Clinical Features, Hemodynamics, and Outcomes of Pulmonary Hypertension Due to Chronic Heart Failure With Reduced Ejection Fraction

Pulmonary Hypertension and Heart Failure

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CME Objective for This Article: After reading this article, the reader should be able to: 1) discuss the causes of pulmonary hypertension in patients with systolic heart failure; 2) have an understanding of the differences between passive and mixed pulmonary hypertension; and 3) discuss the impact of pulmonary hypertension subtypes on disease severity and risk of death.

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Objectives

The purpose of this study was to assess the clinical, functional, and hemodynamic characteristics of passive and mixed pulmonary hypertension (PH), compare outcomes, and contrast conventional and novel hemodynamic partition values in patients with chronic heart failure of reduced left ventricular ejection fraction (HFREF).

Background

PH in HFREF may develop from left-sided venous congestion (passive PH) or the combination of pulmonary arterial disease and venous congestion (mixed PH). Subgroup outcomes are not well defined, and the partition values used to define risk are based largely on consensus opinion rather than outcome data.

Methods

Ambulatory patients referred for hemodynamic catheterization were analyzed retrospectively (N = 463).

Results

Comparing patients with no PH to those with passive PH and mixed PH, a progressive gradient of more severely deranged hemodynamics, diastolic dysfunction, and mitral regurgitation was observed. In multivariate analysis, the presence of any PH or mixed PH was associated with older age, diuretic use, atrial fibrillation, and lower pulmonary artery compliance (PAC). Over a median follow-up of 2.1 years, patients with PH displayed greater risk of death (hazard ratio [HR]: 2.24; confidence limits [95% CL]: 1.39, 3.98; p < 0.001) with mixed PH demonstrating greater risk than passive PH (HR: 1.55; 95% CL: 1.11, 2.20; p < 0.001). Partition values identifying highest risk were pulmonary vascular resistance >4 Wood units, systolic pulmonary artery pressure >35 mm Hg, pulmonary wedge pressure >25 mm Hg, and PAC <2.0 ml/mm Hg.

Conclusions

Among stable HFREF outpatients, PH was associated with markers of greater disease severity and risk of death. However, the presence of pulmonary arterial disease (mixed PH) carries incremental risk. Abnormalities in pulmonary vascular resistance and compliance may serve as novel therapeutic targets. (J Am Coll Cardiol HF 2013;1:290–9) © 2013 by the American College of Cardiology Foundation

The development of pulmonary hypertension (PH) is an important marker in the progression of heart failure with reduced left ventricular (LV) ejection fraction (HFREF) (1–4). Initially, an increase in LV filling pressure causes an elevation in pulmonary venous pressures (5–7), resulting in post-capillary or passive PH (8–10). Some patients also develop abnormalities in pulmonary arterial structure and function resulting in a superimposed pulmonary arterial (pre-capillary) vasoconstrictor component that produces a “mixed” PH characterized by high LV filling pressure and elevated pulmonary vascular resistance (11–13). While PH is well established as an important risk factor for poor outcome in HFREF (8–10), the available data regarding passive and mixed PH subgroups are variable and limited by relatively short-term follow-up, incomplete characterization of left and right ventricular function, and limited data on coexisting valvular pathology (11–15).

Accordingly, the aim of this study was to comprehensively assess the clinical, functional, and hemodynamic characteristics of passive and mixed PH in a large cohort of ambulatory patients with chronic HFREF. Additional aims were to compare long-term outcomes in these subgroups of PH, contrast conventional and novel hemodynamic parameters of PH severity, and to propose partition values that might better stratify mortality risk and potentially serve as novel therapeutic targets in HFREF.

