



Pulmonary vascular response patterns during exercise in interstitial lung disease

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ABSTRACT When overt pulmonary hypertension arises in interstitial lung disease (ILD), it contributes to exercise intolerance. We sought to determine the functional significance of abnormal pulmonary arterial pressure (PAP) responses to exercise in ILD.

27 ILD patients and 11 age-matched controls underwent invasive cardiopulmonary exercise testing (iCPET). Mean PAP (mPAP) was indexed to cardiac output (Q'T) during exercise, with a mPAP-Q'T slope ≥ 3 mmHg·min·L⁻¹ defined as an abnormal pulmonary vascular response.

All control subjects had mPAP-Q'T slopes < 3 mmHg·min·L⁻¹ (mean \pm SEM 1.5 \pm 0.1 mmHg·min·L⁻¹). 15 ILD patients had mPAP-Q'T slopes ≥ 3 mmHg·min·L⁻¹ (4.1 \pm 0.2 mmHg·min·L⁻¹) and were labelled as having ILD plus pulmonary vascular dysfunction (PVD). Subjects without pulmonary hypertension and with mPAP-Q'T slopes < 3 mmHg·min·L⁻¹ (1.9 \pm 0.2 mmHg·min·L⁻¹) were labelled as ILD minus PVD (n=12). ILD+PVD and ILD-PVD patients did not differ in terms of age, sex, body mass index, pulmonary function testing or degree of exercise oxygen desaturation. Peak oxygen consumption was lower in ILD+PVD than in ILD-PVD (13.0 \pm 0.9 versus 17 \pm 1.1 mL·kg⁻¹·min⁻¹, p=0.012) and controls (19.8 \pm 1.7 mL·kg⁻¹·min⁻¹, p=0.003). ILD+PVD patients had increased dead space volume (V_D)/tidal volume (V_T) and minute ventilation/carbon dioxide production at the anaerobic threshold.

In ILD, mPAP-Q'T slope ≥ 3 mmHg·min·L⁻¹ is associated with lower peak oxygen consumption, increased V_D/V_T and inefficient ventilation. While noninvasive parameters were unable to predict those with abnormal pulmonary vascular responses to exercise, iCPET-derived mPAP-Q'T slope may aid in identifying physiologically significant, early pulmonary vascular disease in ILD.



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PAP responses to exercise may help to refine resting phenotypes related to pulmonary vascular dysfunction in ILD <http://ow.ly/M0nMa>

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Introduction

Pulmonary hypertension is common in the setting of interstitial lung disease (ILD) and may contribute to exercise intolerance in this patient population [1]. Currently, the diagnosis of pulmonary hypertension is based only on pulmonary haemodynamics measured at rest, leaving patients with abnormal pulmonary vascular response patterns during exercise unrecognised.

There has been renewed interest in the study of pulmonary vascular responses to exercise and a definition of exercise-induced pulmonary hypertension (Ei-PH) based on the pulmonary arterial pressure (PAP)–cardiac output ($Q'T$) relationship has been suggested to reflect pulmonary vascular disease better than using an absolute cut-off value of mean PAP (mPAP) at peak exercise [2, 3]. A mPAP– $Q'T$ slope ≥ 3 mmHg·min⁻¹ during maximum incremental exercise indicates an abnormal pulmonary vascular response in patients with or without pulmonary hypertension at rest.

The presence of a pulmonary hypertensive response during exercise has been repeatedly associated with reduced exercise capacity in heart failure, pulmonary arterial hypertension (PAH) and valvular disease [4–6]. Moreover, it has been shown to negatively impact survival in patients with heart failure with reduced left ventricular ejection fraction (LVEF) [4] as well as in aortic stenosis [7]. Ei-PH has also been considered a risk factor for developing resting pulmonary hypertension both in chronic obstructive pulmonary disease (COPD) [8] and scleroderma patients [9].

Overt, resting pulmonary hypertension is known to complicate the course of ILD, being associated with poorer functional status and worsened outcomes [10–15], but the clinical significance of abnormal pulmonary vascular responses to exercise in ILD has not been characterised. In this study, we used invasive cardiopulmonary exercise testing (iCPET) to test the hypothesis that abnormal pulmonary vascular responses to exercise (*i.e.* mPAP– $Q'T$ slope ≥ 3 mmHg·min⁻¹) would negatively impact functional capacity in ILD.

