Pulmonary Effective Arterial Elastance as a Measure of Right Ventricular Afterload and its Prognostic Value in Pulmonary Hypertension due to Left Heart Disease

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Abstract

Background—Patients with combined post- and pre-capillary pulmonary hypertension (CpcPH) due to left heart disease (PH-LHD) have a worse prognosis compared with isolated post-capillary (IpcPH). However, it remains unclear if increased mortality in CpcPH is simply a result of higher total right ventricular (RV) load. Pulmonary effective arterial elastance (Ea) is a measure of total RV afterload, reflecting both resistive and pulsatile components. We aimed to test whether pulmonary Ea discriminates survivors from non-survivors in patients with PH-LHD, and if it does so better than other hemodynamic parameters associated with CpcPH.

Methods and Results—We combined three large heart failure patient cohorts (n=1036) from academic hospitals including patients with PH due to heart failure with preserved ejection fraction (HFpEF) (n=232), reduced ejection fraction (HFrEF) (n=335) and a mixed population (n=469). In unadjusted and two adjusted models, pulmonary Ea more robustly predicted mortality than pulmonary vascular resistance (PVR) and the transpulmonary gradient. Along with pulmonary arterial compliance (PAC), pulmonary Ea remained predictive of survival in patients with normal PVR. The diastolic pulmonary gradient did not predict mortality. Additionally, in a subset of patients with echocardiographic data, Ea and PAC were better discriminators of RV dysfunction than the other parameters.

Conclusions—Pulmonary Ea and PAC more consistently predicted mortality than PVR or TPG across a spectrum of left heart disease with pulmonary hypertension including patients with HFpEF, HFrEF, and pulmonary hypertension with a normal PVR.

Keywords

Pulmonary effective arterial elastance; pulmonary arterial compliance; pulmonary hypertension due to left heart disease; combined post- and pre-capillary pulmonary hypertension; diastolic pulmonary gradient

Introduction

Among patients with pulmonary hypertension due to left heart disease (PH-LHD), individuals with combined post- and pre-capillary pulmonary hypertension (CpcPH) have worse prognosis compared with isolated post-capillary pulmonary hypertension (IpcPH) [1, 2]. CpcPH is differentiated from IpcPH hemodynamically by measures that suggest the presence of pulmonary vascular pathology including pulmonary vascular resistance (PVR) 3 Wood units, transpulmonary gradient (TPG) 12-15 mmHg and diastolic pulmonary gradient (DPG) 7mmHg, and each has been associated with worse survival in various heart failure studies [1, 3-5]. However, isolated pressure measures (i.e. TPG or DPG) do not incorporate flow (stroke volume), which may limit their prognostic value, and PVR (which does incorporate flow) only accounts for non-pulsatile afterload. Additionally, it remains unclear if patients with CpcPH simply have worse overall hemodynamics and higher total right ventricular (RV) load compared with IpcPH, and therefore, if markers of total RV load better predict mortality [2]. In the setting of left heart failure, pulmonary arterial compliance (PAC) is determined by both PVR and left heart filling pressures [6]. Consistently, several studies have demonstrated it to be a superior prognostic marker compared with PVR [7-9]. Pulmonary effective arterial elastance (Ea) is a "lumped" measure of RV afterload that more fully incorporates resistive, pulsatile and passive components [10, 11]. We sought to determine if pulmonary Ea as a measure of total RV load is associated with mortality in PH-LHD and compare its prognostic ability to hemodynamic markers of pre-capillary PH.

Methods

Patient populations

The combined patient cohort (A, B, and C) consisted of 1036 patients from three academic institutions. The data, analytic methods, and study materials will not be made available to other investigators.

Cohort A - Johns Hopkins (HFrEF and HFpEF)—As previously reported [12] this cohort included 1236 patients referred to the Johns Hopkins Hospital Cardiomyopathy Service for evaluation of new cardiomyopathy between 1982 and 1997. Heart failure specialists performed all right heart catheterization (RHC) procedures and interpreted the hemodynamic data. A complete set of hemodynamic data was available in 1174 patients. The patients were followed until death, cardiac transplantation or the end of the study period (January 1, 1998). Participants who underwent transplantation were censored at the time of

transplantation. Vital status was obtained from medical records and through a search of the Nation Death Index [13]. The Johns Hopkins Hospital Joint Committee on Clinical Investigation approved the study. There were 193 events recorded in 1608 patient-years.

