DOI: 10.1002/pul2.12311

RESEARCH ARTICLE

Pulmonary Circulation Open Access | PVRI Pulmonary Vascular Research Institute | WILEY

Pulmonary vascular dysfunction without pulmonary hypertension: A distinct phenotype in idiopathic pulmonary fibrosis

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Funding information
None

Abstract

Pulmonary vascular dysfunction in the absence of pulmonary hypertension (PH) has been observed in patients with idiopathic pulmonary fibrosis (IPF). We describe the prevalence and etiology of elevated pulmonary vascular resistance (PVR) without PH among patients with IPF. Hemodynamic, echocardiographic, and functional respiratory imaging (FRI) data was compared between patients with IPF without PH with normal (<3 wood units) and elevated PVR (≥3 wood units). Mortality between these two groups were compared to patients with IPF and PH. Of 205 patients with IPF, there were 146 patients without PH, of whom 114 (78.1%) had a normal PVR and 32 (21.9%) who had a high PVR. Functional testing and hemodynamics were similar in the two groups, except for the cardiac index which was significantly lower in patients with a high PVR (2.3 vs. 2.6 L/min/m^2; $p = 0.004$). Echocardiographic comparison demonstrated a higher tricuspid regurgitant velocity in those with a high PVR (3.4 vs 3.0 m/s; $p = 0.046$). FRI revealed proportionately fewer large vessels as a proportion of the vasculature in the patients without PH and elevated PVRs. Among patients without PH, PVR was associated with increased mortality. In conclusion, patients with IPF without PH but a high PVR appear to be a distinct phenotype with a prognosis between those with and without PH, likely reflecting the continuum of vascular dysfunction. The basis for this unique hemodynamic profile could not be definitively discerned although FRI suggested an aberrant anatomical vascular response.

KEYWORDS
idiopathic pulmonary fibrosis, pulmonary hypertension, pulmonary vascular resistance

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a disease that carries a median survival of 2.5−5 years when left untreated.[1–3] Since the advent of antifibrotic therapy, it does appear that survival has improved.[4–6] How much of this is due to increased disease awareness and earlier disease discovery versus a mortality benefit of the antifibrotics remains uncertain. Pulmonary hypertension (PH) frequently complicates the course of patients with IPF and is associated with a myriad of adverse consequences including higher oxygen needs, reduced functional ability, increased healthcare resource utilization, and increased mortality.[7,8] There is a growing appreciation for the importance of the vasculature in the disease process, including possibly being important in the perpetuation of the fibrosis.[9] In support of this, two studies of PH medications have suggested amelioration of the fibrotic process as evidenced by placebo-corrected improvements in the forced vital capacity.[10,11]

It is likely that the effects on the vasculature are a continuum. Therefore, the current and prior definitions of PH, based on resting hemodynamics, might not be best suited to capture the vasculopathy associated with IPF. Also, up to 30% of IPF patients may have cardiac dysfunction even in the absence of PH.[12,13] How this affects the vasculature and hemodynamic profile of IPF patients is uncertain. Previously, an increased pulmonary vascular resistance (PVR) in the absence of PH has been noted.[13,14] For want of a better term, this has previously been referred to as "pulmonary vascular dysfunction."[14] However, the underpinnings of this particular hemodynamic phenotype including possible right or left ventricular (LV) dysfunction or vascular obliteration have not been previously explored.

We therefore sought to define the prevalence of a high PVR without PH in IPF patients who underwent right heart catheterization (RHC). We also sought to elucidate the contributions of a true low flow state versus low filling pressures. Further, we sought to correlate this with echocardiographic indices to rule out right ventricular (RV) and/or LV dysfunction as contributory mechanisms. Lastly, through functional respiratory imaging (FRI), we sought to quantify the role of excess vessel "drop-out" as a contributory factor.

METHODS

We performed an analysis of patients with IPF evaluated at an advanced lung clinic between May 2004 and April 2022. Patients with IPF who underwent a RHC qualified for the analysis. Patients were subjected to RHC if there was a clinical suspicion of underlying PH or if they were being worked up as potential lung transplant candidates. Of note, it is the policy of our program to evaluate IPF lung transplant candidates early even if they do not yet warrant listing for transplant. RHCs were performed in the resting supine state in the cardiac catheterization laboratory with the thermodilution method employed for calculation of the cardiac output. The focus of the analysis was the subgroup of patients with a high PVR and no PH who were compared to the rest of the patients with no PH (mean pulmonary artery pressure [mPAP] ≤20 mmHg). Those patients with PH, defined as a mPAP >20 mmHg were included for comparison in the outcome and FRI analyses only. Baseline demographics of the patients were collated to include age, gender, race, pulmonary function tests, and six-minute walk test data where available. Patients without PH were categorized into one of two groups; those with no PH and a "normal" PVR (defined as <3 wood units [WU]) (lowPVRnoPH) and those without PH, but with an increased PVR (≥3 WU), which we termed the high PVR no PH group (hiPVRnoPH). The primary outcome was time to mortality from the date of RHC.

A subgroup analysis of patients without PH with available echocardiograms within 6 months of RHC was performed. Echocardiograms were evaluated independently by a cardiologist with expertise in echocardiography who was blinded to their clinical and hemodynamic status (Q. Z.). Echocardiographic data collected encompassed multiple parameters for LV and RV systolic function as well as LV diastolic function. These included; the tricuspid annular plane systolic excursion (TAPSE), the estimated systolic pulmonary artery pressure (sPAP), tricuspid lateral annulus systolic velocity (S'), the RV fractional area change (RV-FAC), the right atrial area, RV basal diameter, RV/LV basal diameter ratio, the LV stroke volume, the LV ejection fraction (LVEF), left atrial volume index, the ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity (E/e' ratio), the ratio of peak pulmonary systolic to peak diastolic flow velocities (pulmonary vein S/D ratio), and the presence of LV diastolic dysfunction. The TAPSE/sPAP ratio, an index of RV uncoupling, was also calculated.[15] Echocardiographic parameters were compared between the patients categorized as hiPVRnoPH and lowPVRnoPH.

