Clinical Characteristics of Pulmonary Hypertension in Patients With Heart Failure and Preserved Ejection Fraction

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Background—Pulmonary vascular disease associated with left-side heart failure and preserved ejection fraction (PH-HFpEF) is an increasingly common cause of pulmonary hypertension. The distinction between PH-HFpEF and pulmonary arterial hypertension (PAH) is important because therapies indicated for PAH can be detrimental in HFpEF. The characteristic features of PH-HFpEF are understudied.

Methods and Results—In a cross-sectional study, we compared the clinical, echocardiographic, and hemodynamic features of PH-HFpEF (n=100), with PAH (n=522), and HFpEF without pulmonary vascular disease (n=45). We determined the clinical characteristics that best differentiated PH-HFpEF from PAH. Compared with patients with PAH, patients with PH-HFpEF were older; had a higher prevalence of cardiovascular comorbidities; had worse exercise capacity and renal function; more frequently had left atrial enlargement; and less frequently had right atrial enlargement. PH was less severe in PH-HFpEF patients than in PAH patients (pulmonary vascular resistance 4.8 [interquartile range 3 to 8.4] versus 10.9 [interquartile range 7.4 to 15.7] Wood units; $P<0.001$). Old age, the presence of hypertension and coronary artery disease, the absence of right atrial enlargement, higher aortic systolic pressure, higher mean right atrial pressure, and higher cardiac output best differentiated PH-HFpEF from PAH (area under the receiver operating characteristics curve; curve 0.97). Compared with HFpEF patients without pulmonary hypertension, PH-HFpEF patients were often female and more symptomatic, more often had right ventricular hypertrophy and right atrial enlargement, and had higher right atrial pressure.

Conclusions—These data should help better identify PH-HFpEF, an entity that has become increasingly recognized and difficult to treat. **(*Circ Heart Fail*. 2011;4:257-265.)**

Key Words: pulmonary vascular disease ■ hemodynamics ■ pulmonary arterial hypertension

Pulmonary hypertension (PH) is a known complication of any disease that elevates left ventricular (LV) filling pressure including LV systolic dysfunction,[1] LV diastolic dysfunction,[2] and left-side valvular heart disease.[3] Chronic elevation in LV filling pressure increases pulmonary venous pressure, which, in some patients, triggers vasoconstriction and arterial remodeling leading to precapillary PH, and increased pulmonary vascular resistance (PVR) superimposed on the elevated pulmonary venous pressure.[4,5] In 1998, the World Health Organization (WHO) endorsed a new classification of PH and grouped PH resulting from left-side heart failure (HF) under category II (pulmonary venous hypertension).[6]

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Left-side heart failure with preserved ejection fraction (HFpEF), defined as symptomatic HF occurring in the setting of a LV ejection fraction (LVEF) ≥50%, accounts for nearly one-half of all hospitalizations for HF in the United States,[7] and is an increasingly common etiology for WHO category II PH.[8] Most HFpEF patients with PH have elevated pulmonary arterial pressure (PAP) because of increased left-side filling pressure with normal PVR or transpulmonary gradient. However, a subset of HFpEF patients develop intrinsic pulmonary vascular disease in addition to elevated filling pressure, leading to not only elevated PAP, but also increased PVR and transpulmonary gradient (TPG).[9] The clinical characteristics of these HFpEF patients with PH because of intrinsic pulmonary vascular disease (PH-HFpEF) have not been well described.

There is concern that PH-HFpEF may often be misclassified as having WHO category I pulmonary arterial hypertension (PAH) because both these patient groups can have a normal LVEF and evidence of LV diastolic dysfunction.[10] The distinction between PH-HFpEF and PAH is particularly important because therapies indicated for PAH can be detri-

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mental in HFpEF.[11–14] Thus, we sought to characterize the clinical, echocardiographic, and hemodynamic features of patients with PH-HFpEF and to determine the clinically relevant differences in these parameters in patients with PAH and in patients with HFpEF who do not have pulmonary vascular disease.

Methods

Study Design

Our study samples consist of patients in the Pulmonary Hypertension Connection (PHC) Registry at the University of Chicago Medical Center and patients from the Northwestern University HFpEF Program. The PHC Registry has been described in detail previously.[15] In brief, the PHC Registry was created as a customized patient database to longitudinally collect specific variables on every patient treated in our practice since 1982. Four physicians acquired the clinical data, which were collected by chart review, and entered using an Internet-based electronic data capture system. Patients were entered retrospectively from 1982 to February 2004 and prospectively from March 2004. Informed consent for participation in the registry was obtained during the initial evaluation for new patients, or during routine office visits for patients who already were being followed before initiation of the registry (<1% refused entry into the study). For all variables, outliers were verified by chart review to minimize data entry errors. The respective institutional review boards based on the location of the practice approved the PHC Registry.