Cohort B - Mayo Clinic Rochester (HFrEF)—This cohort included 490 ambulatory outpatients with HFrEF (LVEF 40%) referred to the Mayo Clinic (Rochester, MI) for a RHC between 2002 and 2008. Exclusion criteria were previously described[14] and included patients with primary parenchymal lung disease, chronic obstructive pulmonary disease, prior valvular surgery, infiltrative, constrictive, or hypertrophic cardiomyopathy, myocardial infarction within 6 months, any history of group 1 (idiopathic, familial, collagen vascular disease, congenital heart disease), group 3 or group 4 (pulmonary thromboembolic disease) PH disease, tachyarrhythmia, chronic kidney disease, history of chest radiation, cardiac or lung transplantation. A complete set of hemodynamic data was available in 478 patients. Patient survival or all-cause mortality status was confirmed through June 30, 2010, using Mayo Clinic (Rochester, MI) electronic medical records, Olmsted County (MI) medical record linkage system and Social Security mortality index. The Mayo Foundation Institutional Research Review Board approved the study and all patients included provided informed consent. There were 140 events recorded in 805 patient-years.

Cohort C - Northwestern University (HFpEF)—Four hundred twenty patients were enrolled prospectively between March 2008 and May 2011 from the outpatient clinic of the Northwestern University HFpEF Program. 293 patients underwent invasive hemodynamic testing and of those 232 subjects met criteria for PH-LHD (defined below). All patients were recruited as outpatients after hospitalization for HF as previously reported[15], and all patients were enrolled into the study based on a left ventricular ejection fraction (LVEF) >50% and the presence of Framingham criteria for HF. Although not required for inclusion into the cohort, all patients had evidence of either significant diastolic dysfunction (grade 2 or 3) on echocardiography, evidence of elevated LV filling pressures on invasive hemodynamic testing, or BNP >100 pg/mL. All enrolled patients followed-up in a specialized HFpEF outpatient program. Patients with greater than moderate valvular disease, prior cardiac transplantation, history of reduced LVEF < 40% (i.e., recovered EF), or diagnosis of constrictive pericarditis were excluded. All participants gave written informed consent, and the institutional review board at Northwestern University approved the study. There were 78 events recorded in 1144 patient-years.

Hemodynamic Measures

PH-LHD was defined as a mean pulmonary artery pressure (mPAP) 25mmHg with a pulmonary artery wedge pressure (PAWP) > 15mmHg. Total RV load was estimated by pulmonary Ea. Historically, systemic Ea was initially derived using parameters from a 3-element arterial Windkessel model[16], but later was simplified to end-systolic pressure (ESP) divided by SV which can be readily obtained from a pressure-volume loop[10]. This simplification was later validated in the RV[17]. Under normal conditions, the RV ejects into a low impedance circuit and pressure declines throughout ejection[18]. Therefore, in the setting of normal afterload, ESP is closely related to mPAP. However, with development of PH, the RV pressure volume loop changes shape with pressure rising throughout ejection and

peaking near end-systole. Therefore, in PH patients end-systolic pressure (ESP) is more closely approximated by systolic pulmonary artery pressure (sPAP), and Ea can be defined as sPAP/SV [19, 20]. Because our cohort included only participants with pulmonary hypertension, this latter definition of Ea (sPAP/SV) was used in all analyses. TPG was calculated as the difference between mPAP and PAWP, and PVR as TPG divided by cardiac output (CO). DPG was calculated as the difference between the diastolic pulmonary artery pressure (dPAP) and PAWP. Pulmonary arterial compliance (PAC) was estimated as stroke volume divided by pulmonary artery pulse pressure. CO was determined by either thermodilution or direct Fick technique in all three cohorts. These calculations are summarized in Supplemental Table 1.

Statistical Analysis

Continuous variables were compared across the 3 cohorts with 1-way ANOVA or Kruskal Wallis if non-normally distributed. Categorical variables were compared with chi-squared test. Hazard ratios of death for PVR, TPG, DPG, PAC and pulmonary Ea were estimated with Cox proportional hazards regression analysis (unadjusted and two adjusted models). We chose to adjust for only age in the first adjusted model given the known impact of aging on PAC and PVR [6]. In the second model, we adjusted for age, body mass index (BMI), heart rate, gender and cohort (cohort only in pooled analysis). We did not adjust for race since these data were not available in cohort B. We tested the proportionality assumption using scaled Schoenfeld residuals on time in each individual cohort and for each variable added to the Cox model. Survival was also estimated with the non-parametric methods of Kaplan and Meier and compared using the log-rank test. Qualitative data on RV function were available in cohort B and C. Each subject was classified as having none, mild-moderate, or severe RV dysfunction. Those who had been reported as moderate-severe were considered severe for our analysis. The ability of Ea, PAC, PVR, TPG, and DPG to discriminate "any RV dysfunction" as well as "severe RV dysfunction" was assessed by calculating a C-statistic. 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 (Systat Software Inc).

