CLINICAL INVESTIGATIONS

Combined Post- and Precapillary Pulmonary Hypertension in Patients With Heart Failure

Michael E. Rezaee MPH | Elizabeth L. Nichols MS | Mandeep Sidhu MD, MBA, FACC, FAHA | Jeremiah R. Brown PhD

Internal Medicine, Oakland University William Beaumont School of Medicine (Rezaee), Rochester, Michigan; The Dartmouth Institute for Health Policy and Clinical Practice (Rezaee, Nichols, Brown), Geisel School of Medicine, Lebanon, New Hampshire; Division of Cardiology (Sidhu), Albany Medical Center, Albany, New York; Department of Medicine (Brown), Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; Department of Community and Family Medicine (Brown), Lebanon, New Hampshire

Dr. Brown received grant funding from Actelion Pharmaceuticals Ltd, Allschwil, Switzerland, for this work.

The authors have no other funding, financial relationships, or conflicts of interest to disclose.

Corresponding Author: Michael E. Rezaee, MPH 216 O'Dowd Hall 2200 N. Squirrel Rochester, MI 48309 (merezaee@oakland.edu)

Background: Pulmonary hypertension (PH) is a well-recognized complication of left ventricular heart failure (HF).

Hypothesis: Differences exist in demographic, clinical, hemodynamic, and survival characteristics of patients with left ventricular HF who have combined postcapillary and precapillary PH (CpcPH), isolated postcapillary PH, or no PH.

Methods: A secondary data analysis was conducted using a large prospective database of patients undergoing right heart catheterization from 1994 to 2012. One-year mortality post-catheterization was assessed between PH groups using Kaplan-Meier and log-rank techniques, as well as a multivariate Cox proportional hazards model adjusted for age, sex, diabetes, chronic kidney disease, atrial fibrillation, and chronic obstructive pulmonary disease. Mortality rates were calculated for each group as deaths per 100 person-years.

Results: Of the 724 patients identified, 29.4% (n = 213) had no evidence of PH, 63.1% (n = 457) had isolated postcapillary PH, and 7.5% (n = 54) had CpcPH. Compared with no PH, there was an increased mortality rate within 1 year for CpcPH patients (crude hazard ratio: 5.22, 95% confidence interval: 2.06-13.22), but not for isolated postcapillary PH patients (crude hazard ratio: 2.12, 95% confidence interval: 0.99-4.57). Adjusted analyses revealed similar results. Mortality rates per 100 person-years were 3.9, 8.4, and 21.0 for no PH, isolated postcapillary PH, and CpcPH patients, respectively.

Conclusions: Heart failure patients with CpcPH are associated with increased death rate 1 year post-cardiac catheterization, compared with patients without PH. They are a high-risk PH group and should be evaluated and diagnosed earlier in the disease state.

KEYWORDS

Pulmonary hypertension, Heart failure/cardiac transplantation/cardiomyopathy/myocarditis, Epidemiology

1 | INTRODUCTION

Heart failure (HF) is one of the 2 cardiovascular conditions still on the rise in the United States; by 2030, 8.5 million Americans are estimated to have this diagnosis.^{1,2} Left ventricular heart failure (LVHF) due to diastolic or systolic dysfunction is one of the most common contributors to pulmonary hypertension (PH).³ Pulmonary hypertension carries a poor prognosis for outcomes and mortality in patients with HF and potentially even worse consequences in patients with

LVHF.³⁻⁵ Using right heart cardiac catheterization (RHC), 2 clinically identifiable types of PH can be recognized: isolated postcapillary PH and combined postcapillary and precapillary PH (CpcPH). Patients with CpcPH may have the poorest outcomes and require modified management, necessitating the need for reliable identification methods. The optimal method for classifying PH groups has been debated to date.⁶⁻⁸