Patients in the Northwestern University HFpEF Program were identified from the electronic inpatient medical record, which is queried daily for (1) diagnosis of heart failure or words "heart failure" anywhere in the inpatient medical record; *or* (2) brain natriuretic peptide >100 pg/mL; *or* (3) intravenous administration of 2 or more doses of diuretics. The list of patients generated on a daily basis is screened, and only those patients who have LVEF >50% and who meet Framingham criteria for HF[16] are referred to the Northwestern HFpEF Program as outpatients where the diagnosis of HF is confirmed by a HF specialist. The diagnosis of HFpEF was in concordance with previously published studies.[17,18] All HFpEF patients were required to have ejection fractions >50%, LV end-diastolic volume index <97 mL/m^2, and elevated LV filling pressures at time of cardiac catheterization. Using this methodology, consecutive HFpEF patients who consented to evaluation in the HFpEF Program were studied prospectively beginning in March 2008. All patients gave written, informed consent, and the institutional review board at Northwestern University approved the study.

Study Groups

For the current analysis, we identified 2 groups of patients (PH-HFpEF and PAH) from the PHC Registry. Patients who met the following inclusion criteria constituted the PH-HFpEF group: presence of signs and symptoms of HF, LVEF ≥50%, pulmonary capillary wedge pressure (PCWP) >15 mm Hg (or left ventricular end-diastolic pressure [LVEDP] >15 mm Hg if a satisfactory PCWP could not be obtained), and PVR >2.5 Woods units and/or TPG >12 mm Hg. Because an elevation in LVEDP will cause an obligatory increase in PAP, using an increase in PAP alone to define the presence of pulmonary vascular disease would be misleading. Thus, we defined PH-HFpEF as patients also having a PVR >2.5 Woods units and/or TPG >12 mm Hg.[19] We excluded patients with significant (> moderate) mitral and aortic valvular heart disease or restrictive cardiomyopathy that was confirmed by biopsy. The diagnosis of PAH required a mean PAP (mPAP) >25 mm Hg at rest, PCWP ≤15 mm Hg at rest, and the exclusion of other WHO categories of PH by clinical evaluation and objective tests.[20] The third group of patients who had HFpEF but no pulmonary vascular disease (PCWP >15 mm Hg, PVR ≤2.5 Wood units, and/or TPG ≤12 mm Hg) came from the Northwestern University HFpEF program. The cut-off date for the data analysis was April 2009.

Patient Characteristics, Comorbidities, and Echocardiography

We analyzed the following baseline variables at the time of referral for characterization of clinical phenotype: demographic data, including age and sex, WHO functional class, comorbidities, serum creatinine, and exercise treadmill testing using the Naughton Balke protocol as a measure of exercise capacity.[21] Patients in the Northwestern University HFpEF program did not undergo exercise treadmill testing. Hypertension was defined by systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg, physician-documented history of hypertension, or use of antihypertensive medications. Diabetes mellitus was defined by the presence of physician-documented history of diabetes mellitus or if the patient was taking oral hypoglycemic agents or insulin for the treatment of hyperglycemia. Coronary artery disease (CAD) was defined by the presence of physician-documented history of CAD, known coronary stenosis >50%, prior history of myocardial infarction, percutaneous intervention, coronary artery bypass grafting, or abnormal stress test consistent with myocardial ischemia. Obesity was defined by a body mass index >30 kg/m^2 or physician-documented history of obesity.

We also collected data on the following baseline echocardiographic variables on available patients: LV mass, LV posterior wall thickness, interventricular septal wall thickness, LVEF, presence of left and right atrial enlargement, right ventricular hypertrophy, and pericardial effusion. Data on all echocardiographic variables were not available for some study patients because of poor image quality. Data on Doppler variables were not included in this study.

Baseline Hemodynamics

All patients from 3 study groups (PH-HFpEF, PAH, and HFpEF without pulmonary vascular disease) underwent baseline hemodynamic assessment by left and right heart catheterization as an outpatient on a stable medical regimen. Hemodynamic testing included measurement of mean right atrial pressure (mRAP), mPAP, PCWP, LVEDP, and cardiac output (CO) by thermodilution method. We calculated TPG and PVR from standard formulas: TPG=mPAP−PCWP and PVR=TPG/CO.

Statistical Analysis

All continuous variables were expressed as mean±SD if the variable was normally distributed and as median (interquartile range) if the variable was not normally distributed. Categorical variables were expressed as frequency and percentages. Between-group differences were assessed by 1-way ANOVA or Kruskal-Wallis test (when appropriate) with a post hoc Bonferroni's test for multiple comparisons. Categorical variables were compared by use of the χ^2 test or Fisher exact test. Because patients with PH-HFpEF were significantly older than PAH patients, we performed age and sex adjustment using logistic regression to determine clinical characteristics that differed between the 3 study groups. We performed additional multivariate logistic regression analyses to determine the clinical characteristics that best differentiated patients with PH-HFpEF from PAH patients. All baseline characteristics were included in our univariate analysis. For our multivariate analysis, we included any variable with a probability value <0.05 on the univariate analysis. We did not include mPAP, TPG, PCWP, LVEDP, CO, and PVR in the multivariate analysis because these variables were used to define the study groups. LV posterior wall thickness correlated significantly with interventricular septal thickness and LV mass (correlation coefficient=0.72, $P<0.0001$ and 0.64, $P<0.0001$, respectively); hence, only LV posterior wall thickness was retained in the final model (because septal wall thickness can be increased from right ventricular hypertrophy alone). To understand the relative value of the factors in differentiating PH-HFpEF from PAH, we constructed 4 separate models. We started with a model including age alone for predicting PH-HFpEF from PAH, and then added into the model all baseline clinical characteristics, followed by echocardiographic characteristics, and finally included hemodynamic data. The predictive value of each model is represented by the C statistic. A nonparametric approach for comparing each C statistic was used. A probability