Results

Study populations

Clinical characteristics and hemodynamics for the combined cohort and each individual cohort is shown Table 1. Cohort A had the youngest patients among the three groups (p<0.001), had a high percentage of non-ischemic cardiomyopathy, and included patients with higher heart rate than the other two cohorts. Cohort C had a higher percentage of female gender and higher BMI than cohorts A and B. In contrast to cohorts A and B, cohort C (HFpEF) also had an overall better hemodynamic profile as evident by the higher CI, PAC, RV stroke work index (RVSWI), left ventricular stroke work index (LVSWI) and lower pulmonary Ea and PVR when compared with the other two groups. Forty percent of cohort A (469 of 1174 subjects), 68% of cohort B (335 of 490 subjects) and 79% of cohort C (232 of 293 subjects) met invasive hemodynamic criteria for PH-LHD. PH-LHD was therefore present in 53% of the combined cohort.

Pulmonary effective arterial elastance is associated with mortality in patients with PH-LHD

In unadjusted and adjusted analyses, pulmonary Ea was significantly associated with increased mortality (adjusted[1] HR per 1 mmHg/mL increase in Ea 1.47 [1.31-1.65], χ^2=44.3, p<0.001 and adjusted[2] HR 1.45 [1.27-1.65], χ^2=29.6, p<0.001) (Table 2). Lower PAC, higher PVR, and higher TPG were also associated with increased mortality in age adjusted analyses (PAC: adjusted[1] HR per 1mL/mmHg decrease in PAC 1.33 [1.22-1.45], χ^2=41.0, p<0.001 and adjusted[2] HR 1.30 [1.18-1.43], χ^2=29.3 p<0.001; PVR: HR per 1 Wood unit increase in PVR 1.15 [1.10-1.20], χ^2=36.5, p<0.001 and adjusted[2] HR 1.14 [1.08-1.19], χ^2=27.8 p<0.001; TPG: adjusted[1] HR per 1mmHg increase in TPG 1.02 [1.00-1.03], χ^2=6.5, p=0.01 and adjusted[2] HR 1.02 [1.01-1.04], χ^2=8.2, p=0.004). Higher PAWP alone also tended to predict mortality: adjusted[1] HR 1.02 per 1mmHg increase, χ^2=3.9, p=0.052 and adjusted[2] HR 1.03 [1.00-1.06], χ^2=4.5, p=0.034. The median pulmonary Ea was 1.036 mmHg/mL. Over a median follow up of 2.8 years, mortality was significantly worse in those patients with an Ea higher than the median (p<0.001)(Figure 1 (pooled cohort) and Supplemental Figure 1(individual cohorts)). Similar pooled data relative to median values is shown for PAC and PVR in Supplemental Figure 2.

DPG is not associated with mortality in patients with PH-LHD

DPG was not associated with mortality in unadjusted or adjusted analyses nor was it using the guideline-recommended cutoff of 7mmHg (p=0.46, Figure 2A). CpcPH defined as DPG 7 mmHg *AND* PVR > 3WU trended toward worse survival compared with the rest of the cohort but did not reach statistical significance (p=0.086, Figure 2B).

Pulmonary Ea and PAC association with RV dysfunction—Qualitative data on RV function determined by echocardiography was available in cohort B and C. In this combined cohort (B and C), pulmonary Ea and PAC discriminated more strongly severe RV dysfunction as well as any RV dysfunction compared with PVR, TPG, and DPG. (Table 3).