Quantitative CT analysis was performed in patients who had chest CTs within 3 months of their RHC, and in an additional control group of subjects with RHC-confirmed precapillary PH, using FRI. Blood vessel structures were subdivided according to the cross-sectional area into (BV) <5 mm^2 representing the volume of segmented vessels smaller than 5 mm^2 (mL), BV 5−10 mm^2 (mL), denoting the volume of segmented vessels 5−10 mm^2, and BV >10 mm^2 (mL), representing

segmented vessels larger than 10 mm^2 (mL). These three vessel sizes were also expressed as a percentage of total pulmonary blood volume.[16] The volume of normal lung (normal iVlobe) (−950 to −600 hounsfield units) was differentiated from abnormal lung (abnormal iVlobe) (<−950 or >−600 hounsfield units). In addition, a textural analysis algorithm was used to compute the specific image-based volume of fibrosis (SIVFIB), as an estimate of the lung region affected by fibrotic findings.

Statistics

Distribution of all continuous data was examined for normality using visual inspection and the Shapiro−Wilk test. Continuous data is presented as median and interquartile range (IQR) where applicable and compared using the Wilcoxon rank sum test or a Kruskal−Wallis *H* test. Categorical data are presented as counts with proportions and compared using Fischer's exact test. Survival analysis with Fine and Gray competing-risk regression treating lung transplantation as a competing risk of death was utilized to evaluate the association of PVR at the time of RHC and the primary outcome. Adjustments to the model were made for potential confounding variables (age, gender, and pulmonary capillary wedge pressure [PCWP]). Adjustment was made for PCWP given the potential that increased PVR could be related to volume status at the time of RHC. The proportionality of subhazards (sHR) was evaluated through the inclusion of time interactions in the model and found to be valid. To reduce bias introduced by listwise deletion of these cases, multiple imputations for all nonredundant variables using chained equations was used for missing data. The model included the event indicator and the Nelson−Aalen estimator of the hazard of death and 20 imputations were performed. A sensitivity analysis examining the association of PVR and time to mortality utilizing the Cox proportional hazards model was performed. In this secondary analysis, patients were right censored at the time of lung transplantation. All relevant statistical tests were two-tailed and a $p < 0.05$ was considered statistically significant. All statistical analysis were performed using STATA/SE 17.0 (StataCorp LP). This study was approved by the Inova Fairfax IRB (U21-02-4389).

RESULTS

There were 205 IPF patients who underwent RHC during the time period. Of these, there were 59 (28.8%) patients with PH who were then only included in the subsequent survival and FRI analyses. Of these 59 patients with PH (mPAP >20 mmHg), 52 (89.7%) had precapillary PH (mPAP >20 mmHg, PVR ≥ 3 WU, and PCWP ≤ 15 mmHg) and 7 had combined pre- and postcapillary PH (mPAP >20 mmHg, PVR ≥ 3 WU, and PCWP > 15 mmHg). The baseline demographics of the remaining 146 patients are provided in Table 1. The proportion of patients who fell into DO-GAP groups 1, 2, and 3 are included which provides insight into the distribution of disease severity among the cohort.[17] There were 114 (78.1%) with a low PVR (<3 WU) and 32 (21.9%) with a high PVR (≥3 WU). Therefore, the overall prevalence of the hiPVRnoPH phenotype among patients with IPF undergoing RHC was 15.6% (32/205). Of these patients, there were 14 (43.8%) who had a PCWP < 8 mmHg and 18 (56.3%) whose PCWP was ≥8 mmHg. There were 8 (25.0%) patients with a low cardiac index (<2.5 L/min/m^2) and 4 (12.5%) patients with both a low cardiac index and a low PCWP. A diagram of patients included in the analysis and a breakdown of all patients with IPF based on RHC findings is displayed in Figures 1 and 2, respectively. Baseline demographics, functional testing, and other hemodynamics were generally similar in the low-PVRnoPH and hiPVRnoPH patients, although notably the cardiac index was significantly lower in the latter group of patients (Table 1).

Among those without PH, the median follow-up was 2.8 years (IQR: 0.99−6.1) during which there were 57 deaths and 73 lung transplants. PVR was associated with mortality in univariate analysis (sHR: 1.39; 95% CI: 1.16−1.67, $p < 0.001$). This relationship persisted when the model was adjusted for age, gender, and PCWP (Table 2). An outcome analysis including all patients categorized into three hemodynamic groups (low-PVRnoPH, hiPVRnoPH, and PH) demonstrated a higher mortality for those with PH (sHR: 2.03; 95% CI: 1.27−3.25, $p = 0.003$, lowPVRnoPH as reference). Likewise, the cumulative incidence of mortality was numerically, though not statistically, higher for hiPVRnoPH compared to lowPVRnoPH (sHR: 1.23; 95% CI: 0.68−2.24, $p = 0.496$) (Figure 3). A sensitivity analysis of these findings was performed utilizing the Cox proportional hazards model. When analyzed without considering transplantation as a competing risk, PVR remained associated with mortality in univariate analysis (HR: 1.08; 95% CI: 1.04−1.11, $p < 0.001$) and when the model was adjusted for age, gender, and PCWP (HR: 1.06; 95% CI: 1.03−1.10, $p = 0.001$). Likewise, mortality for those with PH was significantly higher compared to the lowPVRnoPH group (HR: 2.32; 95% CI: 1.27−4.24, $p = 0.006$) and numerically, though not statistically, higher for the hiPVRnoPH group compared to the lowPVRnoPH group (HR: 1.16; 95% CI: 0.62−2.19, $p = 0.643$).