Table 1. Comparison of Age- and Sex-Adjusted Baseline Clinical and Echocardiographic Characteristics of the Study Groups

Characteristics	HFpEF (n=45)	PAH (n=522)	PH-HFpEF (n=100)	*P* Value
Age, yrs	67±11	48±14	64±13†	<0.0001
Female, n (%)	26 (58)	400 (77)	82 (82)*	0.01
WHO functional class III and IV, n (%)	23 (51)	474 (91)	97 (97)*	0.03
BSA, m^2	2.0±0.3	1.8±0.2	2.0±0.3†	<0.0001
Comorbidities, n (%)				
Hypertension	33 (77)	152 (29)	79 (79)†	<0.0001
Diabetes mellitus	12 (28)	44 (8)	37 (37)†	<0.0001
Obesity	22 (49)	79 (15)	46 (46)†	<0.0001
Coronary artery disease	16 (37)	22 (4)	27 (27)†	<0.0001
Treadmill exercise capacity, Mets	NA	3.8±2.1	2.8±1.2	0.02
Serum creatinine, mg/dL‡	1.1 (0.9–1.5)	1.0 (0.8–1.2)	1.1 (0.9–1.4)†	<0.001
Medications, n (%)				
Calcium channel blockers	10 (22)	168 (32)	38 (38)	0.24
Digoxin	4 (9)	80 (16)	21 (21)	0.27
Coumadin	14 (33)	165 (32)	37 (38)	0.44
Diuretics	33 (73)	238 (46)	81 (81)†	<0.0001
β-blockers	32 (71)	55 (11)	37 (37)*†	<0.0001
ACE inhibitors/ ARB	25 (56)	90 (17)	48 (48)†	<0.0001
Endothelin blockers	0 (0)	31 (6)	6 (6)	<0.0001
PDE-5-Inhibitors	0 (0)	18 (4)	4 (4)	0.17
Prostacyclins	0 (0)	16 (3)	0 (0)	0.14
Echocardiographic variables				
LV mass index, g/m^2	88±28	88±39	78±28	0.09
LV posterior wall thickness, mm	11.3±2.2	10±2	11±3	<0.001
Interventricular septal thickness, mm	11.5±2.7	10.4±2.6	11.3±3.2	0.03
LV ejection fraction, %	60±6	60±10	62±7	0.13
Left atrial enlargement, n (%)§	20 (65)	85 (18)	56 (64)†	<0.0001
Right atrial enlargement, n (%)§	13 (41)	411 (89)	57 (68)*†	<0.0001
RV hypertrophy, n (%)§	7 (22)	240 (57)	32 (45)	<0.0001

HFpEF indicates left-side heart failure with preserved ejection fraction without pulmonary vascular disease; PAH, pulmonary arterial hypertension; PH-HFpEF, pulmonary hypertension because of pulmonary vascular disease associated with left-side heart failure and preserved ejection fraction; BSA, body surface area; METs, metabolic equivalents; ACE, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blocker; PDE, phosphodiesterase; LV, left ventricle; RV, right ventricle; PCWP, pulmonary capillary wedge pressure; PA, pulmonary artery; and PVR, pulmonary vascular resistance.

Data presented as mean±SD and n (%) otherwise specified.

*$P<0.05$ vs HFpEF group; †$P<0.05$ vs PAH group using the Bonferroni post hoc test or χ^2 test for categorical variable.

‡Values expressed as median (interquartile range) due to lack of normal distribution.

§Missing data for these echocardiographic variables because of poor image quality.

value <0.05 was considered statistically significant. All statistical analyses were performed using Stata (version 10 and 11, StataCorp LP, College Station, TX).

Results

From the PHC registry, a total of 100 patients had PH-HFpEF and 522 patients had PAH. Sixty-three of the 100 patients with PH-HFpEF (63%) and 129 of the 522 patients with PAH (25%) were studied prospectively (after February 2004). Of the 522 patients with PAH, 246 patients had idiopathic PAH, 25 patients had hereditable PAH, 156 patients had connective tissue disease, 37 patients had congenital heart disease, 35 patients had portal hypertension, 18 patients had anorexigen-associated PAH, and 5 patients had HIV.

Forty-five patients had HFpEF without pulmonary vascular disease in the Northwestern University HFpEF Program; all these patients were studied prospectively. Tables 1 and 2 compare the baseline clinical, echocardiographic, and hemodynamic characteristics of the study groups after adjusting for age and sex.