Pulmonary Ea and PAC are associated with mortality in subjects with normal PVR

In the subset of subjects with normal PVR (n=685), 212 had an Ea above the median value for the larger cohort and 217 had a PAC below the median for the larger cohort. Pulmonary Ea (adjusted[1] HR 1.31 [1.04-1.66], χ^2=5.2 p=0.022 and adjusted[2] HR 1.34 [0.99-1.81], χ^2=3.6 p=0.057) and PAC (adjusted[1] HR 1.20 [1.09-1.33], χ^2=13.8, p<0.001 and adjusted[2] HR 1.22 [1.08-1.37], χ^2=11.0 p=<0.001) remained predictive of mortality when examining the subgroup of patients with PVR 3WU, whereas PVR did not. PAWP by itself also did not predict mortality in this subset. We then divided the entire combined cohort into tertiles of PVR and plotted pulmonary Ea and PAC as a function of PAWP (Figure 3A and B). Pulmonary Ea increased and PAC decreased as PAWP increased in all PVR tertiles. Data for individual cohorts are shown in Supplemental Figures 3 and 4. As illustrated in these figures, subjects in the two lower PVR tertiles have similar or even higher pulmonary Ea (or lower PAC) than the highest PVR tertile when PAWP is significantly elevated.

Discussion

Main Findings

In an analysis of a large combined cohort of patients with PH due to left heart disease, pulmonary Ea as a hemodynamic marker of total RV afterload was associated with mortality in patients with PH-LHD. Pulmonary Ea and PAC more consistently predicted mortality than PVR or TPG across a spectrum of left heart disease with pulmonary hypertension including patients with HFpEF and HFrEF and were more strongly associated with RV dysfunction. Ea and PAC remained predictive of mortality in a subgroup of patients with normal resistive load. Lastly, DPG was not associated with mortality in this large combined cohort, or in individual cohorts of HFrEF or HFpEF.

RV function is a strong predictor of prognosis in both heart failure with preserved and reduced ejection fraction [21, 22]. The RV is more afterload sensitive (both acutely and chronically) than the left ventricle [11, 23], and it is therefore not surprising that development of PH is itself associated with worse outcomes. Although PH with a pre-capillary component is associated with a worse prognosis than isolated post-capillary PH, those patients with a pre-capillary component also tend to have worse overall hemodynamics and higher total RV load. The gold standard for assessing RV afterload is pulmonary artery input impedance spectra which allows for assessment of total and individual components of afterload [24]. Although resistive load (i.e. PVR) makes up a substantial proportion of total RV load, other components including pulmonary arterial compliance and arterial wave reflections contribute as well. Ea incorporates these other factors and is an attractive hemodynamic marker because it can be derived from a standard right heart catheterization, therefore not requiring more invasive or sophisticated measurement techniques. This study confirms that measures of total RV afterload are more predictive of mortality and RV dysfunction in PH-LHD than measures associated with pre-capillary PH. Ghio and colleagues recently showed significant vasoreactivity and reversibility of the pre-capillary component in those with CpcPH suggesting a significant functional component to the precapillary parameters, including the DPG[25]. One may speculate that this could explain, in part, why therapies targeting the pre-capillary component in LHD have yielded disappointing results. In a post-hoc analysis of the RELAX study, for example, sildenafil failed to significantly lower total RV afterload[26].

In absence of left heart failure and normal PAWP, RV pulsatile load is almost exclusively dependent on resistive load – which is unique compared to the systemic circulation – and therefore is generally constant proportion of total RV load [27]. However, in left heart failure, elevated left atrial pressure (i.e. PAWP) has been shown in a number of studies to reduce PAC out of proportion to PVR, thereby increasing RV pulsatile loading [6, 7, 28, 29]. Thus, in the pulmonary circulation, compliance is also a 'lumped' parameter that is determined by both resistive and pulsatile components of RV load. Similar to the findings in our study, Pellegrini and colleagues showed that PAC remained a predictor of mortality even in subjects with LHD and normal PVR [29]. In this situation, pulsatile loading makes up a higher proportion of total RV load. Because the pulmonary resistance-compliance relationship is steep when PVR is borderline or just mildly elevated, modestly lowering PVR in this setting

may result in robust reductions in pulsatile load [6]. For example, inorganic sodium nitrite, a novel NO-providing agent, increased PAC significantly despite only a modest reduction in resistive load in patients with HFpEF [30]. This effect was also in part due to lowering PAWP.