TABLE 1 Baseline characteristics of patients without pulmonary hypertension categorized by pulmonary vascular resistance.

	All patients $N = 146$	Normal PVR $N = 114$	High PVR $N = 32$	p Value
Demographic data				
Age (years)	64 (61–69)	64 (61–69)	65 (63–66)	0.524
Gender, women	28 (19.2)	18 (15.8)	10 (31.3)	0.073
Race, non-White	29/110 (20.9)	23/109 (21.1)	6/30 (20.0)	0.999
Physiology				
FVC (%)	59 (46–70)	60 (46–69)	59 (48–75)	0.592
FEV1 (%)	63 (50–78)	64 (50–78)	57 (51–78)	0.873
FEV1/FVC	84 (78–88)	84 (79–88)	82 (74–90)	0.208
DLCO (%)	36 (27–48)	36 (28–49)	32 (25–46)	0.358
TLC (%)	57 (49–65)	57 (48–64)	57 (54–70)	0.200
Supplemental oxygen	72/136 (52.9)	56/108 (51.9)	16/28 (57.1)	0.675
6MWT distance (m)	370 (252–457)	378 (258–457)	298 (183–462)	0.121
DO-GAP stage				0.433
I	20/81 (24.7)	18/65 (27.7)	2/16 (12.5)	
II	34/81 (42.0)	27/65 (41.5)	7/16 (43.8)	
III	27/81 (33.3)	20/65 (30.8)	7/16 (43.8)	
CT imaging				
PA dimension (mm)	32.0 (28.0–36.2)	32.1 (28.4–36.3)	29.5 (26.6–34.0)	0.389
PA to aorta ratio	0.94 (0.84–1.01)	0.91 (0.84–1.01)	0.97 (0.82–1.00)	0.729
Right heart catheterization				
RA pressure (mmHg)	5 (2–7)	5 (2–7)	3 (2–6)	0.362
mPAP (mmHg)	16 (15–18)	16 (15–18)	17 (15–18)	0.852
PCWP (mmHg)	9 (6–12)	9 (6–12)	7 (5–12)	0.151
PVR (wood units)	1.9 (1.5–2.6)	1.9 (1.5–2.4)	3.3 (3.2–4.0)	<0.001
Cardiac index (L/min/m^2)	2.5 (2.2–2.9)	2.6 (2.3–2.9)	2.3 (2.0–2.7)	0.004

Note: Data presented as median (25th percentile and 75th percentile) or n (%).

Abbreviations: DLCO, single breath diffusing capacity for carbon monoxide percent predicted; FEV1, forced expired volume in one second percent predicted; FVC, forced vital capacity percent predicted; mPAP, mean pulmonary artery pressure; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RA, right atrium; TLC, total lung capacity percent predicted; 6MWT, six minute walk test.

Echocardiographic subgroup analysis

Among those without PH, echocardiograms that were temporally proximate of the RHC were available in 53 patients (11 hiPVRnoPH, 42 lowPVRnoPH). The median time between the echocardiograms and the RHC was 34 days (IQR: 6–127). Comparison of the echocardiographic indices between the two groups are shown in Table 3. There were no significant differences found between the two groups with regard to the RV size and systolic function, or LV ejection fraction. For LV diastolic function, the hiPVRnoPH group showed an E/e' ratio <8.0, suggesting normal LV filling pressure, which is consistent with a normal or low PCWP in this group. There was no difference in the TAPSE/sPAP ratio between the two groups suggesting that RV uncoupling was unlikely to explain the hiPVRnoPH phenotype.

FRI subgroup analysis

There were 23 CT scans that were temporally proximate to the RHC and technically suitable for analysis with FRI from among patients without PH (16 lowPVRnoPH,

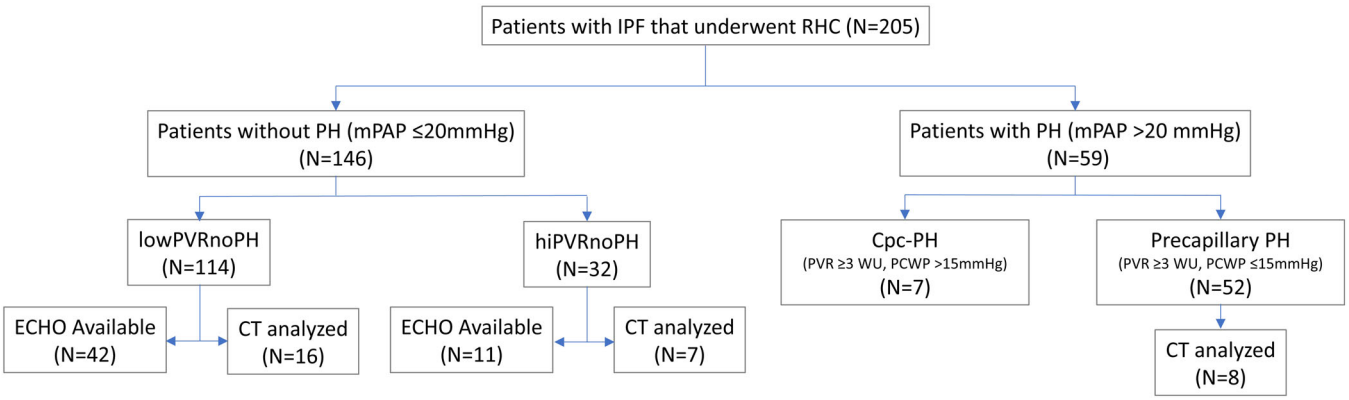


FIGURE 1 Flow chart of patients included in the analysis. Cpc-PH, combined pre- and postcapillary pulmonary hypertension; hiPVRnoPH, high pulmonary vascular resistance and no pulmonary hypertension; lowPVRnoPH, low pulmonary vascular resistance and no pulmonary hypertension; mPAP, mean pulmonary artery pressure; PH, pulmonary hypertension; RHC, right heart catheterization.