PH-HFpEF

Clinical Characteristics

Patients with PH-HFpEF were older than patients with PAH. Both PH-HFpEF and PAH groups had similarly high female predominance. The prevalence of several comorbid conditions, including hypertension, diabetes mellitus, obesity, and

Table 2. Comparison of Age- and Sex-Adjusted Baseline Hemodynamics of the Study Groups

Hemodynamic Characteristics	HFpEF (n=45)	PAH (n=522)	PH-HFpEF (n=100)	*P* Value
Aortic systolic pressure, mm Hg	145±29	127±23	147±33†	<0.001
Aortic diastolic pressure, mm Hg	68±10	74±13	74±15*	0.59
LV end-diastolic pressure, mm Hg	21±8	10±8	21±6†	<0.001
PCWP, mm Hg	20±9	9±4	23±7†	<0.001
Mean right atrial pressure, mm Hg‡	12 (7–16)	9 (5–14)	15 (10–19)†*	<0.0001
Mean PA pressure, mm Hg	28±9	52±13	49±13*	<0.001
Cardiac output, l/min	5.3±1.8	4.1±1.6	5±2†	<0.0001
PA oxygen saturation, %	68±6	59±11	60±11*	<0.001
Transpulmonary gradient, mm Hg	8±3	43±12	26±11*†	<0.001
PVR, Woods unit§	1.6 (1.3–2.0)	10.9 (7.4–15.7)	4.8 (3–8.4)*†	<0.001

HFpEF indicates left-side heart failure with preserved ejection fraction without pulmonary vascular disease; PAH, pulmonary arterial hypertension; PH-HFpEF, pulmonary hypertension because of pulmonary vascular disease associated with left-side heart failure and preserved ejection fraction; LV, left ventricle; RV, right ventricle; PCWP, pulmonary capillary wedge pressure; PA, pulmonary artery; PVR, pulmonary vascular resistance.

Data presented as mean±SD otherwise specified.

*$P<0.05$ vs HFpEF group; †$P<0.05$ vs PAH group; ‡$P<0.05$ against PH-HFpEF using the Bonferroni post hoc test or χ^2 test for categorical variable.

§Values expressed as median (interquartile range).

CAD was increased in patients with PH-HFpEF compared with PAH patients. On exercise treadmill testing, there was no difference in exercise capacity between patients with PH-HFpEF and PAH patients. Patients with PH-HFpEF had worse renal function than patients with PAH. The use of diuretics, β-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers were higher in the PH-HFpEF group compared with the PAH group.

In comparison with patients with HFpEF without pulmonary vascular disease, patients with PH-HFpEF were more often female; had worse WHO functional class; had a similar prevalence of hypertension, diabetes mellitus, obesity, and CAD; and took β-blockers less often.

Echocardiographic Characteristics

PH-HFpEF patients more often had left atrial enlargement, but less often had right atrial enlargement compared with PAH patients. LVEF, LV posterior and interventricular septal thickness, and the presence of right ventricular hypertrophy did not differ between patients with PH-HFpEF and those with PAH. In distinction, there was no difference in the presence of left atrial enlargement between PH-HFpEF patients and HFpEF patients without pulmonary vascular disease, but patients with PH-HFpEF more frequently had right atrial enlargement. There was a trend toward increased right ventricular hypertrophy in PH-HFpEF compared with HFpEF without pulmonary vascular disease ($P=0.08$).

Hemodynamic Characteristics

Patients with PH-HFpEF had a significantly lower TPG and PVR with a higher aortic systolic pressure, CO, and mRAP than patients with PAH (Figure 1). Aortic systolic pressure, CO, PCWP, and LVEDP were comparable between HFpEF patients with and without pulmonary vascular disease. However, patients with PH-HFpEF had a higher aortic diastolic pressure, mRAP, and mPAP with a lower pulmonary arterial saturation compared with HFpEF patients without pulmonary vascular disease.

Characteristics Best Differentiating PH-HFpEF From PAH Patients

Table 3 lists the univariate predictors that were associated with PH-HFpEF. On multivariate analysis, age, hypertension, CAD, right atrial enlargement, aortic systolic pressure, mRAP, and CO remained as independent predictors of PH-HFpEF (Table 4). The model as a whole best differentiated PH-HFpEF from PAH with an area under the receiver operating characteristics curve of 0.97 (Figure 2). Table 5 lists the 4 models we created to differentiate PH-HFpEF from PAH, and the area under the receiver operating characteristics curves of these separate models are presented in Figure 2. Age alone differentiated PH-HFpEF from PAH with a C statistic of 0.81 (95% confidence interval, 0.74 to 0.88). Other baseline clinical characteristics in addition to age were able to differentiate most PH-HFpEF from PAH (C statistic, 0.92; 95% confidence interval, 0.88 to 0.96). Echocardiographic data had no significant incremental value over baseline clinical characteristics (C statistic, 0.93; 95% confidence interval, 0.90 to 0.97; $P=0.05$ versus model 2). The addition of hemodynamic data in the fourth model resulted in a modest, but a statistically significant, incremental value over the clinical and echo characteristics for differentiating PH-HFpEF from PAH (C statistic, 0.97; 95% confidence interval, 0.96 to 0.99; $P=0.005$ versus model 3). The results of our discriminant analysis confirmed our findings on multivariate logistic regression analysis (see online-only Data Supplement).