Importantly, the effects of pulsatile loading are reflected in the sPAP not dPAP. Because mPAP reflects both dPAP and sPAP, it is less reflective of pulsatile loading than sPAP. Indeed, in a recent study of subjects with HFpEF, sPAP was the only hemodynamic parameter associated with cardiac events in multivariate analysis [8]. In addition, Wong et al showed sPAP and heart rate were the two major determinants of RV myocardial oxygen consumption in a group of patients with idiopathic pulmonary arterial hypertension [9]. In our study, Ea – which is estimated by sPAP/SV – and PAC – which is estimated by SV/(sPAP-dPAP) – were more predictive of mortality than measures incorporating mPAP (i.e. PVR). It is also important to consider that Ea can be easily measured non-invasively using echocardiography by simply dividing estimated right ventricular systolic pressure by stroke volume. This could prove to be an attractive, straightforward metric to measure total RV afterload non-invasively and index ventricular function to RV afterload.

Finally, although DPG 7mmHg has been suggested as a diagnostic marker of CpcPH, the findings of this work along with other published data [7, 12, 31-33], call into question its use as a prognostic variable in PH-LHD. The European Society of Cardiology/European Respiratory Society (ESC/ERS) PH Guidelines currently define CpcCH as DPG 7mmHg "and/or" PVR > 3WU. More recently however it has been suggested that this definition should be modified to DPG 7mmHg "AND" PVR > 3WU because DPG 7mmHg in the setting of a PVR < 3WU is likely related to measurement error or tachycardia [34]. In the current study, the group fitting this definition trended toward worse outcome yet did not reach statistical significance. It remains to be seen if DPG may still be valuable as a marker to identify patients with PH-LHD who are responsive to pulmonary vasodilator therapy. Alternatively, therapies targeting total RV load rather than the pre-capillary component, many of which are aimed at treating the left ventricle in tandem with PA vascular loading [30], may be more appropriate.

Strengths and Limitations

A major strength of our study is the large sample size of the combined cohort but also that results were generally concordant among the three independent cohorts, thereby increasing the validity of our findings across the spectrum of ejection fraction in patients with heart failure and left heart disease. Specifically, cohort B (HFrEF) and cohort C (HFpEF) showed similar results. In addition, each of these 3 cohorts included invasive hemodynamic data, which is the gold standard for diagnosing PH-LHD.

We do acknowledge that our analysis has several limitations. First, our retrospective study was composed of three cohorts from three different hemodynamic laboratories and different heart failure cardiologists performed all measurements and interpreted the hemodynamic tracings. Therefore, variation in data analysis might be present. Despite the different operators and patient characteristics, the fact that our results were generally consistent among all three cohorts is reassuring. Although we controlled for cohort in our pooled analysis, there is still the potential of pooled estimates to accentuate confounding and inflate

the effect estimate. Information regarding heart failure therapies including medications, laboratory values, and co-morbidities such as COPD, atrial fibrillation, and renal failure were not available in all cohorts nor where pulmonary vascular pathology samples. Echocardiography was only available in two of the cohorts and only qualitative assessment of RV function was available for our study. Although patients with left heart failure may have elevated PVR, TPG or DPG, significant pulmonary vascular remodeling may be absent in many left heart disease patients based on the relative quick reversal of PH seen after transplant or implant of a mechanical assist device [35]. In those heart failure patients with definite pulmonary vascular disease, such as that seen in pulmonary arterial hypertension, it remains possible that pre-capillary markers of PH have additive value. Lastly, because Ea and PAC incorporate the contributions of elevated left heart pressures, they are not likely to be useful in defining pre-capillary disease for diagnostic purposes.

Conclusion

In conclusion, our study shows that in PH due to left heart failure, higher pulmonary effective arterial elastance and lower pulmonary arterial compliance are associated with mortality and RV dysfunction. These parameters were more consistently associated with mortality across the spectrum of heart failure, and even when resistive load was normal. These findings add support to the idea that worse mortality in CpcPH is a result of higher total RV load.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Clinical Perspective

What is new?

- Pulmonary effective arterial elastance (Ea) is associated with mortality in pulmonary hypertension due to left heart disease (PH-LHD) in both heart failure with preserved and reduced ejection fraction.

- In the setting of PH-LHD, pulmonary Ea and pulmonary arterial compliance (PAC), parameters reflective of total right ventricular afterload, are more consistently associated with right ventricular (RV) dysfunction and prognosis than measures of pre-capillary disease (pulmonary vascular resistance (PVR), transpulmonary gradient, and diastolic pulmonary gradient(DPG)).

- The DPG or combination of PVR>3 Wood units AND DPG 7 mmHg did not predict prognosis in this study.

What are the clinical implications?

- This study confirms that measures of total RV afterload are more predictive of mortality and RV dysfunction in PH-LHD than measures associated with pre-capillary PH.