Methods

Study design

Among 536 patients who underwent iCPET between February 2006 and August 2013 at the Massachusetts General Hospital, Boston, MA, USA, we identified patients with proven ILD based on high-resolution computed tomography (HRCT) findings adjudicated by a thoracic radiologist and/or lung biopsy. Exclusion criteria consisted of: LVEF <50%; more than mild valvular heart disease; and lack of available chest computed tomography images or complete exercise haemodynamic measurements. Age- and sex-matched control subjects with normal aerobic capacity (peak oxygen consumption ($V'O_2$) $\geq 80\%$ of the predicted value on the basis of age, sex and height) and without ILD, pulmonary hypertension or heart disease were selected from the same database. Demographic characteristics of the population, as well as smoking history, pulmonary function test (PFT) results (spirometry, lung volumes and diffusing capacity of the lung for carbon monoxide (DLCO)), arterial blood gas results, resting haemodynamic measurements and radiographic findings for each subject were recorded. Resting pulmonary haemodynamics were assessed by right heart catheterisation performed in the supine position immediately before iCPET. PFTs were performed within 3 months of iCPET. Similarly, radiographic findings (presence of ground-glass opacities, reticulation, traction bronchiectasis and honeycombing) were considered for further analysis only if HRCT imaging was available within 6 months of the iCPET. The study was approved by the Institutional Review Board of the Massachusetts General Hospital and complies with the Declaration of Helsinki.

Cardiopulmonary exercise testing and invasive haemodynamic measurements

The cardiopulmonary exercise testing (CPET) protocol and the methodology to perform invasive hemodynamic measurements during exercise have been previously published [3, 4]. In summary, prior to iCPET, all subjects underwent placement of a pulmonary arterial catheter *via* the internal jugular vein and placement of a systemic arterial catheter *via* the radial artery. Patients and healthy controls underwent a maximal incremental-ramp upright exercise test on an electromagnetically braked cycle-ergometer (5–20-W·min⁻¹ continuous ramp after an initial 2–3-min period of unloaded pedalling; MedGraphics, St Paul, MN, USA) with simultaneous haemodynamic monitoring (Witt Biomedical Inc., Melbourne, FL, USA). mPAP, pulmonary capillary wedge pressure (PCWP), and mean radial arterial pressure were measured in the upright position, and averaged over the respiratory cycle while patients were seated on the bike, at rest and at 1-min intervals during exercise. Simultaneous measurement of arterial and mixed venous oxygen content allowed calculation of arteriovenous oxygen content difference (C_a-vO_2) and, consequently, the minute-by-minute Fick $Q'T$ ($V'O_2=Q'T \times C_a-vO_2$). In one subject, we used simultaneously measured ventriculographic $Q'T$ (*i.e.* left ventricular end-diastolic volume multiplied by LVEF at rest and at peak exercise) to derive mPAP– $Q'T$ slope because supplemental oxygen precluded Fick $Q'T$ measurements.

Definition of haemodynamic groups

Pulmonary hypertension at rest was defined according to current guidelines as mPAP ≥ 25 mmHg [16]. During exercise, we assessed the relationship between mPAP and $Q'T$ augmentation. A slope of a linear regression between mPAP and $Q'T \geq 3$ mmHg·min·L⁻¹ or pulmonary vascular resistance (PVR) ≥ 3 Wood units at peak exercise defined an abnormal pulmonary vascular response to exercise [2, 3]. Patients were said to have normal pulmonary haemodynamics if they presented with mPAP < 25 mmHg at rest and showed mPAP- $Q'T$ slope < 3 mmHg·min·L⁻¹ and PVR < 3 Wood units at peak exercise.