Discussion

This study describes the defining characteristics of patients with PH-HFpEF and provides insight into their distinguishing hemodynamic features. Our data indicate that the patients with PH-HFpEF have clinical, echocardiographic, and hemodynamic characteristics distinct from PAH and from HFpEF

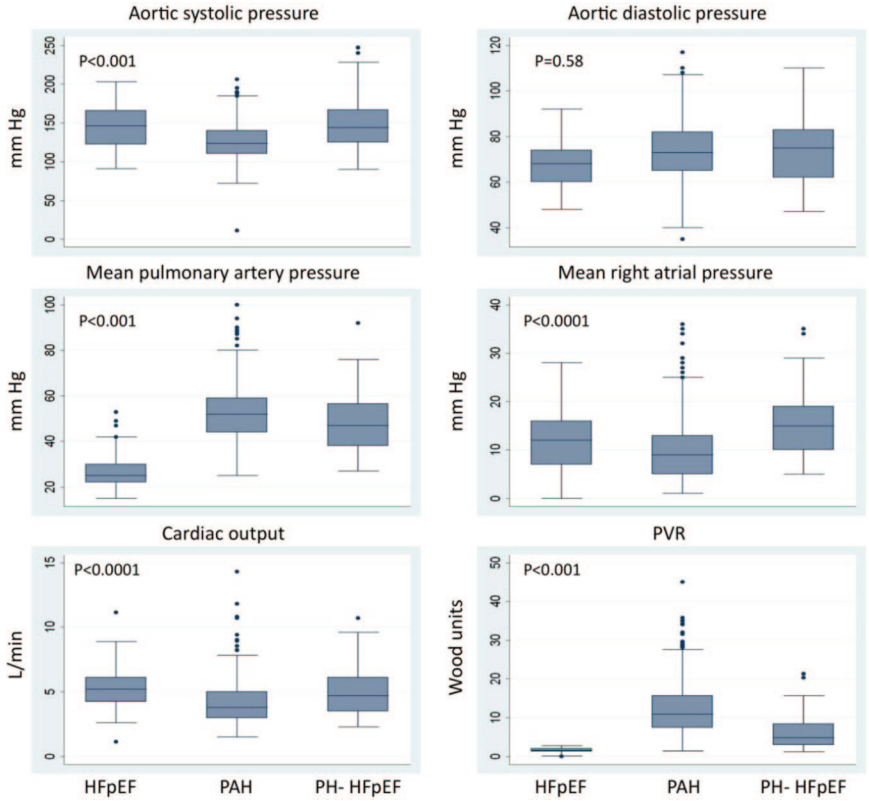

Figure 1. Comparison of hemodynamic characteristics of the study groups. HFpEF indicates heart failure with preserved ejection fraction without pulmonary vascular disease; PAH, pulmonary arterial hypertension; PH-HFpEF, pulmonary hypertension attributable to pulmonary vascular disease resulting from left-side heart failure and preserved ejection fraction.

without pulmonary vascular disease (Table 6). These distinctions support the WHO classification, which places them in a separate group from PAH. Knowing these features may prove helpful for clinicians evaluating patients who present with unexplained PH, especially when making decisions about pulmonary vasodilator drug therapy.

PAH Versus PH-HFpEF

Compared with PAH patients, PH-HFpEF patients are older with a higher prevalence of hypertension, diabetes mellitus, obesity, and CAD. They also are more symptomatic with a worse exercise capacity, which may be related to increased age, comorbidities, or higher PCWP. In addition, compared with PAH, patients with PH-HFpEF more frequently have left atrial enlargement and less frequently have right atrial enlargement. These findings are in keeping with the characteristics of HFpEF as described in previous studies.[22–26] Whereas the patients with PH-HFpEF in our study had a lower mPAP and PVR compared with patients with PAH, they had higher mRAP, a well-known predictor of mortality in PAH and left-heart failure.[27,28] The mechanism behind this finding is unclear. It may reflect worse right-heart function, neurohormonal activation, worse renal function, or increased intravascular volume. It is also possible that the high right atrial pressures in patients with lesser degrees of right atrial enlargement reflect abnormal atrial compliance, perhaps as a manifestation of an overall loss of myocardial diastolic distensibility.