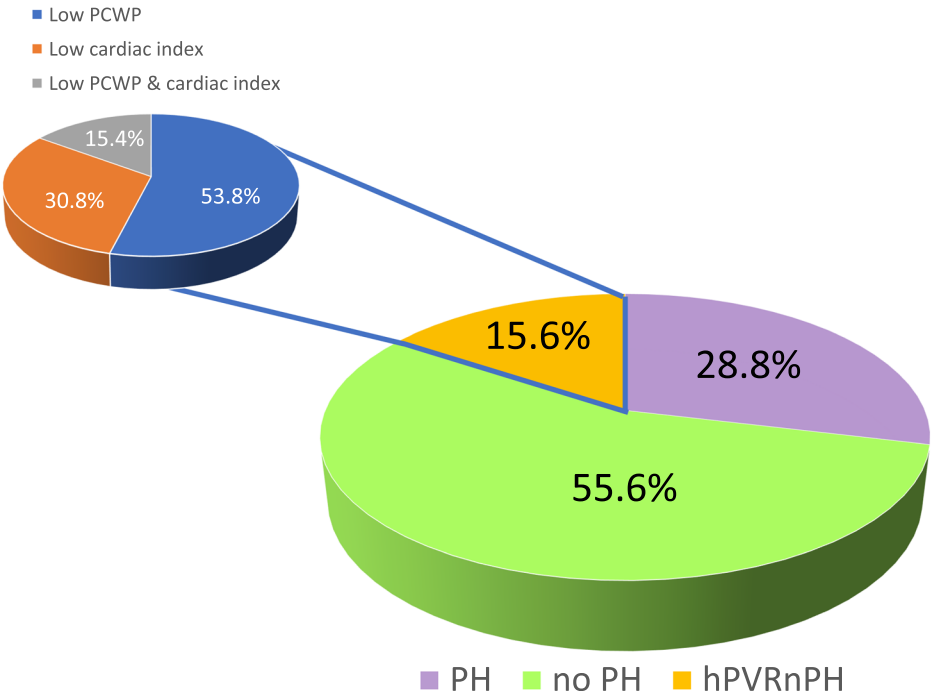


FIGURE 2 Breakdown of patients with IPF based on right heart catheterization findings. hPVRnPH, high pulmonary vascular resistance and no pulmonary hypertension; IPF, idiopathic pulmonary fibrosis; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension.

TABLE 2 Univariate and multivariable analysis for association of pulmonary vascular resistance with mortality in patients with IPF without coexisting pulmonary hypertension.

	Unadjusted sHR (95% CI)	*p* Value	Adjusted sHR (95% CI)[a]	*p* Value	Adjusted sHR (95% CI)[b]	*p* Value
PVR	1.39 (1.16–1.67)	<0.001	1.28 (1.04–1.58)	0.018	1.32 (1.07–1.61)	0.008

Abbreviations: IPF, idiopathic pulmonary fibrosis; PVR, pulmonary vascular resistance; sHR, subhazard ratio.

[a]Adjusted for age and gender.

[b]Adjusted for age, gender, and pulmonary capillary wedge pressure.

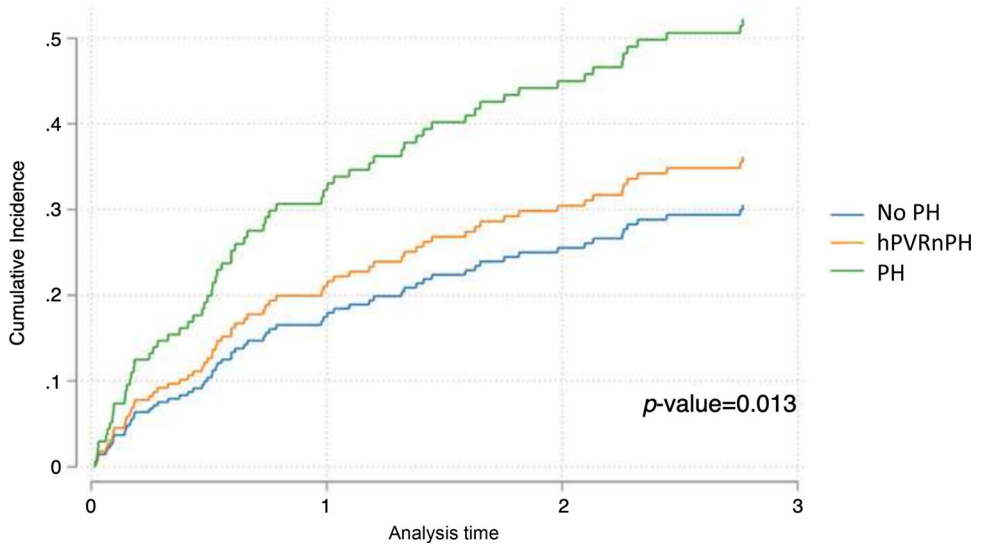


FIGURE 3 Cumulative incidence curve for mortality from time of right heart catheterization based on normal PVR (<3 wood units) and no PH (No PH), high PVR and no PH (hPVRnPH), or pulmonary hypertension (PH).

TABLE 3 Echocardiography (where available) among patients without pulmonary hypertension categorized by pulmonary vascular resistance.