Statistical analysis

Continuous quantitative variables were tested for normality and considered to have a normal distribution, being presented as mean \pm SEM. The independent-samples Student's t-test was used for comparison of parametric data between groups. Pearson's correlation was performed when investigating the relationship between normally distributed variables. Categorical data are presented as frequencies or percentages and the Chi-squared test was used for comparisons when appropriate. Linear regression analysis was used to determine mPAP- $Q'T$ slopes and logistic regression was applied to investigate if noninvasive parameters of the CPET were able to predict an abnormal pulmonary vascular response to exercise. Multiple-subject mPAP- $Q'T$ data were pooled for linearity analysis according to the method of POON [17]. The statistical analysis was performed using SPSS version 20 (SPSS Inc., Chicago, IL, USA) and a p-value < 0.05 was considered statistically significant.

Results

Study population

27 patients with ILD and 11 controls met the study's inclusion criteria, and their baseline characteristics are reported in table 1. Referral for iCPET was uniformly to evaluate dyspnoea on exertion. Clinical diagnoses were taken from medical records and reflect the attending physician's opinion on the cases.

TABLE 1 Demographics, pulmonary function and blood gas analysis

	ILD	Controls	p-value
Subjects n	27	11	
Age years	65.2 \pm 2.4	61.5 \pm 2.0	0.258
Female %	52	54	0.972
Caucasian %	96	100	1.000
Positive smoking history %	59	55	0.534
Smoking history pack-years	35.1 \pm 11.4	25.8 \pm 13.6	0.612
BMI kg·m⁻²	27.8 \pm 1.1	30.0 \pm 1.3	0.081
Radiographic pattern of ILD n			
UIP	18		
NSIP	3		
OP	2		
Smoking-related fibrosis	1		
Lymphocytic interstitial pneumonia	1		
Radiation-induced fibrosis	1		
Sarcoidosis	1		
FEV₁ % predicted	69 \pm 3	102 \pm 5	<0.001
FVC % predicted	68 \pm 3	105 \pm 5	<0.001
FEV₁/FVC % predicted	103 \pm 2	98 \pm 2	0.055
RV % predicted	66 \pm 4	92 \pm 6	0.004
TLC % predicted	69 \pm 3	102 \pm 3	<0.001
RV/TLC % predicted	99 \pm 4	89 \pm 6	0.213
D_{LCO_{hb}} % predicted	45 \pm 4	94 \pm 6	<0.001
Hb g·dL⁻¹	12.8 \pm 0.3	13.5 \pm 0.3	0.118
P_{aO₂} mmHg	82 \pm 3	101 \pm 4	<0.001
S_{O₂} %	96.0 \pm 0.4	97.6 \pm 0.2	0.013

Data are presented as mean \pm SEM unless otherwise stated. ILD: interstitial lung disease; BMI: body mass index; UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; OP: organising pneumonia; FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; D_{LCO_{hb}}: diffusing capacity of the lung for carbon monoxide corrected for haemoglobin; Hb: haemoglobin; P_{aO₂}: arterial oxygen tension; S_{O₂}: oxygen saturation. Bold indicates statistical significance.

They included: idiopathic pulmonary fibrosis (IPF) (n=12; of whom, all were classified as having usual interstitial pneumonia (UIP) radiographically and eight out of eight patients with biopsies showed UIP); combined emphysema plus fibrosis (n=4; of whom, two had UIP, one had smoking-related ILD and one had organising pneumonia radiographically); fibrosis due to connective tissue diseases (CTDs) (Sjögren syndrome, scleroderma or antisynthetase syndrome) (n=6; of whom, one patient with Sjögren's had lymphocytic interstitial pneumonia, one scleroderma patient had organising pneumonia and one had UIP, one subject with CREST (calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly and telangiectasia) syndrome had nonspecific interstitial pneumonia (NSIP) and one had UIP, and one patient with antisynthetase syndrome had NSIP); sarcoidosis (n=1; with biopsy-proven pulmonary sarcoidosis and a radiographic classification of pulmonary sarcoidosis); radiation-induced lung fibrosis (n=1; in whom, the radiographic diagnosis was radiation-induced ILD); and ILD of unknown aetiology (n=3; of whom, two had UIP and one had NSIP radiographically). In each of the 12 subjects who underwent lung biopsy, the anatomopathologic diagnosis with in agreement with the radiographic pattern, which, in turn, was highly consistent with the clinical diagnoses.

