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Pulmonary Vascular and Right Ventricular Burden During Exercise in Interstitial Lung Disease

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BACKGROUND: Pulmonary hypertension (PH) adversely affects patient's exercise capacity in interstitial lung disease (ILD). The impact of pulmonary vascular and right ventricular (RV) dysfunction, however, has traditionally been believed to be mild and clinically relevant principally in advanced lung disease states.

RESEARCH QUESTION: The aim of this study was to evaluate the relative contributions of pulmonary mechanics, pulmonary vascular function, and RV function to the ILD exercise limit.

STUDY DESIGN AND METHODS: Forty-nine patients with ILD who underwent resting right heart catheterization followed by invasive exercise testing were evaluated. Patients with PH at rest (ILD + rPH) and with PH diagnosed exclusively during exercise (ILD + ePH) were contrasted with ILD patients without PH (ILD non-PH).

RESULTS: Peak oxygen consumption was reduced in ILD + rPH (61 ± 10% predicted) and ILD + ePH (67 ± 13% predicted) compared with ILD non-PH (81 ± 16% predicted; $P < .001$ and $P = .016$, respectively). Each ILD hemodynamic phenotype presented distinct patterns of dynamic changes of pulmonary vascular compliance relative to pulmonary vascular resistance from rest to peak exercise. Peak RV stroke work index was increased in ILD + ePH (24.7 ± 8.2 g/m^2 per beat) and ILD + rPH (30.9 ± 6.1 g/m^2 per beat) compared with ILD non-PH (18.3 ± 6.4 g/m^2 per beat; $P = .020$ and $P = .014$). Ventilatory reserve was reduced in ILD + rPH compared with the other groups at the anaerobic threshold, but it was similar between ILD + ePH and ILD non-PH at the anaerobic threshold (0.32 ± 0.13 vs 0.30 ± 0.11; $P = .921$) and at peak exercise (0.70 ± 0.17 vs 0.73 ± 0.24; $P = .872$).

INTERPRETATION: ILD with resting and exercise PH is associated with increased exercise RV work, reduced pulmonary vascular reserve, and reduced peak oxygen consumption. The findings highlight the role of pulmonary vascular and RV burden to ILD exercise limit.

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KEY WORDS: exercise; hemodynamics; interstitial lung disease; pulmonary hypertension; right ventricle

ABBREVIATIONS: AT = anaerobic threshold; CTD = connective tissue disease; HRCT = high-resolution CT; iCPET = invasive cardiopulmonary exercise testing; ILD = interstitial lung disease; ILD + ePH = interstitial lung disease with pulmonary hypertension diagnosed exclusively during exercise; ILD non-PH = interstitial lung disease without resting or exercise pulmonary hypertension; ILD + rPH = interstitial lung disease with pulmonary hypertension at rest; mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; PVC = pulmonary vascular compliance; PVR = pulmonary vascular resistance; RHC = right heart catheterization; RV = right ventricular; RVSWI = right ventricular stroke work index; VO_2 = oxygen consumption; WU = Wood units

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Pulmonary hypertension (PH) associated with interstitial lung disease (ILD) is hemodynamically defined by resting supine right heart catheterization (RHC) as mean pulmonary arterial pressure (mPAP) ≥ 25 mm Hg and pulmonary arterial wedge pressure (PAWP) ≤ 15 mm Hg.[1] Currently, ILD with resting PH (ILD + rPH) is classified as World Health Organization group 3 PH.

ILD + rPH is known to adversely affect a patient's exercise capacity.[2,3] This effect is generally attributed to the combined deleterious effect of abnormal lung mechanics and gas exchange.[4] Associated pulmonary vascular dysfunction has traditionally been believed to be mild and clinically relevant principally in cases of advanced lung disease.[5,6]

In World Health Organization group 1 PH, exercise intolerance is associated with right ventricular (RV) dysfunction and dynamic RV maladaptation to increased RV afterload.[7] A similar pathophysiology has been described in precapillary PH diagnosed exclusively during exercise (ePH),[8] which is believed to be an early stage of rPH.[9-14] In ILD, data from invasive cardiopulmonary exercise testing (iCPET) suggest that abnormal pulmonary vascular responses during exercise contribute to ILD-reduced aerobic exercise capacity.[15] However, the relative contributions of RV afterload, pulmonary mechanics, pulmonary vascular function, and RV function to the exercise limit in ILD remains incompletely characterized.