Methods

Ambulatory outpatients with HFREF referred by their primary cardiologist to the Mayo Clinic Rochester Cardiovascular Catheterization Laboratory for resting right heart hemodynamic catheterization for the period January 1, 2002, to December 31, 2008, were studied retrospectively. Inclusion criteria were age >18 years, LVEF ≤40%, and measurable LV diastolic and mitral valve function by echocardiography-Doppler evaluation at the time of the index catheterization. Exclusion criteria were primary parenchymal lung disease; chronic obstructive pulmonary disease other than mild as defined by pulmonary spirometry testing (forced expiratory volume in 1 s [FEV1] ≥80% of expected normal and the FEV1/forced vital capacity [FVC] ratio <70%) or clinical records description; prior valvular surgery; infiltrative, constrictive, or hypertrophic cardiomyopathy; myocardial infarction within 6 months; any history of risk factors associated with group 1 or group 3 PH (idiopathic, familial or pulmonary thromboembolic disease); congenital heart disease; tachycardia-related dysrhythmia; serum creatinine level ≥2.5 mg/dl; history of chest radiation therapy, collagen vascular disease, or cardiac or lung transplantation; consent for use of patient information for clinical research not available or consent refused. Indications for catheterization based upon referring physician (more than one could be provided) were abstracted from the database. Patient survival or all-cause mortality status was confirmed through June 30, 2010 (censor date), using Mayo Clinic, Rochester, electronic medical records, Olmsted County, Minnesota, medical record linkage system (Rochester Epidemiology Project) and Social Security mortality index. No patients hospitalized for acute decompensated HF were...
The study was approved by the Mayo Foundation Institutional Research Review Board and included only those patients who provided informed consent as required by Minnesota Statute 144.335/CRF 21 (Part 50).

**Invasive hemodynamic characteristics.** Right heart catheterization was performed by flow-directed pulmonary artery catheter using hemodynamic and fluoroscopic guidance. Hemodynamic data were abstracted from the computerized chart records and included the following: pulmonary arterial systolic, diastolic, and mean pressures (sPAP, dPAP, mPAP, respectively); pulmonary capillary wedge pressure (PCWP); right atrial pressure (RAP); transpulmonary gradient (TPG = mPAP–PCWP); cardiac output (CO), pulmonary vascular resistance (PVR) in Wood units (WU) = TPG/CO; systemic blood pressure (systolic/diastolic), and heart rate. Cardiac output was measured by the direct Fick method (i.e., measured oxygen consumption) or by the thermodilution method if Fick method was not performed. Pulmonary artery compliance (PAC) was defined as stroke volume (SV)/[sPAP–dPAP].

**Noninvasive hemodynamic characteristics.** Parameters of LV diastolic function including early transmitial flow velocity (E), late transmitial flow velocity (A), early diastolic mitral annular velocity (e’), the ratio of peak E to peak e’ (E/e’), and to peak A (E/A), and the deceleration time (DT) of the mitral E-wave were abstracted from the Doppler echocardiography evaluations obtained within 3 months of the index catheterization. The presence and extent of mitral valve insufficiency were quantified from the effective mitral regurgitant orifice area (EROA) as previously described (16–18). EROA was considered to be zero in patients with no or trace mitral regurgitation by color flow imaging. Glomerular filtration rate (eGFR [ml/min/1.73 m²]) was estimated using the modification of diet in renal disease equation (19).

**Hemodynamic definitions.** The passive PH cohort was defined as mPAP ≥25 mm Hg, PCWP ≥15 mm Hg, and PVR <3 WU. The mixed PH cohort was defined as mPAP ≥25 mm Hg, PCWP ≥15 mm Hg, and PVR ≥3 WU. The patient subgroup with no PH was defined as mPAP <25 mm Hg. All patients had LVEF ≤40%.