All control subjects were referred for iCPET for investigation of unexplained dyspnoea but were found to have normal physiological responses to maximum incremental exercise testing. Obesity (n=7) was prevalent among controls and may have accounted for dyspnoea despite normal cardiorespiratory fitness in the setting of the high metabolic cost of performing work. Chart review also revealed the presence of other common conditions in individuals with an average age of 61 years: hypertension (n=5), obstructive sleep apnoea (n=4), hypothyroidism (n=2), coronary artery disease with previous percutaneous coronary intervention (n=2), previous deep vein thrombosis without pulmonary embolism (n=1), asthma (n=1) and fibromyalgia (n=1).

Only one patient was on supplemental oxygen at the time of the test, which precluded the measurement of $\dot{V}O_2$.

Haemodynamic profile at rest

ILD subjects had, on average, higher mPAP and PVR at rest than controls ($p < 0.05$) (table 2). Seven (24%) ILD patients had pulmonary hypertension at rest, five of whom were classified as having pre-capillary pulmonary hypertension (mPAP ≥ 25 mmHg and mean PCWP (mPCWP) ≤ 15 mmHg) and two as post-capillary pulmonary hypertension (mPAP ≥ 25 mmHg and mPCWP > 15 mmHg). Despite the higher PVR and mPAP, resting stroke volume, \dot{Q}'_T and cardiac index were relatively preserved and close to those shown by controls.

Exercise gas exchange and haemodynamics

CPET parameters for both groups are presented in table 2. As expected, ILD subjects had worse aerobic capacity based on the % predicted peak $\dot{V}O_2$ and lower achieved workloads than controls ($p < 0.05$). In addition, subjects with ILD had lower arterial oxygen tension (P_{aO_2}), arterial oxygen content and oxygen saturation (SO_2) than did controls, both at rest and at peak exercise. Unlike the controls, dead space ventilation (\dot{V}'_D)/tidal volume (V_T) in ILD patients did not fall appropriately during exercise. No patient demonstrated a primary pulmonary mechanical limit to exercise (*i.e.* minute ventilation/maximum voluntary ventilation > 0.7 at the anaerobic threshold). At peak exercise, ILD subjects had higher mPAP and PVR, and lower \dot{Q}'_T than controls ($p < 0.05$).

Patterns of pulmonary vascular response to exercise

All control subjects showed a normal pulmonary vascular response to exercise, with mPAP- \dot{Q}'_T slope being, on average, 1.5 ± 0.1 mmHg·min·L⁻¹, while the mean group mPAP- \dot{Q}'_T slope for ILD subjects was 3.1 ± 0.3 mmHg·min·L⁻¹. Subjects with ILD due to CTD or sarcoidosis (n=7) showed similar mPAP- \dot{Q}'_T slopes compared to subjects with other causes of ILD (3.1 ± 0.6 versus 2.8 ± 0.3 mmHg·min·L⁻¹, respectively; $p = 0.62$).

15 ILD patients had a mPAP- \dot{Q}'_T slope ≥ 3 mmHg·min·L⁻¹, and were classified as abnormal and labelled as having ILD plus pulmonary vascular dysfunction (PVD) (n=15). Subjects who had no pulmonary hypertension at rest and showed a normal pulmonary vascular response to exercise composed the group ILD minus PVD (n=12).

The ILD+PVD group had higher mPAP at rest and a much steeper slope during exercise (4.1 ± 0.2 mmHg·min·L⁻¹) than did the ILD-PVD (1.9 ± 0.2 mmHg·min·L⁻¹) and the control groups (1.5 ± 0.1 mmHg·min·L⁻¹) ($p < 0.001$) (fig. 1). Poon adjustment yielded similar mPAP- \dot{Q}'_T values in each group (4 ± 0.2 , 1.8 ± 0.2 and 1.5 ± 0.2 mmHg·min·L⁻¹, respectively) (fig. 1a and b). Although the ILD-PVD group started exercise at higher levels of mPAP than controls, their slope was similar to that of the latter ($p > 0.05$).

