, 21). Many factors other than pulmonary vascular remodeling also affect the DPG. DPG is acutely elevated in several different clinical scenarios including hypoxemia in patients with ARDS and COPD (17,22,23), after coronary artery bypass surgery (15), and in sepsis due to acidosis, release of endotoxins, or microthrombi (17,24). Tachycardia, which is commonly encountered in individuals with LHD due to decreased cardiac output, tachyarrhythmias or inotropic support, also increases the DPG (25).

We acknowledge that our retrospective study has several limitations. First, our cohort included patients evaluated for unexplained cardiomyopathy with a broad representation of different heart failure pathologies, which may not necessarily represent the general heart failure population. Although this cohort consisted of patients with both preserved and reduced function, most patients had a diagnosis of a dilated cardiomyopathy, leaving open the possibility that DPG may have a prognostic ability in heart failure with preserved ejection fraction (HFpEF), or in a more select group of heart failure patients. Because the incidence of PH-LHD was relatively low in our population (44%), this could limit our power to detect a difference in survival between the low and high DPG groups. However, TPG, and in particular PVR, did discriminate survivors from non-survivors. The large number of patients with a negative DPG (assuming the negative DPG is the result of measurement error) could bias the results, as the actual DPG may have been elevated in these patients. If this limitation is true then this may speak to a real world limitation to the use of DPG since these measurements were all performed by heart failure cardiologists with significant experience in hemodynamic evaluations. It also remains possible that a very high DPG similar to those seen in idiopathic pulmonary artery hypertension (~20mmHg) (26), could predict survival. Nevertheless, those patients are quite rare in PH-LHD (in this analysis only 9 patients had a DPG>15mmHg and only 4 had a DPG>20mmHg). PVR and TPG may have influenced the decision of who was ultimately transplanted. In accordance with previous investigations on this topic, we censored participants who went on to require transplantation (n=36) at the time of transplantation. Censoring participants at the time of transplant could lead to an underestimation of mortality. Furthermore, information regarding medical therapies, echocardiography and other co-morbid conditions like COPD, smoking, sleep apnea, atrial fibrillation, renal failure etc. was not available and therefore their association with PH-LHD and survival could not be assessed. In addition, our analysis did not correct for multiple comparisons. Finally, hemodynamic data on response to vasodilators to evaluate the reversibility of PH was not routinely tested in this cohort.

In conclusion, our study shows that in a large cohort of patients with PH due to left heart disease, including those with ‘out-of-proportion’ (elevated TPG and PVR) PH, the diastolic pulmonary gradient did not discriminate survivors from non-survivors. Considering the technical limitations interfering with the accurate measurement of DPG and other clinical factors that affect the DPG aside from pulmonary vasculature remodeling, this work argues against the use of DPG as a marker of prognosis in patients with PH-LHD. Likewise, the routine use of DPG in diagnostic algorithms of PH-LHD is premature and requires further validation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

CpcPH	Combined post-capillary and pre-capillary PH
CO	Cardiac output
dPAP	diastolic Pulmonary artery pressure
DPG	Diastolic pulmonary gradient
IpcPH	Isolated post-capillary PH
mPAP	mean Pulmonary artery pressure
PCWP	Pulmonary capillary wedge pressure
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
RVSWI	Right ventricular stroke work index
sPAP	systolic Pulmonary artery pressure
TPG	Transpulmonary gradient