The goal of the current study was to evaluate pulmonary mechanics, circulatory reserve, RV work, and peak oxygen consumption (VO_2) in patients with ILD and PH, contrasting the pathophysiological implications found in ILD patients with resting PH (ILD + rPH) vs those found in ILD patients with ePH (ILD + ePH). We hypothesized that an increased RV afterload and increased RV work are physiologically relevant to the ILD exercise limit in the setting of PH.

Patients and Methods

Design and Study Population

The study analyzed 737 consecutive patients referred to the Dyspnea Clinic at Brigham and Women's Hospital over a 4-year period who underwent clinically indicated resting supine RHC followed by upright symptom-limited iCPET for evaluation of exertional intolerance. Patients with confirmed fibrosis on high-resolution CT (HRCT) lung scans were next identified and selected for analysis. Lung fibrosis was defined as reticular septal thickening/irregular reticular opacities associated with traction bronchiectasis or honeycombing on revised HRCT imaging.[16,17]

Exclusion criteria included anemia, defined as hemoglobin < 10 g/dL, and left heart disease, defined as echocardiographic structural abnormalities. These abnormalities included moderate/severe mitral and/or aortic valvular disease or left ventricular ejection fraction < 0.5 and/or postcapillary PH defined by mPAP ≥ 25 mm Hg and PAWP > 15 mm Hg at resting RHC or PAWP ≤ 15 mm Hg at rest but abnormally elevated during exercise for the patient's age (>19 mm Hg for patients ≤ 50 years old and > 17 mm Hg for > 50 years),[18] associated with a normal peak pulmonary vascular resistance (PVR) (≤ 1.35 Wood units [WU] for patients aged ≤50 years and ≤ 2.10 WU for patients aged > 50 years).

Patients with connective tissue disease (CTD)-related ILD had their CTD diagnosis confirmed by revised clinical presentation, serologic testing, and specific diagnostic criteria when appropriate.[19,20] Partners Human Research Committee approved this study protocol (2011P000272), and written consent was waved for this retrospective analysis.

Hemodynamic Measurements

Our RHC and iCPET methods have been previously described[9,18,21] and are detailed in e-Appendix 1. Briefly, supine RHC was performed by using a pulmonary arterial catheter percutaneously inserted via the internal jugular vein and a simultaneous radial arterial line. Symptom-limited incremental CPET was next performed by using an upright cycle ergometer and a breath-by-breath metabolic cart with patients breathing room air.

Simultaneous pulmonary and systemic hemodynamic monitoring was recorded and pressure waveforms were averaged over three respiratory cycles.[22] Cardiac output was obtained by using the Fick principle (cardiac output = VO_2/[arterial-mixed venous oxygen content]). Maximum voluntary ventilation was taken as resting FEV_1 multiplied by 35. The anaerobic threshold (AT) was defined by the intercept of a best-fit, two-linear segment plot of log-log transformation of minute-per-minute lactate concentration vs the minute-per-minute VO_2.[23] Peak VO_2 was expressed as % predicted and indexed to lean body mass[24] to account for the presence of overweight studied subjects.

PVR and total pulmonary resistance were calculated by: (mPAP – PAWP/cardiac output) and (mPAP/cardiac output), respectively, and expressed as WU. Pulmonary vascular compliance (PVC) was

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calculated by stroke volume/systolic PAP – diastolic PAP. ΔmPAP/Δ cardiac output was calculated by peak mPAP – rest mPAP/peak cardiac output –rest cardiac output. Pulmonary arterial stiffness was calculated by systolic PAP – diastolic PAP/stroke volume index. RV stroke work index (RVSWI) was calculated by: (1.25 mPAP – right atrial pressure × stroke volume index × 0.0136).[25-27]

Hemodynamic Definitions

ILD + rPH was defined by resting supine RHC as mPAP ≥ 25 mm Hg and PAWP ≤ 15 mm Hg.[1] If mPAP was < 25 mm Hg at resting RHC, ILD + ePH was defined by the following age-related exercise hemodynamic criteria[18]: (1) patients aged ≤0 years, peak mPAP > 30 mm Hg and peak PVR > 1.34 WU; and (2) patients aged >50 years, peak mPAP > 33 mm Hg and peak PVR > 2.10 WU. In the absence of the aforementioned hemodynamic criteria, patients were designated as ILD non-PH.