	All patients ***N*** **= 53**	**Normal PVR** ***N*** **= 42**	**High PVR** ***N*** **= 11**	***p*** **Value**
Average E-e' (cm/s) (*N* = 48)	8.9 (6.7–11.2)	9.2 (6.7–11.3)	7.8 (6.5–10.2)	0.471
TR velocity (m/s) (*N* = 34)	3.1 (2.7–3.3)	3.0 (2.6–3.2)	3.4 (3.1–4.0)	0.046
LAVI (mL/m^2) (*N* = 42)	21.3 (18.0–27.5)	21.0 (18.0–27.1)	29.2 (20.0–35.0)	0.211
PV s/d ratio (*N* = 43)	1.3 (1.1–1.5)	1.3 (1.1–1.5)	1.3 (1.1–1.6)	0.836
LVDD presence	7/27 (25.9)	6/23 (26.1)	1/4 (25.0)	0.999
LVEF (%) (*N* = 53)	62.0 (57.0–65.0)	61.0 (57.0–65.0)	64.0 (59.0–65.0)	0.204
sPAP (mmHg) (*N* = 41)	41 (31–49)	41 (31–48)	54 (38–63)	0.146
TAPSE (cm) (*N* = 31)	2.0 (1.7–2.4)	1.9 (1.7–2.4)	2.0 (1.9–2.1)	0.867
S' (cm/s) (*N* = 35)	12.0 (10.4–14.0)	12.0 (10.4–13.7)	11.6 (10.7–16.2)	0.819
RV-FAC (%) (*N* = 40)	29.2 (24.1–36.4)	29.0 (26.0–36.6)	29.3 (23.3–35.7)	0.722
RV basal diameter (cm) (*N* = 42)	3.6 (3.2–4.1)	3.6 (3.3–4.1)	3.3 (2.8–3.6)	0.455
LV basal diameter (cm) (*N* = 42)	3.8 (3.5–4.5)	4.0 (3.5–4.6)	3.6 (3.5–3.7)	0.062
RV to LV basal diameter ratio (*N* = 42)	0.9 (0.8–1.1)	0.8 (0.8–1.0)	1.0 (0.8–1.1)	0.503
RA area (cm^2) (*N* = 38)	13.8 (11.3–16.7)	13.7 (11.9–18.2)	13.9 (9.7–15.5)	0.266
TAPSE/sPAP (mm/mmHg) (*N* = 25)	0.05 (0.03–0.06)	0.05 (0.03–0.06)	0.05 (0.02–0.05)	0.503

Note: Data presented as median (25th percentile and 75th percentile) or *N* (%).

Abbreviations: E/e' ratio, ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity; LAVI, left atrial volume index; LV, left ventricle; LVDD, left ventricular diastolic dysfunction; LVEF, left ventricular ejection fraction; PVR, pulmonary vascular resistance; PV s/d ratio, the ratio of peak pulmonary systolic to peak diastolic velocities; RA, right atrium; RV, right ventricle; RV-FAC, the right ventricular fractional area change; S', tricuspid lateral annulus systolic velocity; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR velocity, tricuspid regurgitant velocity.

TABLE 4 Functional respiratory imaging of patients categorized by presence of pulmonary hypertension and pulmonary vascular resistance.

	No PH and normal PVR ($N = 16$)	No PH and high PVR ($N = 7$)	PH ($N = 8$)	p Value
Abnormal IVLOBE (L)	0.7 (0.5–0.9)	0.9 (0.5–1.4)	0.7 (0.6–1.1)	0.396
Normal IVLOBE (L)	1.9 (1.5–2.6)	1.5 (1.3–2.0)	2.3 (1.5–3.0)	0.259
BV >10 mm^2 (mL)	203.5 (159.8–284.1)	210.7 (132.6–246.9)	236.2 (208.6–285.0)	0.393
BV 5–10 mm^2 (mL)	52.4 (44.2–66.3)	64.1 (53.3–87.0)	64.6 (56.4–75.8)	0.265
BV 5 mm^2 (mL)	65.8 (49.2–87.8)	81.3 (67.0–99.5)	86.7 (65.5–107.6)	0.194
BV >10 mm^2 %	63.0 (57.7–67.9)	54.6 (48.5–62.9)	63.6 (53.8–68.2)	0.192
BV 5–10 mm^2 %	16.0 (14.9–18.4)	19.7 (16.3–23.7)	15.9 (13.4–19.8)	0.0942
BV <5 mm^2 %	21.4 (16.9–23.8)	25.7 (20.7–27.9)	20.8 (17.8–26.8)	0.271
SIVFIB (%)	17.2 (8.1–22.3)	26.7 (15.8–31.8)	17.4 (9.3–25.8)	0.113
BV > 10/SIVFIB	3.7 (2.8–8.5)	2.2 (1.7–3.1)	4.0 (2.5–6.2)	0.047
BV5–10/SIVFIB	1.1 (0.7–1.8)	0.8 (0.6–1.5)	1.1 (0.6–1.8)	0.666
BV < 5/SIVFIB	1.3 (0.8–2.4)	1.0 (0.7–1.8)	1.4 (0.7–2.8)	0.836

Note: Data presented as median (25th percentile and 75th percentile).

Abbreviations: PH, pulmonary hypertension; PVR, pulmonary vascular resistance.

Abnormal IVLOBE-image based volume of lungs with attenuation below −950 or above 600 HU.

Normal IVLOBE-image based volume of lungs with attenuation between −950 and −600 HU.

BV >10 mm^2 (mL), total pulmonary vascular blood volume constituted by blood vessels >10 mm^2 in cross-sectional area.

BV 5–10 mm^2 (mL), total pulmonary vascular blood volume constituted by blood vessels 5–10 mm^2 in cross-sectional area.

BV <5 mm^2 (mL), total pulmonary vascular blood volume constituted by blood vessels <5 mm^2 in cross-sectional area.

BV >10 mm^2 %, blood vessels >10 mm^2 in cross-sectional area as a percentage of total pulmonary vascular volume.