- Pulmonary Ea could prove to be an attractive, non-invasive metric to measure total RV afterload and index ventricular function to RV afterload.

- These findings add support to the idea that worse mortality in combined post- and pre-capillary PH is a result of higher total RV load. Therapies targeting total RV load rather than the pre-capillary component, many of which are aimed at treating the left ventricle in tandem with pulmonary vascular loading, may prove beneficial.
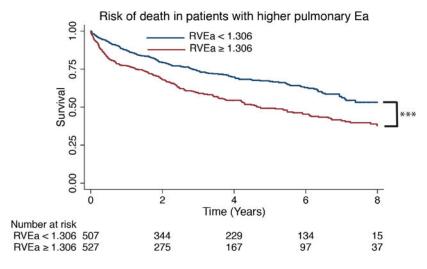
Figure 1.
Kaplan-Meier survival curve of patients with heart failure in combined cohorts. In patients with PH-LHD (mPAP 25mmHg and PAWP >15mmHg), higher pulmonary Ea discriminated survivors. The median pulmonary Ea for all three cohorts combined was used as a cut-off value. *** P<0.001; Ea = effective arterial elastance.
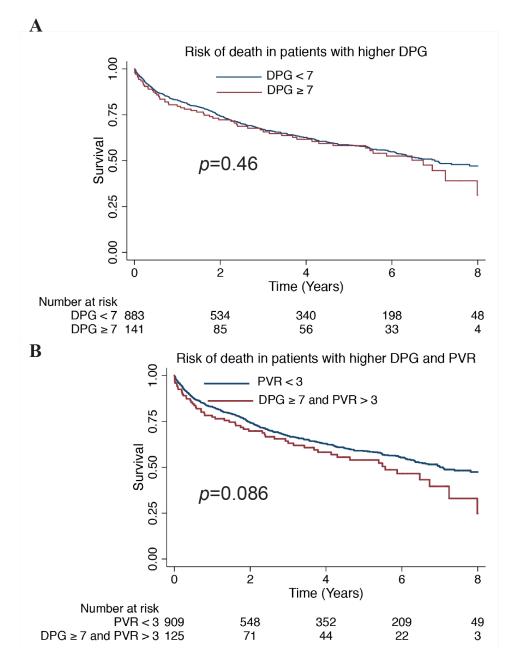
A

B

Figure 2.
Kaplan-Meier survival curve of patients with heart failure in combined cohort. **A.** In patients with PH-LHD (mPAP   25mmHg and PAWP >15mmHg), DPG   7mmHg did not discriminate survivors. **B.** Similarly, in patients with PH-LHD DPG   7 mmHg and PVR >3 WU did not discriminate survivors. DPG = Diastolic pulmonary gradient. PVR = Pulmonary vascular resistance.
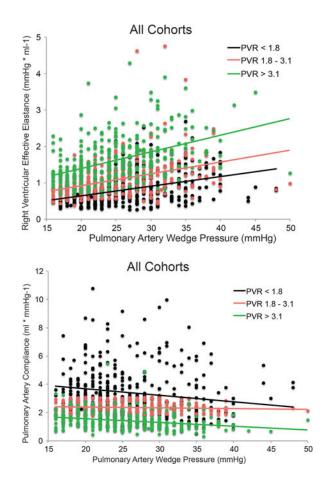
Figure 3.
A. Distribution of pulmonary Ea values and their respective regression lines as a function of PAWP into tertiles of PVR in combined cohort of patients with pulmonary hypertension due to left heart disease. Pulmonary Ea increased as PAWP increased in all tertiles of PVR. When compared to the highest PVR tertile, the two lower PVR tertiles can have similar or even higher pulmonary Ea at significantly elevated PAWP levels. **B.** Distribution of PAC as a function of PAWP into tertiles of PVR in the combined cohorts of patient with pulmonary hypertension due to left heart disease. Similarly, patients in the two lower PVR tertiles had similar or even lower PAC compared to the higher PVR tertile at significantly elevated PAWP.