Statistical Analysis

The statistical analyses were performed by using SPSS software, version 19 (IBM SPSS Statistics, IBM Corporation). Values are expressed as mean ± SD or median [interquartile range], unless otherwise stated. Comparisons of normally distributed continuous variables among ILD non-PH, ILD + rPH, and ILD + ePH were performed by using one-way analysis of variance with a Tukey post hoc analysis. Comparisons of nonnormally distributed continuous variables among the ILD non-PH, ILD + rPH, and ILD + ePH groups were performed by using the Kruskal-Wallis test with Dunn's post hoc test. Normality assessment was based on the Shapiro-Wilk statistic. Comparisons of proportions between groups for categorical variables were compared by using χ^2 and Fisher exact tests. Correlation analysis between peak Pa_{O_2} vs peak PVR and between peak Pa_{O_2} vs peak RVSWI was performed to examine the association between exercise hypoxemia, exercise PVR, and RV work. P values < .05 were considered significant.

Results

Of the 737 iCPET reports analyzed, 66 had fibrotic ILD on HRCT imaging. Seventeen patients were excluded: one due to anemia and 16 because of left heart disease (nine patients with echocardiographic abnormalities and seven with postcapillary PH). The study population therefore comprised 49 patients with ILD. Based on the aforementioned resting and exercise hemodynamic criteria, we identified 13 (26%) patients with ILD + rPH, 14 (29%) with ILD + ePH, and 22 (45%) with ILD non-PH.

The mean age for the study population was 61 ± 12 years, and 78% (n = 38) were aged > 50 years. ILD etiologies included CTD-related ILD (n = 26), combined pulmonary fibrosis and emphysema (n = 7), idiopathic pulmonary fibrosis (n = 5), sarcoidosis (n = 2), chronic aspiration (n = 2), and chronic hypersensitivity pneumonitis (n = 2), among others. Detailed ILD etiologies according to exercise hemodynamic diagnosis are provided in e-Table 1. None of the studied patients was receiving pulmonary vasodilators or supplemental oxygen at the time of iCPET.

ILD + rPH had lower FVC, diffusing capacity of the lung for carbon monoxide, and Pa_{O_2} at rest compared with non-PH. In addition, ILD + ePH had decreased diffusing capacity of the lung for carbon monoxide compared with non-PH. Patients' baseline characteristics are presented in Table 1.

At RHC, ILD non-PH and ILD + ePH had similar cardiac output, PVR, and PVC. As expected, ILD + rPH had higher mPAP and PVR compared with ILD + ePH and ILD non-PH. Resting RHC hemodynamic data are presented in Table 2.

During iCPET, peak VO_2 was reduced in ILD + ePH and ILD + rPH compared with ILD non-PH (Table 3). ILD + ePH and ILD + rPH had an elevated peak alveolar-arterial gradient compared with ILD non-PH. The ventilatory equivalent for CO_2 was not statistically different between ILD non-PH and ILD + ePH. Ventilatory reserve was reduced in ILD + rPH at the AT but similar between ILD + ePH and ILD non-PH both at peak exercise and at the AT. A primary pulmonary mechanical limit to exercise, as identified by the ventilatory reserve at the AT > 0.70,[28] was present in four cases, all of them with ILD + rPH.

ΔmPAP/Δ cardiac output was 2.0 [1.5-2.8] for ILD non-PH, 3.2 [2.5-4.2] for ILD + ePH, and 5.3 [3.2-8.7] for ILD + rPH (overall, P < .001), being statistically different in the post hoc analysis for ILD + ePH vs ILD non-PH (P = .038) and for ILD + rPH vs ILD non-PH (P < .001). Resting pulmonary arterial stiffness was 0.33 ± 0.14 for ILD non-PH, 0.51 ± 0.15 for ILD + ePH, and 0.68 ± 0.25 mm Hg/m^2 per milliliter for ILD + rPH (overall, P < .0001; ILD + ePH vs ILD non-PH, P = .002; ILD + ePH vs ILD + rPH, P = .061; ILD + rPH vs ILD non-PH, P < .0001). Peak exercise pulmonary arterial stiffness was 0.66 ± 0.24 for ILD non-PH, 0.85 ± 0.27 for ILD + ePH, and 1.53 ± 0.48 mm Hg/m^2 per milliliter for ILD + rPH (overall, P < .0001; ILD + ePH vs ILD non-PH, P = .052; ILD + ePH vs ILD + rPH, P = .002; ILD + rPH vs ILD non-PH, P < .0001).