The diastolic pulmonary gradient (DPG), the difference between diastolic mean pulmonary artery pressure (mPAP) and pulmonary

capillary wedge pressure (PCWP), is the current recommended prognostic measure for distinguishing PH types.⁹ Isolated postcapillary PH patients have a DPG <7 mm Hg, as increased hemodynamic pressures due to LVHF have not caused significant vascular alterations to the precapillary vessels. Patients with CpcPH have a DPG $\geq$ 7 mm Hg. Increased pressure from LVHF can lead to arteriolar vasoconstriction, medial hypertrophy, and intimal fibrosis in addition to postcapillary pathophysiological perturbations. Significant alterations to the precapillary vasculature in CpcPH patients increase the diastolic mPAP relative to the PCWP, resulting in an elevated DPG.^{10,11}

Diastolic pulmonary gradient has been shown to be an effective diagnostic marker in multiple retrospective cohort studies.^{12–14} Patients with CpcPH determined by DPG had worse median survival relative to isolated postcapillary PH patients.^{9,12,13} However, some analyses have demonstrated no difference in outcomes for CpcPH patients identified via DPG, calling into question the meaningfulness of DPG as a prognostic marker.^{8,15} There is a need to further evaluate DPG as a marker for CpcPH, yet the clinical phenotypes of PH groups remain understudied due to the limited availability of hemodynamic data measured by RHC. We sought to evaluate survival of patients with HF who have CpcPH, isolated post-capillary PH, or no PH. Similar to other studies, we define CpcPH as PCWP >15 mm Hg, mPAP $\geq$ 25 mm Hg, and DPG $\geq$ 7 mm Hg.^{13,14}

2 | METHODS

2.1 | Study Population

The Dartmouth Dynamic Registry (DDR) is a large, prospective registry of patients undergoing diagnostic or interventional cardiovascular catheterization procedures at Dartmouth-Hitchcock Medical Center. In this registry, we identified 9445 patients who underwent RHC at Dartmouth-Hitchcock Medical Center between 1994 and 2012. Of these patients, 1271 had documented, preexisting HF; a left ventricular ejection fraction (LVEF) $\geq$ 30%; and a left ventricular end-diastolic pressure (LVEDP) >15 mm Hg. The identification of HF was based on whether a history of HF and/or New York Heart Association (NYHA) HF classification was documented in the DDR. In this case, history of HF could be informed by past hospital discharge diagnoses, HF encounters, laboratory values, and/or symptoms. Patients with LVEF <30% were excluded. After excluding patients with a history of significant aortic or mitral valve disease, repair, or replacement ($n = 454$), 817 patients remained in our sample (Figure 1). These patients were excluded because their valve disease may have substantially altered the mechanism of their PH, making them inhomogeneous with other PH populations. Patients were then categorized into 3 groups. The first group consisted of HF patients without PH (mPAP <25 mm Hg at rest). The second consisted of HF patients with isolated postcapillary PH (mPAP $\geq$ 25 mm Hg, PCWP >15 mm Hg, DPG <7 mm Hg), and the third group consisted of HF patients with CpcPH (mPAP $\geq$ 25 mm Hg, PCWP >15 mm Hg, DPG $\geq$ 7 mm Hg). We excluded patients with PCWP $\leq$ 15 mm Hg ($n = 59$) or missing the hemodynamic variables required for categorization ($n = 34$). Our final analytic sample consisted of 724 patients. Development of the DDR and

conduct of this study were approved by the Dartmouth Center for the Protection of Human Subjects.

Data for the study were abstracted from the DDR. Patient characteristics included age in years, sex, NYHA functional class, heart rate (bpm), systolic and diastolic blood pressures (mm Hg), body mass index (kg/m^2), and underlying comorbidities, including coronary artery disease, hypertension, diabetes mellitus (DM), obesity, chronic kidney disease, atrial fibrillation, smoking history, and chronic obstructive pulmonary disease (COPD). Precatheterization medications were collected and included diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and β -blockers. Serum creatinine (mg/dL) was the only laboratory test obtained on all patients and was therefore recorded as the marker of renal function. Estimated LVEF (%) was measured via transthoracic echocardiography. Right heart cardiac catheterization hemodynamics measures at rest included left ventricular systolic pressure (mm Hg); LVEDP (mm Hg); mPAP (mm Hg); right atrial pressure (mm Hg); pulmonary capillary wedge pressure (PCWP; mm Hg, end-expiratory or digitized); pulmonary arterial diastolic pressure (mm Hg); cardiac output (L/min); cardiac index ($\text{L}/\text{min}/\text{m}^2$); pulmonary vascular resistance ($\text{dynes} \times \text{s}/\text{cm}^5$); transpulmonary gradient (TPG, mm Hg), calculated as the difference between mPAP and PCWP; and DPG (mm Hg), calculated as the difference between diastolic mPAP and PCWP.