**Statistical methods.** Data are presented as mean ± SD, medians with interquartile ranges for continuous data, and as number/percentages for categorical data. To assess univariate differences, baseline and hemodynamic variables were compared using Student’s t-test or nonparametric Wilcoxon signed-rank test when normality assumptions were not achieved. Categorical variables were tested for significance using a likelihood ratio chi-square test. Linear regression analyses were used to assess associations between hemodynamic variables. Logistics regression analysis was performed to identify variables associated with the presence of correlates of PH. Results are presented as odds ratios with corresponding c-statistics (measure of predictive accuracy) and p values; the odds ratios for continuous variables are the odds of spanning the range of the data. Survival was estimated using the Kaplan-Meier method with log-rank analysis used to compare the end point of all-cause mortality among subgroups. Mortality was evaluated in univariate and multivariate analyses using Cox proportional hazards models adjusting for relevant baseline differences that would impact mortality. Risk factors that were significantly different among the hemodynamic groups at baseline and factors that were clinically important were evaluated for these models. Cox proportional hazards regression was used to assess the contribution to unadjusted hazards analysis for mortality based upon hemodynamic parameters using different hemodynamic variables to define abnormality. Results are presented as forest plots with corresponding p values and concordance indices. The association of relative risk of death using hemodynamic parameters as continuous variables was investigated using cubic splines with 3 knots within the Cox model. With this approach, we were able to verify the proportional hazards assumption and robustly estimate the functional form of each variable with the risk of death. Analyses were done using SAS statistical software version 9.2 (SAS Institute, Cary, North Carolina) and JMP 8.

**Results**

**Demographic and clinical characteristics.** The study cohort (N = 463) consisted of 126 patients with no PH (27% of total cohort), 151 patients with passive PH (45% of patients with PH, 33% of total), and 186 with mixed PH (55% of patients with PH, 40% of total). Patients with and without PH were of comparable age and sex. An ischemic origin of HFREF was 46% in the patients with passive PH, 54% in mixed PH, and 45% in patients with no PH. The indications for catheterization (as selected by the referring physician) in descending order were: heart failure/dilated cardiomyopathy in 35%, coronary disease in 28%, heart transplant evaluation in 21%, valvular disease in 15%, pulmonary hypertension in 7%, and other in 18%.

Compared to patients without PH, patients with PH demonstrated slightly greater body mass index (BMI) and body surface area, a higher prevalence of diabetes and atrial fibrillation, higher brain natriuretic peptide (BNP) levels, slightly lower hemoglobin levels, and slightly worse renal function. Medications were comparable across the 3 subgroups, with the exception of more diuretic, nitrate, diuretic, and anticoagulation therapies in the PH patients. Patients with passive and mixed PH were distinguishable only by slightly higher body mass, higher BNP level, and slightly worse renal function in mixed PH (Table 1).

**Invasive hemodynamic characteristics.** Both sPAP and PCWP were highly correlated with mPAP (Fig. 1A). Using mPAP as the dependent and sPAP as the independent...
variable, the regression equation was $\text{mPAP} = 0.615, \text{sPAP} + 3$ ($r = 0.93, p < 0.001$). Lesser, but still significant correlations, were also demonstrated for mPAP with PVR ($r = 0.669, p < 0.001$), and TPG ($r = 0.696, p < 0.001$). There was a much weaker correlation between sPAP and systemic arterial pressure ($r = 0.307, p < 0.001$).

As expected, PA pressures, PVR, and TPG were higher, while PAC was lower in patients with PH than in those without PH (Table 2). Other hemodynamic markers of increasing HF severity, including HR, RAP, and PCWP, were higher, while CO and SV were lower in patients with PH than in patients without PH.

Compared to patients with passive PH, those with mixed PH had higher PA pressures, PVR, and TPG, with lower PAC, CO, and SV (Table 2). However, PCWP and RAP were similar in both subgroups, indicating that the presence of pulmonary vascular disease was the principle determinant of mixed PH rather than a difference in downstream left heart filling pressures.

Noninvasive hemodynamic characteristics. Compared to HF patients without PH, patients with PH had similar LV size and mass, slightly lower LVEF, more profound diastolic dysfunction (higher E/A and E/e’ ratio, shorter DT, larger left atrial volume), more severe mitral valve regurgitation, and more right ventricular dysfunction (higher EROA) and tended to display more severe RV dysfunction.