Minute-per-minute PVR vs PVC data during exercise (n = 181 from 22 ILD non-PH patients, n = 112 from 14 ILD + ePH patients, and n = 94 from 13 ILD + rPH patients), as expected, revealed a hyperbolic PVR and PVC correlation for the entire study sample during exercise (Fig 1A). However, each ILD hemodynamic phenotype presented distinct patterns of dynamic

TABLE 1] Baseline Characteristics of Study Patients With Fibrotic ILD

Characteristic	ILD Non-PH (n = 22)	ILD + ePH (n = 14)	ILD + rPH (n = 13)	*P* Value			
				Overall	ePH vs Non-PH	ePH vs rPH	rPH vs Non-PH
Female	17 (77)	6 (43)	7 (54)	.098			
Age, y	61 ± 10	56 ± 14	67 ± 10	.062			
BMI, kg/m^2	28.0 ± 5.5	29.1 ± 6.6	29.8 ± 6.6	.678			
Pulmonary function testing, % predicted[a]							
FEV_1	76 ± 20	72 ± 15	52 ± 19	.002	.771	0.020	.001
FVC	75 ± 18	69 ± 13	54 ± 19	.005	.416	0.116	.003
FEV_1/FVC	100 ± 11	105 ± 9	96 ± 18	.490			
D_{LCO}	58 ± 13	48 ± 19	44 ± 13	.034	.045	0.999	.049
Blood gas analyses at rest							
Sao_2, %	96.9 ± 1.5	96.5 ± 1.7	94.9 ± 2.5	.001	.680	0.016	< .001
Pao_2, mm Hg	93.7 ± 14.3	88.5 ± 14.2	78.4 ± 10.8	.008	.497	0.136	.006
$Paco_2$, mm Hg	36.5 ± 4.2	37.1 ± 4.7	37.4 ± 7.6	.882			
Echocardiography[b]							
LA AP diameter, mm	37 ± 10	33 ± 4	38 ± 8	.135			
LVEF, %	63 ± 5	61 ± 4	64 ± 5	.262			
TRV, m/s	2.4 ± 0.3	2.7 ± 0.4	3.3 ± 0.4	< .001	.159	0.002	< .0001
Estimated sPAP, mm Hg	28 ± 6	34 ± 8	52 ± 14	< .001	.370	0.002	< .0001

Data are expressed as No. (%) or mean ± SD. D_{LCO} = diffusing capacity of the lung for carbon monoxide; ePH = exercise pulmonary hypertension; ILD = interstitial lung disease; LA AP = left atrial antero-posterior; LVEF = left ventricular ejection fraction; Non-PH = no resting/exercise pulmonary hypertension; rPH = resting pulmonary hypertension; Sao_2 = arterial oxygen saturation; sPAP = systolic pulmonary arterial pressure; TRV = tricuspid regurgitant jet velocity.
[a]Subjects with D_{LCO} available: n = 16 for non-PH, n = 13 for ePH, and n = 7 for PH.
[b]Subjects with detectable TRV: n = 15 for non-PH, n = 8 for ePH, and n = 7 for PH.

changes of PVC relative to PVR from rest to peak exercise, pointing to a progressive loss in pulmonary vascular reserve (Fig 1B). Peak RVSWI was progressively increased comparing ILD non-PH, ILD + ePH, and ILD + rPH (Fig 2). The coefficient of determination (R^2) between peak Pao_2 and peak PVR was 0.28 ($P < .001$),

TABLE 2] Resting Supine Right Heart Catheterization

Variable	ILD Non-PH (n = 22)	ILD + ePH (n = 14)	ILD + rPH (n = 13)	*P* Value			
				Overall	ePH vs Non-PH	ePH vs rPH	Non-PH vs rPH
RAP, mm Hg	5 ± 3	6 ± 2	6 ± 3	.523			
mPAP, mm Hg	16 ± 5	19 ± 4	31 ± 7	< .0001	.264	< .001	< .0001
PAWP, mm Hg	10 ± 5	11 ± 4	12 ± 2	.257			
TPG, mm Hg	6 ± 3	8 ± 4	19 ± 7	< .0001	.434	< .001	< .0001
Cardiac output, L/min	5.4 ± 1.2	5.4 ± 1.1	5.9 ± 1.5	.453			
Cardiac index, L/min/m^2	3.0 ± 0.7	2.9 ± 0.6	3.1 ± 0.9	.776			
TPR, WU	3.0 ± 1.0	3.6 ± 1.0	5.7 ± 2.4	< .0001	.542	.001	< .0001
PVR, WU	1.2 ± 0.5	1.5 ± 0.8	3.6 ± 2.0	< .0001	.402	.002	< .0001
PVC, mL/mm Hg	4.8 ± 1.2	4.5 ± 1.7	2.9 ± 1.4	.002	.523	.032	< .001

Data are expressed as mean ± SD. mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PVC = pulmonary vascular compliance; PVR = pulmonary vascular resistance; RAP = right atrial pressure; TPG = transpulmonary gradient; TPR = total pulmonary resistance; WU = Wood units. See Table 1 legend for expansion of other abbreviations.