2.2 | Patient Follow-up

The primary endpoint of this study was survival at 1 year following index cardiac catheterization. All-cause mortality data were obtained for this study by linking the DDR registry with the National Death Index using Social Security number and date of birth.

2.3 | Statistical Analysis

Patient, disease, and hemodynamic characteristics were compared across PH groups (none, isolated post-capillary PH, and CpcPH) using frequency counts, percentages, means $\pm$ SD, medians, and interquartile range. Analysis of variance and χ^2 tests were used to assess differences between PH groups for normally distributed continuous and categorical variables, respectively. Event rates and time-to-event analyses were conducted for mortality. Time zero was defined as the date of index cardiac catheterization and the follow-up period was predefined as 1 year. Kaplan-Meier and log-rank techniques were used to conduct a time-to-event analysis; patients were stratified by PH group. A multivariate Cox proportional hazards model was constructed to assess the impact of PH group on 1-year mortality. The model adjusted for age, sex, DM, chronic kidney disease, atrial fibrillation, and COPD. Mortality event rates were calculated for each PH group as deaths per 100 person-years of follow-up.

3 | RESULTS

3.1 | Baseline Characteristics

Out of 724 patients with HF, 29.4% ($n = 213$) had no PH, 63.1% ($n = 457$) had isolated postcapillary PH, and 7.5% ($n = 54$) met

FIGURE 1 Study flow diagram of patient disposition. Graphic displays how PH groups were derived. Abbreviations: CpcPH, combined postcapillary and precapillary PH; DHMC, Dartmouth-Hitchcock Medical Center; DPG, diastolic pulmonary gradient; EF, ejection fraction; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; LVEDP, left ventricular end-diastolic pressure; mPAP, mean pulmonary artery pressure; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; RHC, right heart cardiac catheterization.

criteria for CpcPH. Demographic, disease, and hemodynamic characteristics for PH groups are compared in Table 1. Body mass index was significantly higher in patients with CpcPH (34.3 kg/m²) compared with isolated postcapillary PH (32.0 kg/m²) and no PH (30.2 kg/m²; $P < 0.01$). The NYHA classification was significantly higher in patients with CpcPH and isolated postcapillary PH compared with patients with no PH. The percentage of patients with comorbid COPD was highest among patients with CpcPH, followed by isolated postcapillary PH and no PH. Comorbid DM was higher in patients with isolated postcapillary PH and CpcPH than those with no PH. As dictated by grouping criteria, significant differences were observed in cardiac hemodynamic metrics (Table 1). pulmonary vascular resistance (PVR) and mPAP were significantly elevated in patients with CpcPH compared with those with isolated postcapillary PH and no PH.

Death or censor was time zero for 2 patients, excluding them from time-to-event analyses. Out of 722 patients in the time-to-event analysis set, 54 patients died within 1 year (7.99 per 100 - person-years); mean follow-up time was 341.8 days, with a total of

676.1 patient-years. One year of follow-up was available for 692 patients (95.8%).

3.2 | Pulmonary Hypertension Group Survival Results

Survival free from death up to 1 year following cardiac catheterization was significantly different between PH groups ($\chi^2 = 13.98$; $P = 0.001$). The Kaplan-Meier 1-year survival curve for PH groups is shown in Figure 2. Compared with no PH, there was a statistically significant increased rate of death within 1 year for patients with CpcPH (crude hazard ratio [HR]: 5.22, 95% confidence interval [CI]: 2.06-13.22; Table 2), but not for patients with isolated postcapillary PH (crude HR: 2.12, 95% CI: 0.99-4.57). Adjusted analyses revealed similar results for CpcPH (adjusted HR: 5.44, 95% CI: 2.09-14.17) and isolated postcapillary PH groups (adjusted HR: 1.59, 95% CI: 0.72-3.50). Crude mortality rate per 100 person-years was 3.9 for patients with no PH, 8.4 for isolated PH patients, and 21.0 for CpcPH patients (log-rank $P = 0.001$, Table 3).