Table 1

	All Cohorts (n=1036)	Cohort A (n=469)	Cohort B (n=335)	Cohort C (n=232)	p- value
Demographics					
Age (years)	57 [45-67]	49 [34-64]	59 [49-68]	63 [57-71]	<0.001
Body Mass Index (kg/m2)	27.7 [23.9-33.3]	26.2 [19.1-33.4]	28.4 [25.0-33.0]	31.8 [26.0-38.4]	<0.001
Female Gender	400 (39)	167 (36)	89 (27)	144 (61)	<0.001 [*]
Race					
Black	256 (37)	169 (36)		87 (38)	
Caucasian	411 (59)	289(62)	NA	122 (52)	
Other	32 (4)	9(2)		23 (10)	<0.001 [*]
Diagnosis					
Non-Ischemic	557 (80)	423 (90)	NA	134 (58)	
Ischemic	144 (20)	46 (10)	NA	98 (42)	<0.001 [*]
Hemodynamics					
Heart rate (beats per minute)	81 [69-97]	92 [75-111]	75 [66-87]	71 [63-80]	<0.001
Systemic Blood Pressure					
Systolic (mmHg)	121 [106-139]	118 [91-145]	NA	124 [112-138]	0.097 [†]
Diastolic (mmHg)	75 [66-84]	78 [62-94]	NA	70 [60-77]	<0.001 [†]
Mean (mmHg)	90 [81-102]	91 [73-109]	NA	87 [81-97]	<0.001 [†]
Systemic Vascular Resistance (WU)	18 [13-25]	21 [12-30]	NA	12.3 [9.4-15.5]	<0.001 [†]
Left Ventricular Stroke Work Index (mmHg ml/m2)	1685 [1154-2510]	1375 [654-2096]	NA	2595 [1886-3168]	<0.001 [†]
Right Atrial Pressure (mmHg)	13 [9-18]	11 [5-17]	14.7 [10-19]	15 [12-20]	<0.001
Pulmonary Artery Pressures					
Systolic (mmHg)	53 [45-63]	52 [40-64]	54 [46-64]	53 [45-66]	0.038
Diastolic (mmHg)	27 [22-31]	27 [21-33]	26 [22-31]	27 [23-33]	0.051
Mean (mmHg)	35 [30-42]	35 [27-43]	36 [30-42]	36 [30-43]	0.130
Pulmonary Artery Wedge Pressure (mmHg)	25 [20-35]	25 [19-31]	24 [20-28]	25 [21-31]	0.006
Cardiac Index (L/min/m2)	2.2 [1.7-2.7]	1.9 [1.3-2.5]	2.0 [1.7-2.4]	2.9 [2.4-3.4]	<0.001
Right Ventricular Stroke Work Index (mmHg ml/m2)	598 [407-835]	517 [275-761]	629 [410-846]	866 [612-1200]	<0.001
Pulmonary Effective Arterial Elastance (mmHg/ml)	1.0 [0.7-1.5]	1.3 [0.6-2.0]	1.0 [0.8-1.4]	0.6 [0.5-0.9]	<0.001

	All Cohorts (n=1036)	Cohort A (n=469)	Cohort B (n=335)	Cohort C (n=232)	p- value
Pulmonary Artery Compliance (ml/mmHg)	2.0 [1.4- 2.9]	1.6 [0.7-2.6]	1.9 [1.4-2.5]	3.2 [2.4-4.7]	<0.001
Pulmonary Vascular Resistance (WU)	2.3 [1.4-3.5]	2.4 [0.5-4.3]	2.8 [1.8-4.1]	1.7 [1.1-2.5]	<0.001
Transpulmonary Gradient (mmHg)	11 [7-14]	9 [3.5-14.5]	11 [7.0-15.3]	10 [8.0-14.0]	<0.001
Diastolic Pulmonary Gradient (mmHg)	1 [-1.0 – 5.0]	1 [-3.9 – 5.9]	1.3 [-1.0 – 5.0]	0 [0 – 3.0]	0.078
RA/PCWP	0.5 [0.3-0.7]	0.4 [0.2-0.6]	0.5 [0.4-0.70]	0.6 [0.4-0.7]	<0.001

Data presented as median [interquartile range]