TABLE 3] Upright Invasive Cardiopulmonary Exercise Testing

Variable	ILD Non-PH (n = 22)	ILD + ePH (n = 14)	ILD + rPH (n = 13)	*P* Value			
				Overall	ePH vs Non-PH	ePH vs rPH	Non-PH vs rPH
Peak work, Watts	96 ± 27	94 ± 30	57 ± 35	.002	.979	.008	.002
Peak VO_2, % predicted	81 ± 16	67 ± 13	61 ± 10	< .001	.016	.508	< .001
Peak VO_2 indexed to LBM, mL/kg/min	26.2 ± 4.7	22.6 ± 3.4	18.6 ± 3.0	< .0001	.029	.033	< .0001
VO_2 at the AT, % VO_{2MAX} predicted	42 ± 10	37 ± 12	37 ± 5	.117			
Peak heart rate, % predicted	86 ± 9	89 ± 11	78 ± 13	.025	.715	.025	.078
Peak RER	1.14 ± 0.13	1.14 ± 0.15	1.07 ± 0.17	.233			
Peak $P_{A-a}O_2$, mm Hg	31.0 ± 20.2	46.9 ± 17.0	55.9 ± 13.9	< .001	.033	.393	< .001
Peak Pao_2, mm Hg	86.6 ± 22.1	69.7 ±16.3	60.7 ± 11.2	< .001	.027	.395	< .001
Peak Sao_2, %	94.7 ± 3.7	91.3 ± 5.2	87.8 ± 6.0	.001	.049	.252	< .001
Peak V_D/V_T	0.25 ± 0.10	0.31 ± 0.12	0.30 ± 0.21	.524			
VE/VCO_2 slope	34.2 ± 8.2	35.5 ± 6.6	41.7 ± 10.6	.072			
VE_{MAX}/MVV	0.73 ± 0.24	0.70 ± 0.17	0.98 ± 0.42	.085			
VE_{AT}/MVV	0.30 ± 0.11	0.32 ± 0.13	0.49 ± 0.18	< .001	.921	.006	< .001
Peak lactate, mg/dL	4.9 ± 1.8	4.6 ± 1.2	4.2 ± 1.5	.452			
Peak RAP, mm Hg	4 ± 3	5 ± 3	7 ± 4	.105			
Peak mPAP, mm Hg	27 ± 5	40 ± 8	51 ± 10	< .0001	.0001	.163	< .0001
Peak PAWP, mm Hg	10 ± 4	12 ± 4	15 ± 6	.037	.207	.512	.018
Peak TPG, mm Hg	17 ± 5	28 ± 8	36 ± 10	< .0001	< .001	.145	< .0001
Peak cardiac output, L/min	11.2 ± 2.8	10.9 ± 1.8	9.3 ± 2.5	.101			
Peak cardiac index, L/min/m^2	6.1 ± 1.4	5.7 ± 0.9	4.8 ± 1.2	.025	.775	.139	.020
Peak TPR, WU	2.6 ± 0.7	3.8 ± 0.8	5.8 ± 1.8	< .0001	.007	< .0001	< .0001
Peak PVR, WU	1.6 ± 0.6	2.6 ± 0.7	4.1 ± 1.4	< .0001	.005	< .001	< .0001
Peak PVC, mL/mm Hg	3.2 ± 1.3	2.5 ± 0.8	1.4 ± 0.6	< .0001	.239	.004	< .0001

Data are expressed as mean ± SD. AT = anaerobic threshold; LBM = lean body mass; MVV = maximal voluntary ventilation; $P_{A-a}O_2$ = alveolar–arterial oxygen tension difference; RER = respiratory exchange ratio; Sao_2 = arterial oxygen saturation; TPG = transpulmonary gradient; VCO_2 = CO_2 production; V_D = dead space volume; VE = minute ventilation; VE_{AT} = minute ventilation at the anaerobic threshold; VE_{AT}/MVV = ventilatory reserve at the anaerobic threshold; VE_{MAX} = minute ventilation at peak exercise; VE_{MAX}/MVV = ventilatory reserve at peak exercise; VE/VCO_2 slope = ventilatory equivalent for CO_2 VO_2 = oxygen uptake; VO_{2MAX} = maximal oxygen uptake; V_T = tidal volume. See Table 1 and 2 legends for expansion of other abbreviations.

and between peak Pao_2 and peak RVSWI it was 0.27 ($P < .001$).