TABLE 1 Characteristics by PH Group

	No PH, n = 213	Isolated PH, n = 457	CpcPH, n = 54	P Value
Demographics and examination				
Age, y (SD)	63.4 (12.1)	66.3 (11.3)	63.9 (10.5)	0.006
Female sex, n (%)	99 (46.5)	198 (43.3)	26 (48.2)	0.644
NYHA classification, n (%)				0.011
I	0 (0.0)	1 (0.7)	0 (0.0)	
II	21 (39.6)	27 (18.6)	0 (0.0)	
III	27 (50.9)	92 (63.5)	15 (83.3)	
IV	5 (9.4)	25 (17.2)	3 (16.7)	
HR, bpm (SD)	68.0 (15.3)	73.1 (15.5)	74.1 (16.4)	0.001
BMI, kg/m ² (SD)	30.2 (11.7)	32.0 (8.5)	34.3 (7.6)	0.008
Precatheterization medications, n (%)				
Diuretics	2 (0.9)	5 (1.1)	0 (0.0)	0.739
CCBs	0 (0.0)	6 (1.3)	1 (1.9)	0.213
ACEIs/ARBs	0 (0.0)	6 (1.3)	0 (0.0)	0.171
β-Blockers	1 (0.5)	6 (1.3)	1 (1.9)	0.537
Antiplatelets	2 (0.9)	6 (1.3)	0 (0.0)	0.658
Anticoagulants	1 (0.5)	5 (1.1)	1 (1.9)	0.586
Arterial vasodilators	0 (0.0)	1 (0.2)	0 (0.0)	0.746
Comorbidities, n (%)				
CAD	57 (27.7)	127 (29.2)	11 (22.0)	0.552
HTN	124 (59.6)	287 (64.6)	34 (64.2)	0.458
DM	13 (26.9)	161 (36.6)	20 (37.0)	0.045
Obesity	13 (7.8)	87 (23.8)	14 (31.8)	<0.001
CKD	40 (23.0)	93 (24.2)	7 (15.6)	0.432
AF	19 (9.5)	131 (31.4)	11 (22.5)	<0.001
Smoking history	84 (40.0)	194 (44.0)	28 (52.8)	0.227
COPD	25 (12.9)	100 (25.1)	15 (31.3)	0.001
Laboratory tests/echocardiography				
sCr, mg/dL (SD)	1.07 (0.67)	1.06 (0.59)	1.08 (0.43)	0.978
Estimated LVEF, % (SD)	50.7 (15.6)	49.8 (14.8)	51.5 (16.7)	0.621
RHC hemodynamics				
LVSP, mm Hg (SD)	135.7 (27)	136.0 (28)	140.4 (28)	0.529
LVEDP, mm Hg (SD)	20.5 (5.5)	23.4 (6.9)	23.3 (7.9)	<0.001
RVSP, mm Hg (SD)	34.0 (7.0)	50.7 (12.5)	61.4 (16.8)	<0.001
mPAP, mm Hg (SD)	19.7 (3.6)	35.0 (7.3)	43.6 (10.0)	<0.001
RAP, mm Hg (SD)	6.9 (3.4)	12.7 (5.1)	15.5 (5.1)	<0.001
PCWP, mm Hg (SD)	13.7 (5.0)	24.6 (6.1)	21.9 (4.9)	<0.001
PA diastolic pressure, mm Hg (SD)	12.3 (5.3)	22.4 (5.8)	32.3 (6.4)	<0.001
Cardiac output, L/min (SD)	5.19 (1.46)	4.95 (1.57)	5.02 (1.34)	0.350
Cardiac index, L/min/m ² (SD)	2.58 (0.85)	2.43 (0.67)	2.38 (0.54)	0.123
PVR, Wood units (SD)	1.33 (1.19)	2.20 (1.30)	5.0 (2.75)	<0.001
TPG, mm Hg (SD)	6.05 (5.04)	10.4 (5.5)	21.7 (8.2)	<0.001
DPG, mm Hg (SD)	-1.39 (5.57)	-2.28 (5.06)	10.39 (4.70)	<0.001