BV 5–10 mm^2 %, blood vessels 5–10 mm^2 in cross-sectional area as a percentage of total pulmonary vascular volume.

BV <5 mm^2%, blood vessels <5 mm^2 in cross-sectional area as a percentage of total pulmonary vascular volume.

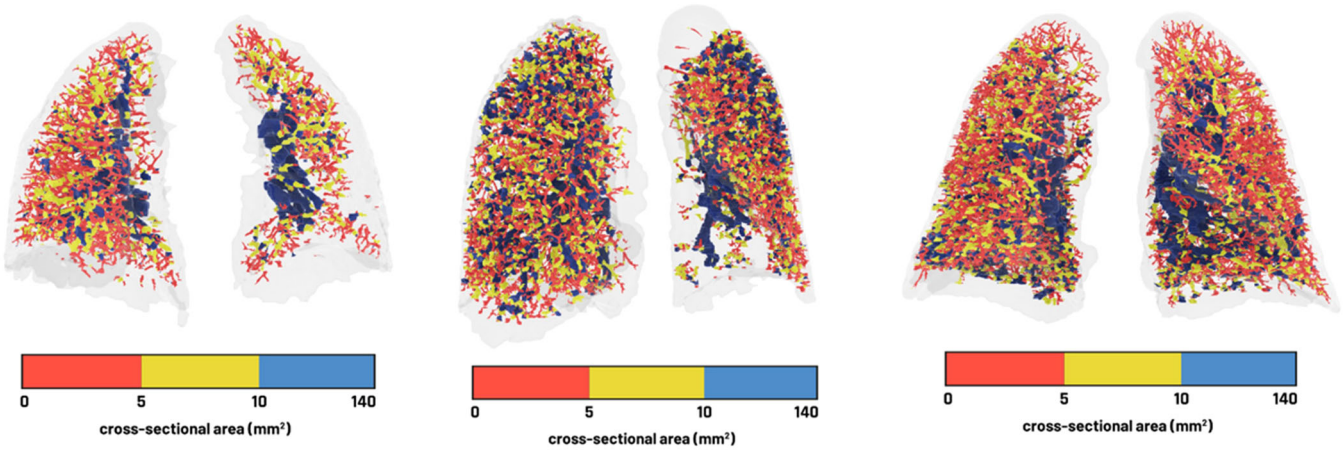
SIVFIB%, volume of fibrotic lung as a percentage of total lung volume.

7 hiPVRnoPH). An additional 8 CT scans from patients with precapillary PH (patients with mPAP >20 mmHg, PVR ≥ 3 WU, and PCWP ≤ 15 mmHg) were included for comparison. These patients were from the among the 59 patients with IPF who were excluded from the prior analyses, but who were included in the PH survival analysis. The median time between the CTs and the RHC was 16 days (IQR: 8–32 days). The comparisons between these groups are shown in Table 4. There was no difference in the volume of blood within the vessels of varying size among the three groups of patients (low-PVRnoPH, hiPVRnoPH, and precapillary PH). There was also no difference in the vessel size distribution as a percentage contributing to the total blood volume across the three groups. The only significant difference was in the BV10 (large blood vessels) corrected for lobar percentage of fibrosis, with the hiPVRnoPH group having a relatively smaller contribution by these larger vessels to the total blood volume ($p = 0.047$). Representative images and clinical information from three of the cases are shown in Figure 4.

DISCUSSION

We describe a phenotype of patients with a high PVR, but who do not qualify as having PH from a series of IPF patients who underwent RHC. Compared to IPF patients without PH and a normal PVR, these patients had significantly lower cardiac indices, higher tricuspid regurgitant velocity on transthoracic echocardiography, and possibly a worse prognosis. FRI also provided evidence of fewer large vessels as a proportion of their total pulmonary vasculature. There was no difference in the baseline demographics between the lowPVRnoPH and hiPVRnoPH; notably, both had diffusing capacities that were similarly reduced, and this did not discern between the two groups.

The pulmonary vasculature is invariably involved and impacted by the fibrotic process that accompanies IPF. However, there is a poor correlation between the extent of fibrosis with the presence or severity of PH, as evaluated by either lung function tests or chest imaging.[18,19] This disconnect infers that there are other



High PVR no PH case	
mPAP	19
PVR	3.21
CI	1.64
FVC%	37
BV5	42.2
BV5-10	36.0
BV10	66.5

Precapillary PH case	
mPAP	34
PVR	4.90
CI	2.8
FVC%	54
BV5	83.8
BV5-10	77.6
BV10	219.0

No PH normal PVR case	
mPAP	16
PVR	1.35
CI	3.8
FVC%	70
BV5	115.6
BV5-10	74.5
BV10	188.4

FIGURE 4 Functional respiratory imaging from three representative cases with vessel size color coded. BV5, blood vessels $<5\,mm^2$ in cross-sectional area as a percentage of total pulmonary vascular volume; BV 5–10, blood vessels $5–10\,mm^2$ in cross-sectional area as a percentage of total pulmonary vascular volume; BV 10, blood vessels $>10\,mm^2$ in cross-sectional area as a percentage of total pulmonary vascular volume; FVC%, forced vital capacity percent predicted; PVR, pulmonary vascular resistance.

factors, aside from the fibrosis, impacting the vasculature. Whether the vasculature itself is an "innocent bystander" or has a direct role in perpetuating the fibrotic process requires further exploration.

How pulmonary vascular involvement has previously been regarded in IPF and other ILDs has hinged mostly on the presence or absence of hemodynamically defined PH. However, this distinct categorization fails to recognize earlier and potentially important vascular abnormalities that do not meet this definition. Indeed, in recognition of this process, the European Society of Cardiology and European Respiratory Society have recently recommended a change in the definition of PH, to include patients with PVRs >2 WU.[20] Our description of IPF patients with hiPVRnoPH meets the bar of a new phenotype, since it is associated with an incrementally worse prognosis than IPF patients without PH, although it does appear to have a better prognosis than those patients with PH. Therefore, it likely represents pulmonary vascular disease that exists within a continuum of severity. The number of patients qualifying as this phenotype is not insignificant at 15.6%. However, there is a bias to this estimate based on who was chosen to undergo RHC. Whether the true prevalence is higher or lower in a broader range of IPF patients warrants further study.