Discussion

The current study found that ILD is associated with increased RV work and decreased pulmonary vascular reserve and an associated reduced peak VO_2 during exercise, both in the setting of resting or exercise PH. We also observed that reduced peak VO_2 in ILD + ePH occurs at similar ventilatory reserve compared with ILD non-PH, suggesting therefore that the pulmonary vascular and RV burden in ILD are relevant to their exercise limit, irrespective of exercise ventilatory limitation.

Pulmonary vascular dysfunction and decreased circulatory reserve lead to increased RV afterload, which in turn, directly affects RV function.[29] The RVSWI estimates the amount of work expended by the right ventricle per beat to generate RV stroke volume for a given RV afterload and therefore represents an index of RV function and contractility,[27] indirectly evaluating hemodynamic coupling. Increased RVSWI has been associated with poor outcomes in patients with left heart disease.[30,31] In patients with parenchymal lung disease, an elevated RVSWI has been associated with increased mortality in patients prior to lung transplant.[32] In the current study, ILD + ePH had a significantly increased peak RVSWI compared with

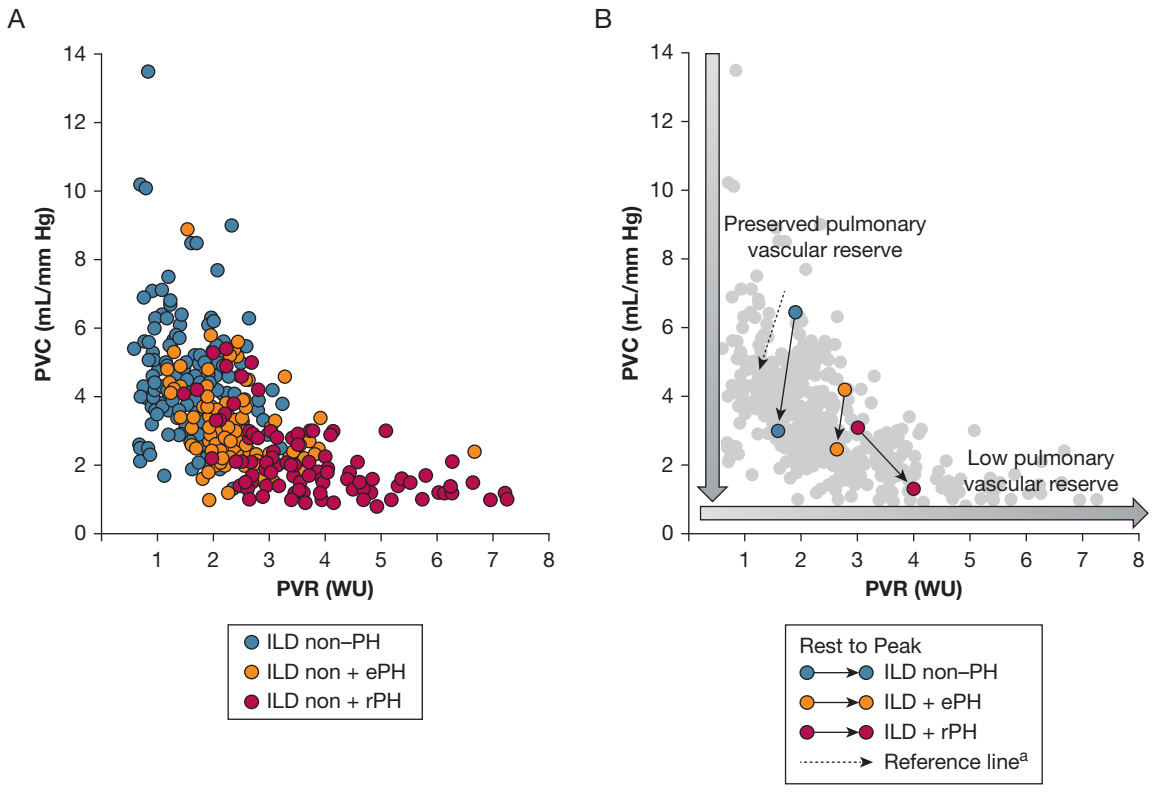

Figure 1 – *PVC vs PVR during exercise in patients with ILD non-PH, ILD + ePH, and ILD + rPH. Data are presented as (A) minute-per-minute individual data points (n = 387), which included rest, freewheeling, and minute-per-minute incremental data until symptom-limited peak exercise for the entire study sample (n = 181 from 22 ILD non-PH patients, n = 112 from 14 ILD + ePH patients, and n = 94 from 13 ILD + rPH patients) and as (B) the mean values at rest and the mean values at peak exercise (colored points). The arrows indicate the direction of the changes from rest to peak exercise and from a preserved pulmonary vascular reserve to an impaired pulmonary vascular reserve (background gray points represent the minute-per-minute individual data points from panel A).* [a]*Reference line is based on previously published data for normal subjects > 50 years old.*[18] *PVC decreases during exercise from a mean value of 7.0 mL/mm Hg at rest to a mean value of 4.7 mL/mm Hg at peak exercise; PVR decreases during exercise from a mean value of 1.7 WU at rest to a mean value of 1.2 WU at peak exercise. ePH = exercise pulmonary hypertension; ILD = interstitial lung disease; Non-PH = no resting/exercise pulmonary hypertension; PH = pulmonary hypertension; PVC = pulmonary vascular compliance; PVR = pulmonary vascular resistance; rPH = resting pulmonary hypertension; WU = Wood units.*