Correlates of pulmonary hypertension in HFREF. Clinical and hemodynamic variables associated with PH (passive or mixed) by unadjusted univariate and multivariate analyses are shown in Table 3. In univariate analysis, diabetes, atrial fibrillation, diuretic use, hemoglobin, renal function, LVEF, and PAC were predictors of the presence of PH. Age was a borderline univariate predictor but was included in the multivariate analysis because of its common association with PH. After multivariate adjustment, age,
diuretic use, atrial fibrillation, and PAC remained independent predictors of PH. After multivariate adjustment, age, atrial fibrillation, and PAC remained predictors of mixed PH as compared to passive PH.

**Relationship of PH subtypes to mortality.** There were 171 deaths (37%) over a median follow-up of 2.1 (95% confidence interval [CI]: 0.1 to 3.8) years. Using PVR to define the PH subgroups, we found a gradient of increasing risk of death from patients with no PH to those with passive PH and to those with mixed PH (Fig. 2A). However, when passive and mixed PH were defined according to TPG (passive, TPG <12 mm Hg; mixed, TPG ≥12 mm Hg), there were no differences in mortality between mixed and passive PH (Fig. 2B).

Table 4 shows univariate and multivariate clinical and hemodynamic predictors of mortality for the patient cohort. Both passive and mixed PH, defined using PVR, were predictors of death in addition to the previously described clinical variables. FAC was also associated with increased risk of death. In multivariate models including CO and mPAP, mixed PH remained an independent predictor of mortality, along with age, renal function, and hemoglobin.

**Hemodynamic predictors of mortality.** Increasing mPAP was associated with greater mortality risk than compared with no PH, although there were no statistically significant differences from one cutoff point to the other (Fig. 3). Similarly, pulmonary venous hypertension was associated with increased mortality with no differences between mild-moderate or severe elevations (PCWP ≥15 mm Hg and ≥22 mm Hg, respectively). A TPG ≥12 mm Hg also is often used to define mixed PH, but a partition value of 18 mm Hg provided more robust identification of risk relative to TPG <12 mm Hg (HR: 1.81, 95% CI: 1.23 to 2.65, p = 0.002 vs. HR: 1.22, 95% CI: 0.06 to 1.73, p = 0.257, respectively).

PAC, which has been shown to predict mortality in group 1 PH, demonstrated a separation of mortality risk in HFREF (Fig. 3). A PAC ≥2.0 ml/mm Hg conveyed a 3.5-fold increased risk (95% CI: 1.74, 3.35, p < 0.0001) relative to PAC values >5.0 ml/mm Hg. Using the median PAC value (2.3 ml/mm Hg) to define subgroups (i.e., mPAP ≥25 mm Hg, PCWP ≥15 mm Hg, and PAC ≤/≥2.3) revealed PAC values less than the median identified the subgroup of PH patients with highest risk (HR: 2.28, 95% CI: 1.64, 3.15, p < 0.001) (Fig. 4). PVR ≥3.5 WU identified greater risk of death (HR: 1.97, 95% CI: 1.42 to 2.74, p < 0.0001) (Fig. 3), while partition values <3.5 WU were statistically less predictive.

Figure 5 shows the hazard ratio (95% CL) of death as a function of PVR (Fig. 5A), sPAP (Fig. 5B), PCWP (Fig. 5C), and PAC (Fig. 5D) as continuous variables of risk. The inflection points of these curves suggest that PVR >~4.0 WU, sPAP >~35 mm Hg, PCWP >~25 mm Hg, and PAC <~2.0 ml/mm Hg might identify patients at highest risk for all-cause mortality. Hazard ratios crossing unity signifying threshold increases in risk were demonstrated for pulmonary vascular resistance at 1.5 WU, systolic pulmonary artery pressure at 25 mm Hg, pulmonary wedge pressure at 14 mm Hg, and PAC at 2.5 ml/mm Hg.