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CpcPH, combined post-capillary and precapillary pulmonary hypertension; DM, diabetes mellitus; DPG, diastolic pulmonary gradient; HR, heart rate; HTN, hypertension; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; LVSP, left ventricular systolic pressure; mPAP, mean pulmonary artery pressure; NYHA, New York Heart Association; PA, pulmonary arterial; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RHC, right heart cardiac catheterization; RV, right ventricular; RVSP, right ventricular systolic pressure; sCr, serum creatinine; SD, standard deviation; TPG, transpulmonary gradient.

FIGURE 2 Kaplan-Meier 1-year survival curve for PH groups. Kaplan Meier survival up to 1 year following cardiac catheterization for PH groups none, isolated, and combined precapillary and postcapillary (log-rank test $P < 0.001$). Hash marks have been plotted for each censor date. Abbreviations: PH, pulmonary hypertension.

TABLE 2 Crude and Adjusted HRs for 1-Year Mortality Following RHC

	Crude			Adjusted ¹		
	HR	95% CI	P Value	HR	95% CI	P Value
PH						
None	1	(Ref)		1	(Ref)	
Isolated	2.12	0.99-4.57	0.054	1.59	0.72-3.50	0.254
CpcPH	5.22	2.06-13.22	<0.001	5.44	2.09-14.17	0.001
Age, y	1.07	1.04-1.10	<0.001	1.05	1.02-1.09	0.002
Female sex	0.88	0.55-1.44	0.630	0.80	0.46-1.39	0.424
DM	1.26	0.77-2.06	0.363	1.68	0.96-2.96	0.070
CKD	2.93	1.79-4.79	<0.001	2.28	1.21-4.31	0.011
AF	2.23	1.36-3.64	0.001	1.55	0.87-2.77	0.140
COPD	0.98	0.54-1.80	0.952	0.75	0.36-1.54	0.426

Abbreviations: AF, atrial fibrillation; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CpcPH, combined postcapillary and precapillary pulmonary hypertension; DM, diabetes mellitus; HR, hazard ratio; Ref, reference; RHC, right heart cardiac catheterization.

¹ Adjusted for age, sex, DM, CKD, COPD, and AF.

4 | DISCUSSION

We found a statistically significant increased rate of death 1 year post-cardiac catheterization among patients with CpcPH compared with patients without PH. Conversely, patients with isolated postcapillary PH were not found to have an increased risk of death when compared with patients without PH. Mortality rate per 100 person-years in HF patients with CpcPH was found to be 2.5× and 5.3× higher when compared with patients with isolated postcapillary PH and no PH, respectively.

Pulmonary hypertension is a common complication of LVHF and is strongly associated with all-cause mortality in HF patients with either systolic or diastolic dysfunction.^{11,16,17} In fact, chance of death is known to increase by 1.2 for every 10-mm Hg increase in pulmonary artery systolic pressure in HF patients.¹¹ In an effort to identify high-risk PH subgroups that may benefit from targeted intervention,

TABLE 3 Mortality Rates for HF Patients Within 1 Year of RHC

	N	Time at Risk, y	Mortality Rate ¹	P Value ²
All Patients	67/815	758.3	8.84	
PH				0.0009
None	8/212	201.7	3.97	
Isolated	36/456	426.8	8.44	
CpcPH	10/54	47.6	21.02	

Abbreviations: CpcPH, combined postcapillary and precapillary pulmonary hypertension; HF, heart failure; PH, pulmonary hypertension; RHC, right heart cardiac catheterization.

¹ Incidence rate per 100 person-years.

² P value from log-rank test.

2 clinically identifiable types of PH have been defined: (1) isolated postcapillary PH, or "passive PH"; and (2) CpcPH, otherwise known as "out-of-proportion PH," "reactive PH," or "mixed PH." The

hemodynamic metrics used to define these 2 groups have evolved over time and are still being evaluated and debated to date, most currently in regard to the prognostic value of DPG among left heart disease PH.⁸ In this analysis of HF patients, we defined PH groups using hemodynamic criteria utilized by the most recent studies.^{9,13} Due to the limited availability of high-quality invasive–cardiac catheterization data to distinguish between PH subtypes in HF patients, little information is available in the literature regarding the epidemiology and prognosis of these conditions.