ILD non-PH (Fig 2) at a similar peak cardiac output (Table 3). This finding likely indicates early RV dysfunction and dynamic RV-pulmonary arterial uncoupling in the setting of early pulmonary vascular dysfunction, and it indicates the deleterious effect of minor increases of RV afterload to ILD exercise tolerance.

The resting mPAP for the ILD + ePH group in the current study was 19 ± 4 mm Hg. Two previous studies have identified mild elevations of resting mPAP as independent predictors of mortality in fibrotic ILD. Hamada et al[33] reported reduced survival in ILD with resting supine mPAP ≥ 17 mm Hg, and Kimura et al[34] identified an mPAP > 20 mm Hg as an independent prognostic factor in ILD. Given the substantial overlap between mildly elevated resting mPAP and ePH,[8,35] and the impact of both hemodynamic conditions on RV-pulmonary arterial coupling, aerobic capacity, and outcomes,[8,15,36-38] the current study highlighted the possible complex interplay of increased resting mPAP values, ePH, and outcomes in ILD.

Abnormal pulmonary vascular responses to exercise are increasingly recognized as a feature of parenchymal lung disease. For instance, in COPD, Hilde et al[39] reported a high occurrence of exercise abnormal pulmonary vascular responses among patients without rPH. In ILD, Degani-Costa et al[15] found a 28% prevalence of ePH determined by mPAP/cardiac output slope during maximal exercise testing, with associated reduced aerobic exercise capacity. ePH is currently believed to be at the early and mild end of the pulmonary vascular disease severity spectrum, and in line with this hypothesis, the current ILD + ePH cohort had a similarly reduced peak VO_2 compared with ILD + rPH.

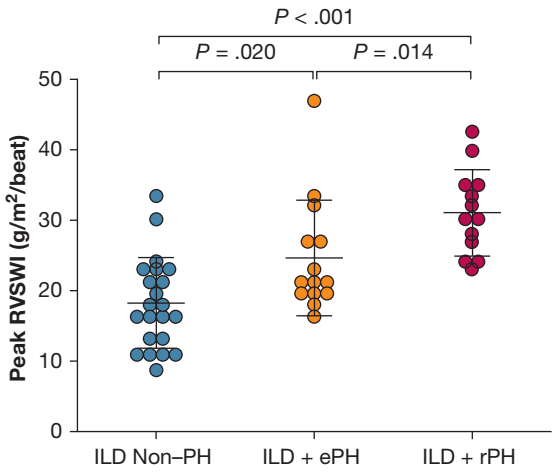

Figure 2 – *RVSWI at peak exercise in ILD non-PH, ILD + ePH, and ILD + rPH. Data are expressed as individual data points and as mean ± SD (error bars). RVSWI = right ventricular stroke work index. See Figure 1 legend for expansion of other abbreviations.*

The relation between PVC and PVR might be considered an indirect measure of pulmonary vascular reserve.[40] In pulmonary arterial hypertension, during the natural history of the disease, first there is a reduction in PVC without increases in PVR. Only after achieving a "critical" PVC value (that likely varies on an individual basis) does PVR start to increase.[41] During exercise, the PVC vs PVR dynamic relation varies according to the degree of RV afterload impairment,[42] being dynamically down-right oriented in the PVC vs PVR hyperbolic curve according to the disease severity.[8]