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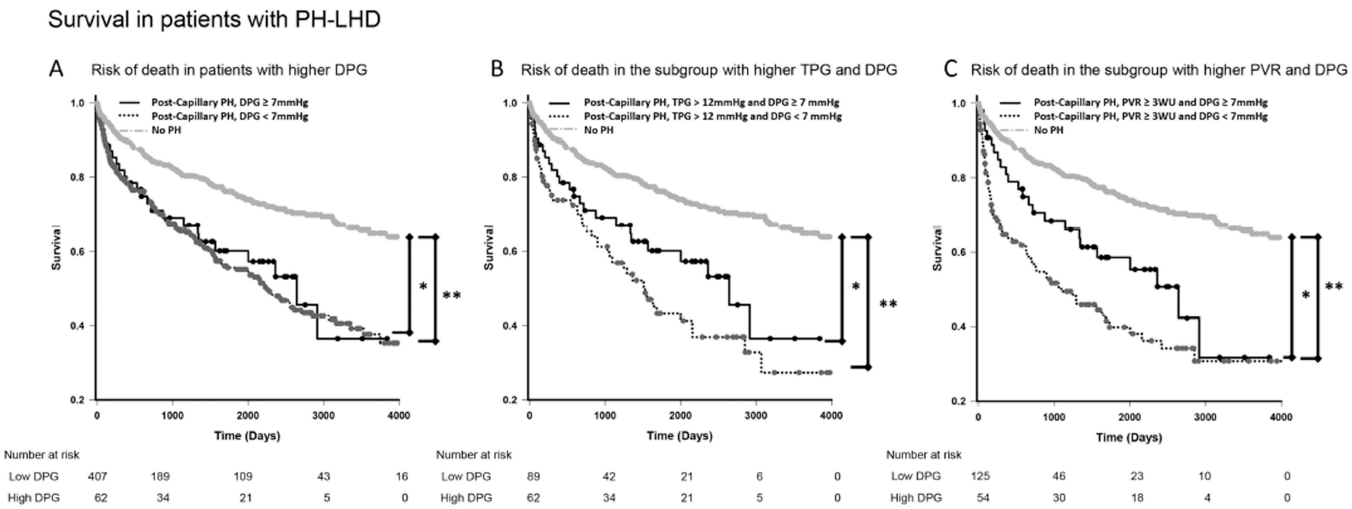

Figure 1. Kaplan-Meir survival curves in all patients evaluated for heart failure

A. In patients with PH-LHD (mPAP ≥25mmHg and PCWP >15mmHg), higher DPG (≥7mmHg) failed to discriminate survivors. Patients without PH had better survival. **B.** In the subgroup of increased TPG, low DPG did not discriminate survivors. **C.** In subjects with PH-LHD and PVR ≥3WU, lower DPG showed a trend towards worse survival (*P*=0.051). * *P* <0.05, ** *P* <0.001; PH = Pulmonary Hypertension. DPG = Diastolic Pulmonary Gradient. TPG = Transpulmonary Gradient. PVR = Pulmonary Vascular Resistance. WU = Wood units.

Table 1

Hazard of death in DPG, TPG, or PVR.

	Hazard Ratio (95% CI) per unit increase	Hazard Ratio (95% CI) per interquartile increase	p-value
DPG			
Unadjusted	1.02 (1.00–1.05)	1.15 (0.98–1.34)	0.08
Adjusted	1.02 (1.00–1.05)	1.14 (0.98–1.34)	0.10
TPG			
Unadjusted	1.03 (1.00–1.05)	1.20 (1.02–1.41)	0.03
Adjusted	1.02 (1.00–1.05)	1.19 (1.00–1.40)	0.046
PVR			
Unadjusted	1.13 (1.06–1.20)	1.29 (1.12–1.48)	<0.001
Adjusted	1.11 (1.04–1.19)	1.25 (1.09–1.44)	0.002

Adjusted model accounts for age, gender, race and body mass index

PH-LHD = Pulmonary Hypertension due to left heart disease. DPG = Diastolic Pulmonary Gradient. TPG = Transpulmonary Gradient. PVR = Pulmonary Vascular Resistance. CI: Confidence Intervals.

Table 2

Hazard of death for participants using a variety of commonly used DPG cut-offs.