We utilized DPG as the defining characteristic in identifying CpcPH, rather than TPG or pulmonary vascular resistance, as used in early studies.^{18–20} Diastolic pulmonary gradient is thought to be a more sensitive and specific marker for CpcPH, compared with TPG.²¹ Studies have also shown worse survival in CpcPH patients defined by DPG relative to patients with isolated postcapillary and no PH,^{13,22} as well as CpcPH patients identified using TPG.¹⁴

In a 2013 analysis of HF patients by Gerges and colleagues, patients with CpcPH were found to have worse median survival compared with patients with isolated postcapillary PH (78 months vs 101 months; $P = 0.01$).²² At 1-year follow up, approximately 22% of CpcPH, 5% of isolated postcapillary, and zero patients without PH were deceased in this sample.¹³ Histochemical tissue analysis revealed an association between elevated DPG and enhanced pulmonary vascular remodeling in these patients.¹³ We did not have access to survival data beyond 1 year but also observed decreased survival among patients with CpcPH. We found that 19% of CpcPH, 7.9% of isolated postcapillary, and 3.8% of patients without PH were deceased at 1 year post–cardiac catheterization. Using DPG, we observed comparable 1-year survival in PH groups to the Gerges and colleagues study, which utilized an analogous methodology.

Similarly, in a 2015 retrospective cohort analysis of HF patients undergoing RHC, Dragu and colleagues utilized TPG to examine mortality risk of patients with CpcPH and isolated postcapillary PH compared with patients with no PH. The CpcPH patients (HR: 3.98, 95% CI: 2.48–6.39) were found to have higher mortality risk than patients with isolated postcapillary PH (HR: 1.95, 95% CI: 1.17–3.27).²² Using DPG, we observed a statistically significant increased risk of death among CpcPH patients (HR: 5.44, 95% CI: 2.09–14.17). However, we did not observe a statistically significant increased risk of death for patients with isolated postcapillary PH (HR: 1.59, 95% CI: 0.72–3.50). In part, this difference may be explained by sample size, as Dragu and colleagues had approximately 150 fewer patients in their isolated postcapillary PH group.²² However, Dragu and colleagues found that only 32.1% ($n = 40$) of their patients with CpcPH as measured by TPG could be identified as CpcPH after using DPG for classification.²² Multiple studies have demonstrated increased mortality among patients with isolated postcapillary PH when utilizing TPG for classification.^{18–20} Conversely, we did not observe decreased survival in isolated postcapillary PH patients as measured by DPG. Our findings may demonstrate the strength of DPG as a prognostic indicator to identify the sickest of patients at the highest risk of death and classify them as CpcPH.

In a 2015 retrospective cohort study by Tampakakis and colleagues, DPG was not found to be associated with decreased survival (HR: 1.02, $P = 0.1$).⁸ The CpcPH patients identified using DPG had

similar mortality compared with patients with isolated postcapillary PH.⁸ As the authors note, their findings may not be reflective of a typical HF population and may be skewed due to a large number of incorrect DPG values.⁸ Our study demonstrates the value of DPG as a prognostic indicator. However, further research is needed to better understand the utility of DPG, especially in relation to pulmonary arterial capacitance, which has been reported to have greater discriminatory ability than DPG, TPG, and pulmonary vascular resistance.¹⁵

The exclusion of patients with LVEF <30% eliminated a significant portion of patients with HF with reduced ejection fraction (HFrEF) from the analysis. Unlike HF with preserved ejection fraction (HFpEF), studies have shown that HFrEF can be successfully managed with common pharmacotherapies.²³ Compared with HFpEF with PH, HFrEF with PH is associated with a better prognosis and less health care utilization.²³ HFpEF also accounts for 50% of all HF cases, and this percentage is expected to rise as the US population ages and the prevalence of co-occurring chronic illness advances.²³ Our emphasis on patients with a higher LVEF was an attempt to better recognize HF patients who are growing in prevalence and who would likely benefit from the development of unique, targeted therapies. Regardless, it is important to note that a limitation of this study is the applicability of these results to patients with definitive HFrEF with an LVEF <30%.