Gradual changes in PVC relative to PVR during exercise were observed among the three study groups (Fig 1B). As an index of pulmonary vascular reserve[40,43] and dynamic RV afterload, the different patterns of changes of PVR relative to PVC from rest to peak exercise observed for each subgroup, in addition to the associated increase in pulmonary arterial stiffness from rest to peak exercise, indicate a progressive loss in pulmonary vascular reserve from ILD non-PH to ILD + ePH to ILD + rPH. In ILD + rPH, it is possible that the loss in pulmonary vascular reserve was additionally influenced by exercise PAWP. Taken together, the observed gradual changes in PVC relative to PVR during exercise suggest that the pulmonary vascular function might be affected much earlier than the onset of established PH in ILD; these data provide an interesting insight about the continuum of pulmonary vascular deterioration and RV-pulmonary arterial uncoupling in ILD. Furthermore, our observations add framework for the understanding of reported PVR and PVC prognostic implications in the setting of parenchymal lung disease.[44]

Ventilatory reserve was similar in ILD + ePH and ILD non-PH, both at the AT and at peak exercise, indicating a similar ventilatory reserve during exercise in ILD patients with and without ePH (Table 3). However, peak VO_2 was significantly reduced in ILD + ePH, pointing to pulmonary vascular and RV dysfunction as an important cause of exercise intolerance in ILD + ePH. ILD + rPH presented an associated pulmonary mechanical limitation to exercise. In this subgroup, the more severe parenchymal lung disease worsened ventilation/perfusion matching and ventilatory efficiency, resulting in decreased ventilatory reserve and overall exercise capacity. Of note, ILD + ePH desaturated during exercise, but this finding is likely the result of, rather than the cause of, PH.[45] Furthermore, based on the coefficient of determination between peak Pa_{O_2} and peak PVR and peak RVSWI, < 30% of exertional PVR and RV work was explained by exercise hypoxemia.

These findings confirm the previous noninvasive observations from Hansen and Wasserman,[46] which suggested that exercise intolerance in ILD is associated more with cardiopulmonary function than with ventilatory mechanics. It is important to note, however, that pulmonary vascular impairment in ILD can result from interstitial fibrosis, hypoxia, inflammation, and/or intrinsic pulmonary vascular disease,[47] with or without pulmonary vascular remodeling. Given that the current study does not have the power to define physiologic mechanisms of pulmonary vascular dysfunction in ILD, we are unable to determine the primary cause of the observed pulmonary vascular impairment. Nonetheless, irrespective of the underlying cause of pulmonary vascular dysfunction, the findings suggest that dynamic increases of RV afterload affect RV function (and therefore cardiopulmonary function) during exercise in ILD, negatively influencing their exercise capacity.

Among noninvasive indexes of abnormal exercise physiology, ventilatory inefficiency has already been shown to help noninvasively identify pulmonary vascular dysfunction in ILD.[2,3,48] In the current study, the ventilatory equivalent for CO_2 during exercise was similar between ILD + ePH and ILD non-PH. Therefore, our findings suggest limited ability of noninvasive exercise testing in identifying early PH and pulmonary vascular disease in ILD, highlighting the added value of invasive hemodynamic evaluation during exercise for early disease detection.

The current study did have some limitations. Studied patients were derived from a single tertiary center and may not represent an overall community-based ILD population; therefore, the generalization of our findings should be done with caution. The study sample size was relatively small, which affected study power and precluded a more robust statistical analysis; in addition, the use of multiple statistical hypothesis tests increased the chance of a type I error. However, the literature on directly measured pulmonary hemodynamics during exercise in ILD is scarce, and the current study potentially provides useful insights into the pathophysiology underlying the exercise limit in ILD. The prevalence of CTD-related ILD was elevated among study patients, and the overall pulmonary function impairment in patients without resting PH was mild, which might suggest primary pulmonary vascular dysfunction in this subgroup. However, CTD-related ILD is of major clinical interest and is believed to represent a distinct clinical phenotype in relation to CTD without ILD that imposes additional impact on patient outcomes.[49] Finally, ePH was defined based on age-related upper limits of normal for upright exercise pulmonary hemodynamics[18] and a dual criteria of elevated peak mPAP and peak PVR. These criteria likely decrease false- positive/false-negative diagnoses of ePH as a function of normal aging,[8] given that exercise hemodynamics during exercise are known to vary considerably according to age.[50] In addition, the ePH criteria used in the current study aim for better sensitivity and specificity in detecting pulmonary vascular dysfunction and therefore allow for the proper identification of exercise-limiting pulmonary vasculopathy.

Conclusions

The current study showed that ILD with resting or exercise PH is associated with increased RV work and decreased pulmonary vascular reserve during exercise, with an associated reduced peak VO_2. The latter occurs at a similar ventilatory reserve in ILD with and without exercise PH. These findings highlight the potential role of the pulmonary vascular and RV burden to the exercise limit in ILD.

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Additional information: The e-Appendix and e-Table can be found in the Supplemental Materials section of the online article.

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