Our findings are consistent with 2 previous studies that described the characteristic features of PH-HFpEF. Shapiro et al[10] reported that patients with PAH and elevated PCWP were older and more likely to have cardiovascular disease and increased vascular and diastolic stiffness. Robbins et al[29] also noted that HFpEF with PH was frequently associated with the metabolic syndrome. Our study builds on these previous reports by identifying the clinical characteristics that best differentiate PH-HFpEF from PAH using multivariate analysis. Although there are important differences between PH-HFpEF and PAH, we found that older age, the presence of obesity or CAD, the absence of right atrial enlargement, the presence of left atrial enlargement, higher aortic systolic pressure, and higher mRAP best differentiated PH-HFpEF from PAH (area under the curve 0.97).

PH-HFpEF is currently distinguished from PAH based on a demonstration of an elevated PCWP,[30] which occasionally can be difficult to ascertain.[31,32] Additionally, when PH-HFpEF patients develop severe right ventricular failure and a low cardiac output, the PCWP might fall, making the diagnosis uncertain.[9] Furthermore, PCWP can sometimes be discrepant from LVEDP.[33] Our data show that, in addition to LVEDP, the characteristic features we have described for PH-HFpEF (Table 6) could complement the LVEDP, and thus, assist clinicians in better differentiating PH-HFpEF from PAH. However, it should be emphasized that these characteristic features should not replace the LVEDP to differentiate PH-HFpEF from PAH.

HFpEF Versus PH-HFpEF

Most HFpEF patients will have some elevation in PAP secondary to elevated left-side filling pressures. However, a subset of these patients develops intrinsic pulmonary vascular disease in addition to elevated LV filling pressure, leading to

Table 3. Univariable Predictors of PH-HFpEF Versus PAH

Characteristics	OR (95% CI)	*P* Value	OR Adjusted for Age and Sex (95% CI)	*P* Value
Age	1.09 (1.07–1.11)	<0.0001	1.09 (1.07–1.11)	<0.0001
Female	1.39 (0.80–2.41)	0.24	0.98 (0.54–1.79)	0.95
WHO functional class III & IV	3.27 (1.0–10.72)	0.05	2.67 (0.74–9.66)	0.13
BSA	10.17 (3.97–26.04)	<0.0001	49.02 (14.56–164.99)	<0.0001
Comorbidities				
Hypertension	9.13 (5.44–15.31)	<0.0001	4.50 (2.57–7.88)	<0.0001
Diabetes mellitus	6.35 (3.81–10.58)	<0.0001	5.16 (2.93–9.09)	<0.0001
Obesity	4.76 (3.00–7.54)	<0.0001	6.81 (3.90–11.89)	<0.0001
Coronary artery disease	8.39 (4.54–15.50)	<0.0001	5.02 (2.55–9.89)	<0.0001
Treadmill exercise capacity	0.70 (0.53–0.92)	0.01	0.83 (0.62–1.11)	0.21
Serum creatinine	1.46 (1.13–1.88)	0.003	1.34 (1.06–1.70)	0.01
Medications				
Calcium channel blockers	1.29 (0.83–2.01)	0.26	0.91 (0.55–1.49)	0.71
Digoxin	1.49 (0.87–2.55)	0.15	1.57 (0.86–2.90)	0.14
Coumadin	1.30 (0.83–2.03)	0.26	1.30 (0.79–2.16)	0.30
Diuretics	5.09 (3.0–8.63)	<0.0001	3.24 (1.85–5.70)	<0.0001
β-blockers	4.99 (3.05–8.16)	<0.0001	3.56 (2.05–6.19)	<0.0001
ACE inhibitors/ ARB	4.43 (2.82–6.97)	<0.0001	3.09 (1.87–5.08)	<0.0001
Echocardiographic variables				
LV mass index	1.01 (1.0–1.02)	0.16	1.00 (0.99–1.02)	0.53
LV posterior wall thickness	1.20 (1.07–1.34)	0.002	1.13 (1.0–1.27)	0.06
Interventricular septal thickness	1.12 (1.01–1.23)	0.02	1.09 (0.98–1.22)	0.10
LV ejection fraction	1.02 (0.99–1.06)	0.15	1.00 (0.97–1.04)	0.89
Left atrial enlargement	8.03 (4.88–13.22)	<0.0001	5.10 (2.95–8.80)	<0.0001
Right atrial enlargement	0.26 (0.15–0.45)	<0.0001	0.29 (0.16–0.55)	<0.0001
RV hypertrophy	0.62 (0.37–1.03)	0.06	0.68 (0.39–1.19)	0.18
Hemodynamic characteristics				
Aortic systolic pressure	1.03 (1.02–1.04)	<0.0001	1.02 (1.01–1.03)	<0.0001
Aortic diastolic pressure	1.00 (0.98–1.01)	0.89	1.03 (1.0–1.04)	0.02
LV end diastolic pressure	1.35 (1.26–1.44)	<0.0001	1.35 (1.25–1.46)	<0.0001
PCWP	1.78 (1.57–2.01)	<0.0001	1.78 (1.56–2.04)	<0.0001
Mean right atrial pressure	1.13 (1.09–1.16)	<0.0001	1.16 (1.11–1.21)	<0.0001
Mean PA pressure	0.98 (0.96–0.99)	0.008	1.0 (0.98–1.02)	0.73
Cardiac output	1.29 (1.10–1.85)	<0.0001	1.41 (1.22–1.63)	<0.0001
PA oxygen saturation	1.01 (0.97–1.03)	0.51	1.01 (0.98–1.03)	0.55
Transpulmonary gradient	0.87 (0.85–0.90)	<0.0001	0.88 (0.86–0.91)	<0.0001
PVR	0.76 (0.71–0.81)	<0.0001	0.77 (0.71–0.83)	<0.0001