	Hazard Ratio per interquartile range (95% CI)	p-value
DPG: Cut-off 1mmHg		
(251 participants with high DPG, 218 with low DPG)		
Unadjusted	1.21 (0.92–1.61)	0.18
Adjusted	1.20 (0.90–1.60)	0.21
DPG: Cut-off 3mmHg		
(174 participants with high DPG, 295 with low DPG)		
Unadjusted	1.30 (0.98–1.73)	0.07
Adjusted	1.28 (0.96–1.71)	0.09
DPG: Cut-off 5mmHg		
(117 participants with high DPG, 352 with low DPG)		
Unadjusted	1.15 (0.84–1.58)	0.40
Adjusted	1.19 (0.87–1.64)	0.28
DPG: Cut-off 7mmHg		
(62 participants with high DPG, 407 with low DPG)		
Unadjusted	0.91 (0.60–1.38)	0.66
Adjusted	0.93 (0.61–1.42)	0.74
DPG: Cut-off 9mmHg		
(37 participants with high DPG, 432 with low DPG)		
Unadjusted	0.74 (0.43–1.28)	0.28
Adjusted	0.75 (0.42–1.31)	0.31

Adjusted model accounts for age, gender, race and body mass index

DPG = Diastolic Pulmonary Gradient. CI: Confidence Intervals.

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Table 3

Demographic, diagnostic and hemodynamic data of the different patient cohorts.

	DPG ≥7 (n=62)	DPG <7 (n=407)	p-value†	No PH (n=650)	p-value‡
Demographics					
Age (years)	49.3 [39.5–58.5]	49.0 [36.7–60.9]	0.98	46.7 [35.4–57.4]	0.11
Height (m)	1.75 [1.65–1.80]	1.73 [1.68–1.83]	0.08	1.73 [1.35–1.98]	0.21
Weight (kg)	83.8 [68.7–98.0]	79.0 [65.9–91.8]	0.15	76.8 [63.6–89.0]	0.017
Body Mass Index (kg/m2)	27.3 [22.9–30.7]	26.1 [22.9–30.9]	0.47	25.5 [22.4–29.1]	0.021
Female Gender	18 (29)	149 (37)	0.31*	274 (42.1)	0.045*
Race					
Black	29 (47)	140 (35)		208 (32)	
Caucasian	32 (52)	257 (63)		425 (66)	
Other	1 (2)	8 (2)	0.18*	12 (2)	0.24*
Diagnosis					
Idiopathic	27 (44)	205 (50)		326 (50)	
Coronary artery disease	5 (8)	41 (10)		36 (6)	
Myocarditis	4 (6)	28 (7)		76 (12)	
Toxic/Metabolic	5 (8)	19 (5)		28 (4)	
Other	21 (34)	114 (28)	0.63*	184 (28)	0.033*
Hemodynamics					
Heart rate (beats per minute)	94 [82–107]	93 [80–106]	0.69	84 [72–95]	<0.001
Systemic Blood Pressure					
Systolic (mmHg)	128 [105–151]	117 [104–138]	0.04	120 [107–137]	0.09
Diastolic (mmHg)	82 [72.0–90.3]	77.5 [68.0–86.0]	0.01	73 [67.0–81.2]	<0.001
Mean (mmHg)	98.2 [87.2–111.3]	90.7 [80.7–105.4]	0.01	89.5 [81.0–100.0]	0.001
Systemic Vascular Resistance (Wood units)	22.6 [16.3–30.1]	20.6 [16.4–27.3]	0.52	19.1 [15.2–23.1]	<0.001
Left Ventricular Stroke Work Index (mmHg ml/m2)	1521 [1208–2236]	1342 [1033–1870]	0.035	2316 [1766–3041]	<0.001
Right Atrial Pressure (mmHg)	13 [8.8–17.0]	10.0 [7.0–15.0]	0.048	4 [2.0–6.0]	<0.001
Pulmonary Artery Pressures					
Systolic (mmHg)	60.0 [51.5–70.0]	52.0 [45.0–59.0]	<0.001	28 [23.0–33.0]	<0.001
Diastolic (mmHg)	31.5 [28.0–36.5]	26.0 [22.0–30.0]	<0.001	11.5 [8.0–15.0]	<0.001