**Discussion**

The findings of this study address important knowledge gaps regarding the prevalence, definition, and prognostic significance of PH subgroups in HFREF (20–22) by presenting a comprehensive description of clinical, hemodynamic, and echocardiographic features in a large, well-described cohort of patients with HFREF. We found that approximately 75% of the catheterization laboratory referral
Table 2  Invasive and Noninvasive Hemodynamic Features PH Defined by PVR < or ≥ 3 WU

<table>
<thead>
<tr>
<th>Invasive hemodynamics</th>
<th>Passive PH (n = 186)</th>
<th>Mixed PH (n = 186)</th>
<th>p Value*</th>
<th>No PH (n = 126)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic blood pressure (S/D, mm Hg)</td>
<td>110 ± 22/64 ± 12</td>
<td>115 ± 24/64 ± 12</td>
<td>0.051/0.999</td>
<td>110 ± 22/62 ± 13</td>
<td>0.338/0.294</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>78 ± 18</td>
<td>77 ± 16</td>
<td>0.591</td>
<td>73 ± 17</td>
<td>0.035</td>
</tr>
<tr>
<td>Mean PAP</td>
<td>34 ± 6</td>
<td>42 ± 8</td>
<td>&lt;0.001</td>
<td>19 ± 4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PASP (mm Hg)</td>
<td>48 ± 9</td>
<td>62 ± 14</td>
<td>&lt;0.001</td>
<td>30 ± 6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>24.0 ± 5.9</td>
<td>24.5 ± 5.7</td>
<td>0.432</td>
<td>11.2 ± 4.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TPG (mm Hg)</td>
<td>9.4 ± 3.7</td>
<td>17.3 ± 6.1</td>
<td>&lt;0.001</td>
<td>8.1 ± 3.2</td>
<td>0.001</td>
</tr>
<tr>
<td>mRAP (mm Hg)</td>
<td>14.6 ± 7.2</td>
<td>15.0 ± 6.7</td>
<td>0.181</td>
<td>6.8 ± 3.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PVR (Wood units)</td>
<td>2.0 ± 0.7</td>
<td>5.0 ± 1.9</td>
<td>&lt;0.001</td>
<td>1.8 ± 0.8</td>
<td>0.011</td>
</tr>
<tr>
<td>PAC (ml/mm Hg)</td>
<td>2.8 ± 1.0</td>
<td>1.6 ± 0.7</td>
<td>&lt;0.001</td>
<td>4.4 ± 2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SVR (Wood units)</td>
<td>18 ± 5</td>
<td>24 ± 9</td>
<td>&lt;0.001</td>
<td>17 ± 5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>4.8 ± 1.2</td>
<td>3.7 ± 1.1</td>
<td>0.001</td>
<td>4.9 ± 1.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>64 ± 22</td>
<td>50 ± 17</td>
<td>0.001</td>
<td>72 ± 25</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean ± SD or % of cohort. Passive PH was defined as mPAP ≥25 mm Hg; PCWP ≥15 mm Hg; and PVR < 3 WU. Post-capillary passive PH was defined as mPAP ≥25 mm Hg; PCWP ≥15 mm Hg; and PVR ≥3 WU. *Mixed PH compared with passive PH; †No PH compared with Passive PH-mixed PH.

CO = cardiac output; LA = left atrial; LV = left ventricular; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; mPAP = mean pulmonary artery pressure; MV DT = mitral valve deceleration time; MV ERO = mitral valve effective regurgitant orifice; PAC = pulmonary artery compliance (stroke volume/pulmonary artery pulse pressure); PAP = pulmonary artery pressure; PASP = pulmonary artery systolic pressure; RVSP = right ventricular systolic pressure; S/D = systolic/diastolic; SVR = systemic vascular resistance; TPG = transpulmonary gradient; other abbreviations as in Tables 1 and 2.

population meeting study criteria displayed PH and that among these patients over half showed evidence of pulmonary vascular disease (mixed PH) superimposed on elevations in left heart filling pressures. Patients with any PH and particularly those with mixed PH displayed progressively more severe hemodynamic derangements with greater burden of diastolic dysfunction, mitral regurgitation, and right ventricular dysfunction despite grossly similar clinical profiles. Sensitivity analyses were performed to evaluate partition values of hemodynamic parameters that identified greater risk of death, and we further show that PAC refines risk assessment in group 2 PH and may be a novel therapeutic target in addition to PVR and mPAP. These data reinforce the important role of PH in the...
pathophysiology and progression of HF with reduced LVEF and support the need for trials of agents targeting passive and mixed PH in HF.