ANOVA or Kruskal Wallis test unless otherwise indicated

*
Chi-square,

†
Rank Sum test

() = Percentage

Table 2

	All Cohorts			Cohort A			Cohort B			Cohort C		
	Hazard Ratio (95% CI) per unit increase	P-value	x^2	Hazard Ratio (95% CI) per unit increase	P-value	x^2	Hazard Ratio (95% CI) per unit increase	P-value	x^2	Hazard Ratio (95% CI) per unit increase	P-value	x^2
Ea												
Unadjusted	1.41 (1.26-1.59)	<0.001	34.0	1.26 (1.06-1.51)	0.009	6.9	1.65 (1.23-2.22)	0.001	10.9	1.60 (1.13-2.27)	0.008	7.0
Adjusted*	1.47 (1.31-1.65)	<0.001	44.3	1.25 (1.08-1.49)	0.012	6.3	1.64 (1.22-2.20)	0.001	10.9	1.44 (0.99-2.10)	0.053	7.8
Adjusted†	1.45 (1.27-1.65)	<0.001	29.6	1.30 (1.08-1.56)	0.005	7.8	1.72 (1.23-2.42)	0.002	9.8	1.47 (0.97-2.23)	0.069	3.3
PAC‡												
Unadjusted	1.30 (1.19-1.41)	<0.001	35.8	1.22 (1.03-1.45)	0.021	5.3	1.45 (1.18-1.82)	0.001	11.3	1.22 (1.06-1.41)	0.006	7.7
Adjusted*	1.33 (1.22-1.45)	<0.001	41.0	1.19 (1.02-1.41)	0.033	4.5	1.37 (1.11-1.72)	0.004	8.3	1.16 (1.01-1.35)	0.042	4.1
Adjusted†	1.30 (1.18-1.43)	<0.001	29.3	1.26 (1.04-1.52)	0.017	5.6	1.37 (1.09-1.73)	0.007	7.2	1.15 (0.99-1.34)	0.076	3.2
PVR												
Unadjusted	1.16 (1.11-1.21)	<0.001	40.2	1.13 (1.06-1.20)	<0.001	12.9	1.12 (1.04-1.21)	0.002	9.3	1.18 (1.01-1.37)	0.035	4.4
Adjusted*	1.15 (1.10-1.20)	<0.001	36.5	1.10 (1.03-1.18)	0.004	8.4	1.11 (1.03-1.20)	0.007	7.3	1.11 (0.94-1.30)	0.22	1.5
Adjusted†	1.14 (1.08-1.19)	<0.001	27.8	1.11 (1.04-1.19)	0.003	8.8	1.12 (1.03-1.21)	0.005	7.8	1.08 (0.92-1.28)	0.36	0.8
TPG												
Unadjusted	1.02 (1.00-1.04)	0.003	8.8	1.02 (1.00-1.05)	0.025	5.0	1.01 (0.99-1.04)	0.15	2.1	1.03 (0.99-1.06)	0.17	1.9
Adjusted*	1.02 (1.00-1.03)	0.011	6.5	1.02 (1.00-1.05)	0.071	3.2	1.02 (0.99-1.04)	0.12	2.4	1.02 (0.98-1.06)	0.27	1.2
Adjusted†	1.02 (1.01-1.04)	0.004	8.2	1.03 (1.00-1.05)	0.042	4.1	1.02 (1.00-1.05)	0.063	3.4	1.02 (0.98-1.06)	0.27	1.2
DPG												
Unadjusted	1.01 (0.99-1.03)	0.30	1.0	1.02 (1.00-1.05)	0.095	2.6	1.00 (0.97-1.03)	0.90	0.1	0.98 (0.90-1.06)	0.55	0.3
Adjusted*	1.01 (0.99-1.03)	0.29	1.0	1.02 (0.99-1.05)	0.12	2.2	1.01 (0.98-1.04)	0.44	0.6	0.98 (0.90-1.06)	0.66	0.2
Adjusted†	1.01 (0.99-1.03)	0.17	1.9	1.02 (1.00-1.05)	0.099	2.7	1.01 (0.99-1.04)	0.36	0.8	0.99 (0.91-1.07)	0.78	0.1

The outcome is all-cause mortality.

*
Adjusted model accounts for age.

†
Adjusted model accounts for age, gender, body mass index, heart rate, and cohort.

‡
HRs are per one-unit decrease in PAC. Ea = Pulmonary effective elastance. PAC = Pulmonary artery compliance, PVR = Pulmonary vascular resistance. TPG = Transpulmonary gradient. DPG = Diastolic pulmonary gradient.

Table 3

	C-statistic for Severe RV dysfunction	**C-statistic for Any RV dysfunction**
Ea	0.78	0.72
PAC	0.78	0.71
PVR	0.67	0.65
TPG	0.52	0.52
DPG	0.52	0.51

RV = Right Ventricular, Ea = Pulmonary effective arterial elastance. PAC = Pulmonary arterial compliance, PVR = Pulmonary vascular resistance.
TPG = Transpulmonary gradient. DPG = Diastolic pulmonary gradient.