4.1 | Study Limitations

There are several other limitations of our study to consider. First, although RHC is required for the diagnosis of PH, hemodynamic measurements obtained via this procedure can be subject to a high degree of variability and may not always be applicable to clinical practice. Measurement of DPG can be affected by technical errors, heart rate, hypoxia, motion, catheter whip, and the utilization of computer-generated measurements. In some cases, these factors can lead to implausible DPG measures that are negative or high DPG values without PH. In our analysis, negative DPG values were found in the no PH and isolated postcapillary PH groups, but not in the CpcPH group. Guidelines exist to standardize measurement of PCWP and mPAP, but negative DPG values have been observed in numerous studies.²³ Although beyond the scope of this study, further recommendations for improvement of this measurement are warranted.

Second, our follow-up period was 1-year post–cardiac catheterization. An extended follow-up period with specific cause-of-death information would provide clearer insight into the long-term prognosis of patients with different PH subtypes. Third, we lacked important covariates in adjusted analyses related to the development of PH, including sleep apnea, pulmonary embolism, congenital heart defects, COPD stage, and connective-tissue disorders, which may have somewhat overestimated our effect sizes. Although the DDR is known for its completeness and quality of invasive hemodynamic, echocardiographic, laboratory, and comorbidity information, it is limited in other regards. For this analysis in particular, data were incomplete for pre-catheterization and unavailable for postcatheterization medications. Therefore, the medication data displayed in Table 1 should be interpreted with caution. Finally, identification of HF was based on

whether a history of HF or NYHA HF class was documented in the DDR. The use of electronic data sources for the identification of HF has been well documented with sensitivity up to 76%.²⁴

Strengths of our study include our sample size, demonstration of results from a US cohort (as many studies have been conducted internationally), the use of current hemodynamic criteria to define PH groups, and an adequate follow-up period to ensure comparability of results to the most recently published studies.

5 | CONCLUSION

In regard to clinical implications, our results demonstrate that there is opportunity to improve PH-associated mortality in HF patients through the development of targeted intervention for the high-risk CpcPH subtype. Definitive pharmaceutical therapies for PH in HF currently do not exist.²⁵ However, a number of randomized controlled trials are currently in progress to evaluate the role of medications approved for the treatment of pulmonary arterial hypertension, including endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and prostanoids, in patients with PH and HF.^{25–27} As noted by Cheli and Vachiéry, only 1 RCT is currently being conducted that acknowledges patients who specifically meet criteria for CpcPH.²⁵

In summary, HF patients with CpcPH were found to be associated with an increased rate of death at 1 year post-cardiac catheterization when compared with patients without PH. Isolated postcapillary PH patients were not found to be associated with increased mortality risk when compared with patients with no PH. Heart failure patients with CpcPH represent a high-risk PH group that should be appreciated and targeted for intervention.