HFpEF indicates left-side heart failure with preserved ejection fraction without pulmonary vascular disease; PAH, pulmonary arterial hypertension; PH-HFpEF, pulmonary hypertension because of pulmonary vascular disease associated with left-side heart failure and preserved ejection fraction; OR, odds ratio; CI, confidnence interval; BSA, body surface area; METs, metabolic equivalents; ACE, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blocker; PDE, phosphodiesterase; LV, left ventricle; RV, right ventricle; PCWP, pulmonary capillary wedge pressure; PA, pulmonary artery; PVR, pulmonary vascular resistance.

an increased PVR. It is unknown why some patients with HFpEF develop intrinsic pulmonary vascular disease, whereas others do not. In addition, there is paucity of data comparing the clinical characteristics of HFpEF patients with and without pulmonary vascular disease. Our results suggest that patients with PH-HFpEF are more likely to be women, compared with HFpEF patients without pulmonary vascular disease. Patients with PH-HFpEF had a worse functional class, which probably reflects the influence of RV dysfunction, and they have an increased prevalence of right atrial enlargement and right ventricular hypertrophy, which probably reflects the presence of an increased RV afterload from the pulmonary vascular disease. Patients with HFpEF without pulmonary vascular disease and PH-HFpEF had remarkably similar hemodynamics, with the exception of a higher pulmonary artery pressure, aortic diastolic pressure, and mRAP

Table 4. Multivariable Predictors of PH-HFpEF Versus PAH

Baseline Characteristics	OR (95% CI)	*P* Value
Age (per 10-y increase)	2.23 (1.28–3.90)	0.005
Hypertension	7.88 (1.80–34.04)	0.006
Coronary artery disease	14.53 (3.18–66.37)	0.001
Right atrial enlargement	0.14 (0.03–0.65)	0.012
Aortic systolic pressure (per 10 mm Hg increase)	1.45 (1.12–1.90)	0.006
Mean right atrial pressure (per 5 mm Hg increase)	4.93 (2.65–9.17)	<0.0001
Cardiac output (per l/min increase)	2.10 (1.41–3.14)	<0.0001

PH-HFpEF indicates pulmonary hypertension because of pulmonary vascular disease associated with left-side heart failure with preserved ejection fraction; PAH, pulmonary arterial hypertension; OR, odds ratio; CI, confidence interval.

in PH-HFpEF. Whereas PH-HFpEF shares some clinical features with both PAH and HFpEF, these data suggest that PH-HFpEF is more likely the result of the development of pulmonary vascular disease in patients with HFpEF rather than the development of HFpEF in patients with PAH.

Lam et al[34] compared the characteristics of 244 community-based HFpEF patients with and without PH. In their observation, HFpEF patients with PH were older, and they had larger left atria compared with HFpEF patients without PH. The PH-HFpEF patients in our study were similarly older, but our patients were more often female and we found no difference in the left atrial size. These differences may be methodological because those patients were from a community-based cohort and were not diagnosed as PH-HFpEF from cardiac catheterization. In addition, differences in the method of determining left atrial size (ie, left atrial volume versus left atrial diameter) may have contributed to our inability to detect a difference in left atrial size

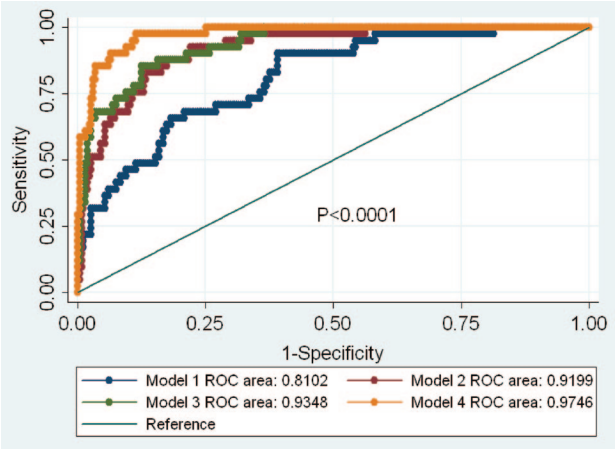

Figure 2. Receiver operating characteristics curve of the 4 models for the differentiation of PH-HFpEF from PAH. ROC indicates receiver operating characteristics curve; PH-HFpEF, pulmonary hypertension attributable to pulmonary vascular disease resulting from left-side heart failure and preserved ejection fraction; PAH, pulmonary arterial hypertension. Model 1 included age alone. Model 2 included all baseline clinical characteristics including age. Model 3 included model 2+echocardiographic predictors. Model 4 included model 3+hemodynamic predictors (full model).