Numerous studies have shown that PH carries a greater risk of death in HF than LV dysfunction alone, but there have been few studies in HFREF patients that have evaluated the prognostic implications of the different subtypes of PH (11,15). These studies were performed in hospitalized patients with acute decompensated HF (ADHF), with heterogeneous clinical and PH origin status, relatively short-term follow-up (6 months), and conflicting results. Using data from the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial, Khush et al. (11) found no differences in clinical outcomes between patients with passive and those with mixed PH and also no differences in mortality compared with patients without PH. In contrast, using data from the VMAC (Vasodilation in the Management of Acute Congestive Heart Failure) trial, Aronson et al. (12) demonstrated a significant increased risk of death advancing from no PH to passive and mixed PH, similar to our current findings. A key difference between these studies was in the timing of the assessment of PH subgroups: prior to treatment of ADHF (11) and after treatment (15). By comparison, our data reflect the largest and most comprehensively phenotyped cohort of outpatients with chronic HFREF where causes of PH other than LV systolic dysfunction were excluded, and baseline right heart hemodynamic catheterization data were collected under stable therapeutic conditions and with long follow-up.

The partition values currently used to identify “abnormal” hemodynamics have been based largely on consensus opinion, and few studies have provided objective sensitivity analyses to identify which cutoff values best stratify risk. The adoption of empirically derived partition values may better align the magnitude of abnormalities with objective risk. Our sensitivity analyses suggest that cutoff points of PVR of ≥3.0 WU and PAC of ≤2.0 ml/mm Hg (unadjusted) are most strongly associated with risk separation, although risk of death was suggested to be increased above unity, even at

![Figure 2 Survival of HFREF Patients With PH](image)

**Figure 2** Kaplan-Meier estimates of survival in patients with heart failure of reduced left ventricular ejection fraction (HFREF) relative to passive pulmonary hypertension (PH) and mixed PH as defined by pulmonary vascular resistance (PVR) < or ≥3.0 Wood units (WU) and no PH. (B) Kaplan-Meier estimates of survival in patients with HFREF relative to passive PH and mixed PH as defined by transpulmonary gradient (TPG) < and ≥12 mm Hg and no PH.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted Hazard Ratio (95% CL)</th>
<th>p Value</th>
<th>Adjusted Hazard Ratio (95% CL)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed PH defined as PVR ≥3.0 WU</td>
<td>3.06 (1.98–4.89)</td>
<td>&lt;0.001</td>
<td>2.31 (1.24–4.52)</td>
<td>0.008</td>
</tr>
<tr>
<td>Passive PH defined as PVR &lt;3.0 WU</td>
<td>1.97 (1.27–3.14)</td>
<td>0.002</td>
<td>1.48 (0.82–2.78)</td>
<td>0.190</td>
</tr>
<tr>
<td>Age</td>
<td>1.43 (1.28–1.61)</td>
<td>&lt;0.001</td>
<td>1.31 (1.14–1.51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.36 (1.02–1.84)</td>
<td>0.038</td>
<td>1.06 (0.72–1.51)</td>
<td>0.773</td>
</tr>
<tr>
<td>eGFR</td>
<td>1.24 (1.15–1.34)</td>
<td>&lt;0.001</td>
<td>1.16 (1.06–1.28)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>2.77 (1.82–4.23)</td>
<td>&lt;0.001</td>
<td>1.94 (1.21–3.14)</td>
<td>0.006</td>
</tr>
<tr>
<td>PA compliance</td>
<td>1.85 (1.43–2.45)</td>
<td>&lt;0.001</td>
<td>1.11 (0.78–1.62)</td>
<td>0.586</td>
</tr>
</tbody>
</table>

PA = pulmonary artery; other abbreviations as in Tables 1 and 3.
PVR values less than 2.5 WU (Fig. 5). If these risk markers are validated in other HFREF populations, they may serve valuable roles in both risk stratification and potentially as modifiable endpoints in treatment trials.