The high PVR was driven by a low cardiac output in 37.5% of the patients which raises the issue of a primary cardiac issue. However, our independent echocardiographic analysis did not reveal any differences in multiple indices reflective of left or right-sided cardiac function that might have been contributory. Notably, there were no differences in any right or LV systolic or diastolic parameters, or evidence of RV uncoupling.[15] The echocardiographic analysis did however demonstrate a higher TR velocity in the hiPVRnoPH group, but this is not surprising given the increased PVR. What of LV underfilling as the cause of the low cardiac output? Although some of the patients had low PCWPs that contributed to the increased transpulmonary gradient, this should mostly be accompanied by a lower mPAP, as well as a proportionately lower cardiac output with no

net change in the PVR. It is conceivable however, that volume depletion may result in a component of pulmonary vasoconstriction contributing to an increased PVR. However, this is an unlikely explanation for the increased PVR given that there was no significant difference in the PCWP between the hiPVRnoPH and lowPVRnoPH groups.

To address whether increased vessel dropout could account for this unique phenotype, we evaluated vessel volumes with FRI in patients with and without PH, including those with normal and elevated PVRs. There was no difference in the volume of blood contained within the vessels of varying size and therefore we were unable to demonstrate "vascular dropout" being associated with this phenotype. Nonetheless, we were able to demonstrate a smaller contribution to blood volume by larger vessels in the hiPVRnoPH group when corrected for the % fibrosis (as manifest by a lower BV > 10/SIVFIB ratio). This is further supported by visual inspection of the vessel distribution across the three groups of patients where it appears that the lowPVRnoPH and PH patients have a very similar distribution of vessel sizes compared to the hiPVRnoPH group (Figure 5). This raises the possibility of a vascular maladaptive process in the hiPVRnoPH group to explain their unique physiology.

The existence of this hiPVRnoPH phenotype does raise the issue of how best to address the vasculature in future IPF studies, including trials of therapy. Should we be bound by our current PH definition when it's likely that the vasculature is involved at a much earlier phase? IPF clinical trials of antifibrotic therapies have typically adopted the tactic of only including patients with mild to moderate disease. The pretext for this has been predicated on the concept that early intervention would be more likely to demonstrate success. Should a similar tactic be adopted for therapies targeting the pulmonary vasculature in IPF? Therefore, whether hiPVRnoPH patients should be targeted for therapy with pulmonary vasodilator therapy is another area that warrants further study. Given the reduced cardiac output, is there a role for inotropic agents? Will such a strategy improve tissue oxygen delivery and improve exercise ability, or will it then result in overt PH and potentially be deleterious? There are examples in the heart failure literature of inotropic agents improving patient's functional status, but at the expense of an earlier demise.[21,22] In fact, by increasing flow through the pulmonary circulation, this might paradoxically worsen oxygenation due to the hastened capillary transit time and less time for optimal oxygenation, especially in the context of a fibrotic interface.

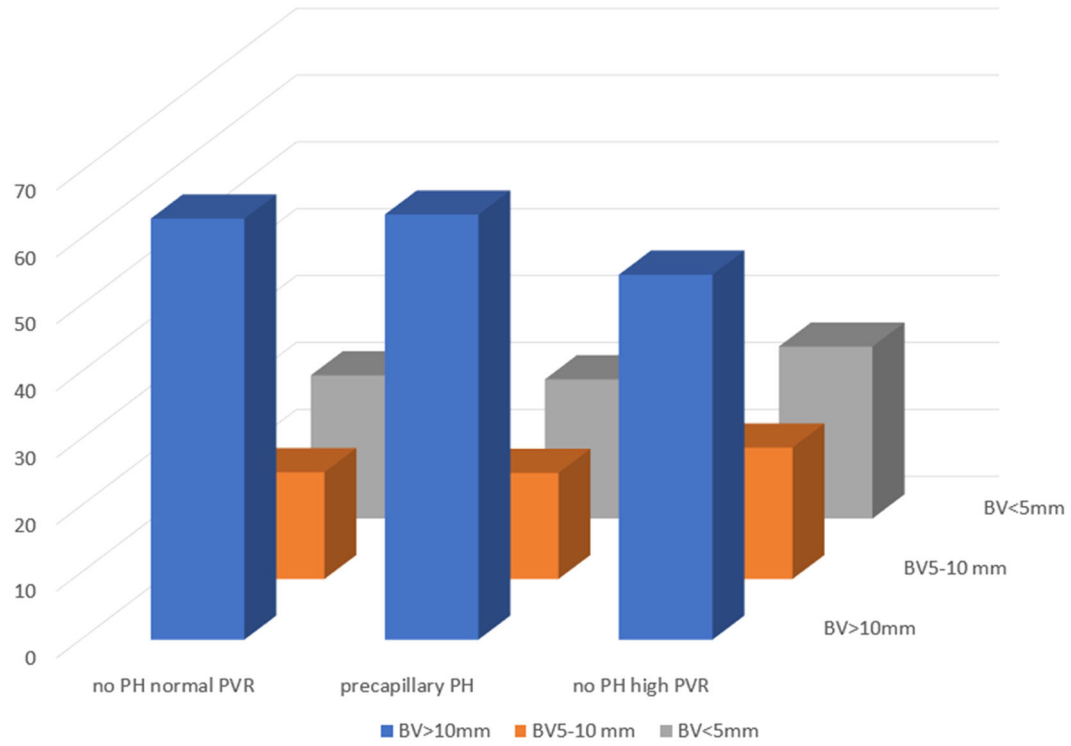


FIGURE 5 Pattern of distribution of blood vessels in patients without pulmonary hypertension and a pulmonary vascular resistance <3, patients without PH and a pulmonary vascular resistance ≥3, and patients with precapillary pulmonary hypertension. PH, pulmonary hypertension.