Table 5. Different Models for Predicting PH-HFpEF Versus PAH

Model	Variables
Model 1	Age
Model 2	Model 1+WHO functional class, hypertension, obesity, diabetes mellitus, coronary artery disease, serum creatinine, diuretic, beta-blocker, and ACE inhibitors/ARB
Model 3	Model 2+left ventricular posterior wall thickness, left atrial enlargement, and right atrial enlargement
Model 4	Model 3+aortic systolic pressure, mean right atrial pressure, mean pulmonary artery pressure, and cardiac output

WHO indicates World Health Organization; ACE, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker.

when comparing patients with PH-HFpEF and those with HFpEF without pulmonary vascular disease. In a recent multivariate analysis by Leung,[35] age >80, morbid obesity, chronic obstructive pulmonary disease, atrial arrhythmias, LVEDP ≥25 mm Hg, and dyspnea on exertion were associated with PH in patients with HFpEF. In contrast, we did not observe any of these differences, with the exception that PH-HFpEF patients in our study also were elderly and had worse WHO functional class compared with HFpEF patients without pulmonary vascular disease.

Limitations

The results of the present study should be interpreted in the context of several limitations. The PHC Registry is a longitudinal observational study with data collection starting in 2004. Therefore, 37% of patients with PH-HFpEF and most PAH patients were entered retrospectively. Our study results could be confounded by the significant difference in the sample size between our 3 study cohorts. The present study includes patients referred to tertiary medical centers, and thus, these observations may not be generalizable to the patients in the general community. We also compared HFpEF patients with and without pulmonary vascular disease from 2 different registries (the PHC Registry and the Northwestern University HFpEF program). Thus, differences noted between these 2 patient cohorts, such as age and sex, may be

Table 6. Distinguishing Clinical Features of the Study Groups

Characteristics	HFpEF	PAH	PH-HFpEF
Age	Older	Younger	Older
Comorbidities	Frequent	Rare	More frequent
Right atrial enlargement	Absent	More frequent	Less frequent
Left atrial enlargement	Frequent	Absent	Frequent
Aortic systolic pressure	Elevated	Normal	Elevated
Mean right atrial pressure	Normal	Normal-High	High
Cardiac output	Normal	Low	Normal
Pulmonary vascular resistance	Normal	Markedly elevated	Moderately elevated

Comorbidities include hypertension, diabetes mellitus, obesity, and coronary artery disease. PAH indicate mean pulmonary artery pressure; PH-HFpEF, pulmonary hypertension because of pulmonary vascular disease associated with heart failure and preserved ejection fraction; HFpEF, heart failure with preserved ejection fraction without pulmonary vascular disease.

influenced by the inherent differences in the registry design and patient referral.

Conclusion

We provide a detailed description of the clinical, echocardiographic, and hemodynamic characteristics of patients with pulmonary hypertension attributable to pulmonary vascular disease resulting from left-side heart failure with preserved ejection fraction. These data allowed us to identify the characteristics that help distinguish these patients from patients with PAH and from those with HFpEF but without pulmonary vascular disease. Studies to determine why some patients with HFpEF develop pulmonary vascular disease, whereas others do not, are needed to better understand the pathophysiology of PH-HFpEF. Because of the increasing frequency in which these patients are becoming diagnosed, a better understanding of their outcome and response to treatments is urgently needed.

Disclosures

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CLINICAL PERSPECTIVE

Pulmonary vascular disease associated with left-side heart failure and preserved ejection fraction (PH-HFpEF) is an increasingly common cause of pulmonary hypertension. There is concern that PH-HFpEF may often be misclassified as having WHO category I pulmonary arterial hypertension (PAH) because both these patient groups can have a normal left ventricular ejection fraction and evidence of left ventricular diastolic dysfunction. The distinction between PH-HFpEF and PAH is particularly important because therapies indicated for PAH can be detrimental in HFpEF. Thus, we sought to characterize the clinical, echocardiographic, and hemodynamic features of patients with PH-HFpEF and to determine the clinically relevant differences in these parameters in patients with PAH and in patients with HFpEF who do not have pulmonary vascular disease. Compared with PAH patients, PH-HFpEF patients are more symptomatic with a worse exercise capacity, which may be related to increased age, comorbidities, or higher pulmonary capillary wedge pressure. Compared with HFpEF patients without pulmonary vascular disease, patients with PH-HFpEF also had a worse functional class, which probably reflects the influence of RV dysfunction. Patients with HFpEF without pulmonary vascular disease and PH-HFpEF had remarkably similar hemodynamics, with the exception of a higher pulmonary artery pressure, aortic diastolic pressure, and mRAP in PH-HFpEF. These data suggest that PH-HFpEF is more likely the result of the development of pulmonary vascular disease in patients with HFpEF, rather than the development of HFpEF in patients with PAH. Because of the increasing frequency in which these patients are becoming diagnosed, a better understanding of their outcome and response to treatments is urgently needed.