We found that PH and particularly mixed PH were quite common in this referral population. While the cause of mixed PH cannot be determined from this analysis (i.e., structural vs. functional changes), the current and previously published data (23,24) suggest that it may relate to increasing severity and chronicity of the underlying HFREF, as there was progressively more severe diastolic dysfunction, mitral regurgitation, and right ventricular dysfunction identified progressing from no PH to passive and mixed PH. It is also notable that these groups were nearly indistinguishable on clinical grounds, with similar chamber remodeling, right- and left-sided filling pressures, and LVEF. The concept that mixed PH is associated with greater anatomic pulmonary artery remodeling is supported by the above-cited small study in transplant patients (23), where relative medial thickness was greater in the group with mixed PH than in those with passive PH. Future studies correlating clinicopathologic findings with pulmonary hemodynamics might offer further insight into the mechanism of disease.

Prior studies in healthy controls and in patients with group 1 PH have shown that PA systolic, mean, and diastolic pressures are very highly correlated, and we show that this relationship also extends to group 2 PH. Interestingly, the linear least squares regression equation relating mPAP to sPAP in the current sample was remarkably similar to that reported by Chemla et al. (25). A practical implication of these findings is that an assessment of sPAP is as valid as mPAP for identifying PH, with sPAP values of <2135 mm Hg corresponding to mPAP of <2125 mm Hg, based upon current and prior data. Often sPAP is reported in the context of systemic blood pressure, implying that there is some mechanistic relationship between the 2 parameters. However, the poor correlation observed between sPAP and systolic systemic BP in the current study (Fig. 1B) suggests that this is not a valid conclusion.

Previous studies have variably used PVR and TPG in the nomenclature of PH. An advantage of PVR is that in addition to assessing the hydraulic pressure drop across the pulmonary vascular bed, it accounts for flow (CO), which varies directly with TPG. The current findings support the use of PVR rather than TPG to identify mixed PH. Indeed, outcomes were similar between mixed and passive PH when the subgroups were defined using TPG <2112 mm Hg. However, as shown in our sensitivity analyses, defining mixed PH by PVR <212.5 WU or PAC >202.0 ml/mm Hg better identified patients at higher risk who might benefit from more aggressive or novel therapies. Intriguingly, these objectively defined partitions are in line with prior publications (26,27). The fact that the mixed PH phenotype remained a significant predictor of mortality even after adjusting for CO and mPAP further supports the concept that mixed PH represents a more malignant phenotype which may respond differently to therapies. These issues require further study.

Study limitations. In interpreting these data, several issues should be considered. One issue is the retrospective design of the study with its associated inherent limitations including possible referral bias. Additionally, exercise and vasodilator hemodynamic data which might provide further information on the prevalence and prognostic significance of the subgroups of PH are not available for this sample. Prior studies have
shown that the RV response to PH is as important or more important than the extent of pulmonary vascular disease present (13). While we provide qualitative assessment of RV function from echocardiographic evaluations, more quantitative assessment might further refine risk stratification in addition to the hemodynamic parameters. Cardiopulmonary exercise testing is a validated prognostic tool in HFREF, and this study does not provide data regarding exercise capacity. Further studies are warranted to explore potential relationships between pulmonary hemodynamics and exercise physiology. The cubic spline analyses (Fig. 5) were unadjusted, and comparisons were made only with the reference levels.

Conclusions

Group 2 PH is commonly identified in patients with chronic stable HFREF and carries a significantly increased mortality risk. The development of mixed PH with structural and/or functional pulmonary vascular disease is related to other markers of increased HF severity and chronicity, and carries incrementally greater risk of death. While several parameters can be used to distinguish the subgroups of PH, PVR and PAC appear most robust in separating patients at higher risk and may serve as novel targets for therapy.

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REFERENCES


Key Words: heart failure • mixed pulmonary hypertension • outcomes • passive pulmonary hypertension • risk prediction.