	DPG ≥7 (n=62)	DPG <7 (n=407)	p-value†	No PH (n=650)	p-value‡
Mean (mmHg)	40.2 [36.7–48.8]	34.0 [29.7–40.0]	<0.001	17 [13.7–10.7]	<0.001
Pulmonary Capillary Wedge Pressure (mmHg)	22.0 [18.0–27.0]	26.0 [22.0–30.0]	<0.001	10 [7.0–13.0]	<0.001
Cardiac Index (L/min/m2)	1.90 [1.55–2.5]	1.93 [1.60–2.35]	0.96	2.4 [2.0–2.8]	<0.001
Right Ventricular Stroke Work Index (mmHg ml/m2)	604 [456–795]	511 [354–665]	0.001	369 [322–432]	<0.001
Pulmonary Vascular Resistance (Wood units)	4.7 [3.5–6.3]	2.2 [1.4–3.3]	<0.001	1.37 [0.95–2.0]	<0.001
Transpulmonary Gradient (mmHg)	18.3 [16.3–21.8]	8.3 [5.7–11.7]	<0.001	6.3 [4.7–8.3]	<0.001
Diastolic Pulmonary Gradient (mmHg)	9.0 [8.0–11.0]	0 [−3.0–3.0]	<0.001	1 [−1.0–3.0]	<0.001
RA/PCWP	0.54 [0.42–0.69]	0.40 [0.29–0.56]	<0.001	0.4 [0.25–0.57]	<0.001

No variable was missing in more than 3.3% of participants.
Data presented as median [interquartile range]

† DPG ≥7 vs. DPG <7; Rank Sum test unless otherwise indicated

‡ Comparison of all three groups; ANOVA unless otherwise indicated

* Chi-square; () = Percentage

Table 4

Hazard of death for participants for a variety of commonly used TPG and PVR cut-offs.

	Hazard Ratio per interquartile range (95% CI)	p-value
TPG: Cut-off 6mmHg		
(362 participants with high TPG, 107 with low TPG)		
Unadjusted	1.26 (0.90–1.78)	0.18
Adjusted	1.29 (0.91–1.84)	0.16
TPG: Cut-off 9mmHg		
(236 participants with high TPG, 233 with low TPG)		
Unadjusted	1.34 (1.01–1.77)	0.04
Adjusted	1.34 (1.00–1.79)	0.05
TPG: Cut-off 12mmHg		
(152 participants with high TPG, 317 with low TPG)		
Unadjusted	1.24 (0.92–1.66)	0.14
Adjusted	1.19 (0.88–1.60)	0.26
TPG: Cut-off 15mmHg		
(89 participants with high TPG, 380 with low TPG)		
Unadjusted	0.91 (0.60–1.38)	0.66
Adjusted	0.93 (0.61–1.42)	0.74
PVR: Cut-off 2WU		
(298 participants with high PVR, 171 with low PVR)		
Unadjusted	1.60 (1.18–2.18)	0.003
Adjusted	1.48 (1.07–2.03)	0.02
PVR: Cut-off 2.5WU		
223 participants with high PVR, 246 with low PVR)		
Unadjusted	1.78 (1.34–2.36)	<0.001
Adjusted	1.59 (1.18–2.13)	0.002
PVR: Cut-off 3WU		
184 participants with high PVR, 285 with low PVR)		
Unadjusted	1.79 (1.35–2.36)	<0.001
Adjusted	1.57 (1.18–2.10)	0.002
PVR: Cut-off 3.5WU		
(132 participants with high PVR, 337 with low PVR)		
Unadjusted	1.60 (1.18–2.18)	0.003
Adjusted	1.48 (1.07–2.03)	0.02

Adjusted model accounts for age, gender, race and body mass index

TPG = Transpulmonary Gradient. PVR = Pulmonary Vascular Resistance. WU= Wood units. CI: Confidence Intervals