REFERENCES

- Braunwald E. Shattuck lecture—cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. *N Engl J Med*. 1997;337:1360–1369.
- Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail*. 2013;6:606–619.
- Haddad F, Kudelko K, Mercier O, et al. Pulmonary hypertension associated with left heart disease: characteristics, emerging concepts, and treatment strategies. *Prog Cardiovasc Dis*. 2011;54:154–167.
- Kovács Á, Papp Z, Nagy L. Causes and pathophysiology of heart failure with preserved ejection fraction. *Heart Fail Clin*. 2014;10:389–398.
- Thenappan T, Shah SJ, Gomberg-Maitland M, et al. Clinical characteristics of pulmonary hypertension in patients with heart failure and preserved ejection fraction. *Circ Heart Fail*. 2011;4:257–265.
- Guazzi M, Borlaug BA. Pulmonary hypertension due to left heart disease. *Circulation*. 2012;126:975–990.
- Ghio S, Gavazzi A, Campana C, et al. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. *J Am Coll Cardiol*. 2001;37:183–188.
- Tampakakis E, Leary PJ, Selby VN, et al. The diastolic pulmonary gradient does not predict survival in patients with pulmonary hypertension due to left heart disease. *JACC Heart Fail*. 2015;3:9–16.
- Vachiéry JL, Adir Y, Barberà JA, et al. Pulmonary hypertension due to left heart diseases. *J Am Coll Cardiol*. 2013;62(25 suppl):D100–D108.
- Guazzi M, Vicenzi M, Arena R, et al. Pulmonary hypertension in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition in a 1-year study. *Circulation*. 2011;124:164–174.
- Lam CS, Roger VL, Rodeheffer RJ, et al. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. *J Am Coll Cardiol*. 2009;53:1119–1126.
- Gerges M, Gerges C, Pistrutto AM, et al. Pulmonary hypertension in heart failure: epidemiology, right ventricular function and survival. *Am J Respir Crit Care Med*. 2015;192:1234–1246.
- Gerges C, Gerges M, Lang MB, et al. Diastolic pulmonary vascular pressure gradient: a predictor of prognosis in “out-of-proportion” pulmonary hypertension. *Chest*. 2013;143:758–766.
- Ibe T, Wada H, Sakakura K, et al. Pulmonary hypertension due to left heart disease: the prognostic implications of diastolic pulmonary vascular pressure gradient. *J Cardiol*. 2016;67:555–559.
- Al-Naamani N, Preston IR, Paulus JK, et al. Pulmonary arterial capacitance is an important predictor of mortality in heart failure with a preserved ejection fraction. *JACC Heart Fail*. 2015;3:467–474.
- Cappola TP, Felker GM, Kao WH, et al. Pulmonary hypertension and risk of death in cardiomyopathy: patients with myocarditis are at higher risk. *Circulation*. 2002;105:1663–1668.
- Kjaergaard J, Akkan D, Iversen KK, et al. Prognostic importance of pulmonary hypertension in patients with heart failure. *Am J Cardiol*. 2007;99:1146–1150.
- Tatebe S, Fukumoto Y, Sugimura K, et al. Clinical significance of reactive post-capillary pulmonary hypertension in patients with left heart disease. *Circ J*. 2012;76:1235–1244.
- Miller WL, Grill DE, Borlaug BA. Clinical features, hemodynamics, and outcomes of pulmonary hypertension due to chronic heart failure with reduced ejection fraction: pulmonary hypertension and heart failure. *JACC Heart Fail*. 2013;1:290–299.
- Aronson D, Eitan A, Dragu R, et al. Relationship between reactive pulmonary hypertension and mortality in patients with acute decompensated heart failure [published correction appears in *Circ Heart Fail*. 2012;5:e18]. *Circ Heart Fail*. 2011;4:644–650.
- Naeije R, Vachiéry JL, Yerly P, et al. The transpulmonary pressure gradient for the diagnosis of pulmonary vascular disease. *Eur Respir J*. 2013;41:217–223.
- Dragu R, Rispler S, Habib M, et al. Pulmonary arterial capacitance in patients with heart failure and reactive pulmonary hypertension. *Eur J Heart Fail*. 2015;17:74–80.
- Dixon DD, Trivedi A, Shah SJ. Combined post- and pre-capillary pulmonary hypertension in heart failure with preserved ejection fraction. *Heart Fail Rev*. 2016;21:285–297.
- Alqiasi F, Williams LK, Peterson EL, et al. Comparing methods for identifying patients with heart failure using electronic data sources. *BMC Health Serv Res*. 2009;9:237.
- Cheli M, Vachiéry JL. Controversies in pulmonary hypertension due to left heart disease. *F1000Prime Rep*. 2015;7:07.
- Montani D, Chaumais MC, Guignabert C, et al. Targeted therapies in pulmonary arterial hypertension. *Pharmacol Ther*. 2014;141:172–191.
- Waxman AB. Pulmonary hypertension in heart failure with preserved ejection fraction: a target for therapy? *Circulation*. 2011;124:133–135.

How to cite this article: Rezaei ME, Nichols EL, Sidhu M, Brown JR. Combined Post- and Precapillary Pulmonary Hypertension in Patients With Heart Failure, *Clinical Cardiology*, 2016;39(11):658–664.