Further validation of our findings is necessary, and therefore our study opens the door for other investigations, including how best to define a pulmonary vasculopathy in the context of IPF. An intriguing concept is whether the pulmonary vascular involvement perpetuates the fibrotic disease process, and can this be gleaned by evaluating the rate of FVC decline in those with and without a pulmonary vasculopathy? If so, can inclusion of the former group be used as an enrichment strategy for future IPF clinical trials? Should surrogates of a pulmonary vasculopathy be incorporated as secondary endpoints in trials of antifibrotic therapy? What are the factors affecting the pulmonary vasculature on a cellular and mediator level and how best and when to target these?

Our study does have certain limitations. It was not a prospective study and there were varying time intervals between the various studies performed; therefore, this might have impacted our ability to demonstrate important associations. In addition, although the multivariable model was adjusted for important covariates, all important confounders may not have been accounted for. Indeed, we only had evaluable echocardiographic and FRI data on small subsets of patients. The modest subset of patients with evaluable echocardiograms significantly hinders our ability to analyze potential differences in the patterns of cardiac dysfunction between the hiPVRnoPH and lowPVRnoPH groups. Results of this analysis should be considered exploratory and the comparison of cardiac function between these two groups is an important area that warrants further investigation. Moreover, FRI was performed on CT data without consistent acquisition and reconstruction characteristics, which could have impacted the results. Therefore, both our echocardiography and FRI results should be interpreted with caution and regarded as hypothesis generating, but nonetheless serve to lay a foundation for future similar analyses. In any event, all outcomes were determined from the date of the RHC, which underscores an important aspect of our analysis; namely that this phenotype has a different course and prognosis. Our cohort was accrued over an 18-year period and there have been changes in the diagnosis and management of IPF over this time. For example, antifibrotic therapy became available in 2014 and the use of this could possibly have influenced our survival analysis. Although a sizeable number of patients underwent lung transplantation, we did not perform a pathologic analysis since their hemodynamic profiles likely changed significantly from the time of their index RHC.[22] We also performed our analysis using the 2018 World Symposium definition of PH and not the more recent ESC/ERS definition, since this has not been universally adopted as yet.[18] As would be expected, there are even more patients ($N = 81$) with pulmonary vascular dysfunction and no PH if we had used this lower PVR threshold (mPAP ≤20 mmHg and PVR ≥ 2 WU). Although use of this proposed lower PVR threshold (≥2 WU) results in a more equitable distribution of patients between the two no PH groups, the use of the higher PVR threshold underscores the main message of this analysis; namely the existence of a significant vasculopathy in the absence of PH.

In conclusion, we describe an underappreciated vascular phenotype in patients with IPF without PH but with elevated PVRs. Although not qualifying as having PH, these patients might have worse outcomes compared to other patients without PH. Our description further underscores the potential importance of the pulmonary vasculature in IPF and raises questions about how best to define this for future mechanistic and therapeutic studies. Appreciation for a significant vasculopathy that is not captured by any definition of PH raises the issue of whether RHC is always necessary in Group 3 clinical trials. Perhaps the paradigm needs to shift to studies targeting the vasculature in lung disease, rather than studies targeting PH. This will circumvent the field being "boxed in" by definitions that are apt to change, and patients from being "boxed out" from enrollment in future clinical trials from which they might benefit.

AUTHOR CONTRIBUTIONS

Steven D. Nathan takes full responsibility for the content of this paper and acts as the guarantor for the data. Steven D. Nathan, Ben R. Lavon, Christopher S. King, and Abhimanyu Chandel conceived the study design. Abhimanyu Chandel and Ben R. Lavon performed the data analysis. Benham Tehrani, Qiong Zhao, Rafael Arias, Dennis Kim, Antonia Pellegrini, A Claire Collinslaire Collinslaire Collins, Jack Diviney, Shourjo Chakravorty, Vikramjit Khangoora, Oksana A. Shlobin, and Christopher Thomas collected and analyzed study data. All authors contributed to the interpretation of the findings, critically revised the paper for intellectual content, and approved the final version of the manuscript.

ACKNOWLEDGMENTS

The authors have no funding to report.

CONFLICTS OF INTEREST STATEMENT

S. D. N. is a consultant for United Therapeutics, Roche, Bellerophon, and Merck. He is on the speaker bureau for United Therapeutics and Boehringer-Ingelheim. O. A. S. is a consultant for United Therapeutics, Janssen, and Altavant, and serves on the speaker bureau of United

Therapeutics, Bayer, and Janssen. B. R. L. is an employee of Fluidda, Inc. C. S. K. is a consultant for United Therapeutics, Actelion, Altavant, Merck, and Boehringer-Ingelheim. The remaining authors declare no conflict of interest.

ETHICS STATEMENT

This study was approved by the Institutional Review Board at Inova Fairfax hospital (U21-02-4389). The requirement for informed consent was waived.

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How to cite this article: Nathan SD, Tehrani B, Zhao Q, Arias R, Kim D, Pellegrini A, Collins AC, Diviney J, Chakravorty S, Khangoora V, Shlobin OA, Thomas C, Lavon BR, King CS, Chandel A. Pulmonary vascular dysfunction without pulmonary hypertension: a distinct phenotype in idiopathic pulmonary fibrosis. Pulm Circ. 2024;13:e12311. https://doi.org/10.1002/pul2.12311