TABLE 2 Haemodynamics, blood gas and cardiopulmonary exercise testing parameters at rest and at maximum exercise in interstitial lung disease (ILD) patients and controls

	ILD [#]		Controls [¶]		p-value	
	Rest	Peak exercise	Rest	Peak exercise	Rest	Peak
mPAP-Q'T slope mmHg·min·L ⁻¹		3.1±0.3		1.5±0.1		<0.001
Maximum workload W		83±7		121±12		0.014
V'O ₂ mL·kg ⁻¹ ·min ⁻¹		14.3±0.8		19.7±1.6		0.017
V'O ₂ % predicted		61±3		90±4		<0.001
O ₂ pulse		8.7±0.5		12.7±1.1		0.006
SV mL	65±4	84±4	68±4	96±7	0.651	0.176
Q'T L·min ⁻¹	4.90±0.28	10.80±0.63	4.76±0.27	13.06±0.85	0.707	0.044
CI L·min ⁻¹ ·m ⁻²	2.66±0.14	5.77±0.27	2.29±0.14	6.27±0.38	0.123	0.233
HR beats·min ⁻¹	77±2	131±4	70±3	139±5	0.056	0.228
SBP mmHg	143±4	186±5	155±6	195±10	0.352	0.423
DBP mmHg	74±2	85±3	76±2	94±4	0.595	0.072
mPAP mmHg	20±1	37±2	14±1	26±2	<0.001	<0.001
PCWP mmHg	6±1	11±1	4±1	10±2	0.052	0.696
PVR Woods unit	2.9±0.3	2.3±0.2	2.0±0.2	1.3±0.1	0.019	0.003
PaO ₂ mmHg	82±3	62±3	101±4	107±4	<0.001	<0.001
So ₂ %	96±1	89±1	98±1	98±1	0.013	<0.001
ΔSo ₂ %		-7.2±1.0		0.1±0.3		<0.001
PA-aO ₂ mmHg		58±5		14.3±3.2		<0.001
V'E _{max} /MVV %		82.6±3.3		71.2±5		0.072
V _D /V _T %	37.6±1.5	34.9±1.6	34.2±2.8	23.9±1.9	0.296	<0.001
V'E/V'CO ₂ at AT		42.2±1.5		39.3±3.4		0.446

Data are presented as mean±SEM, unless otherwise stated. mPAP: mean pulmonary arterial pressure; Q'T: cardiac output; V'O₂: oxygen consumption; SV: stroke volume; QT: cardiac output; CI: cardiac index; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; PaO₂: arterial oxygen tension; So₂: oxygen saturation; Δ: change in; PA-aO₂: alveolar-arterial oxygen tension difference; V'E_{max}: maximum minute ventilation at peak exercise; MVV: maximum voluntary ventilation; V_D: dead space volume; V_T: tidal volume; V'E: minute ventilation; V'CO₂: carbon dioxide production; AT: anaerobic threshold. #: n=27; ¶: n=11. Bold indicates statistical significance.

When analysing the patterns of pulmonary vascular response to exercise in ILD+PVD, there were eight patients who developed abnormal pulmonary vascular responses to exercise without having pulmonary hypertension at rest. All patients with PVR at peak exercise ≥3 Wood units also showed a mPAP-Q'T slope ≥3 mmHg·min·L⁻¹. However, it is interesting to note that five ILD subjects with mPAP-Q'T slope ≥3 mmHg·min·L⁻¹ presented with PVR <3 Wood units at peak exercise; therefore, peak PVR cannot be used as a single criterion to define abnormal pulmonary vascular response to exercise (fig. 2).

Using a cut-off value of 30 mmHg for peak mPAP to define Ei-PH would have led to misclassification of 42% of the ILD-PVD subjects, who had normal pulmonary vascular responses to exercise but reached high levels of peak mPAP solely on account of the increased Q'T (fig. 3). A similar phenomenon was seen in the control group, as four of the 11 subjects achieved peak mPAP ≥30 mmHg despite having normal aerobic capacity and mPAP-Q'T slope.

ILD+PVD versus ILD-PVD comparison

There were no differences in terms of age, sex, body mass index (BMI), PFT or radiographic findings between ILD+PVD and ILD-PVD subjects (table 3). The prevalence of smokers and ex-smokers tended to be higher in the ILD+PVD group, but this difference was not statistically significant (p=0.096). The ILD+PVD group demonstrated higher mPAP (22±1 versus 16±1 mmHg in ILD+PVD and ILD-PVD, respectively; p=0.001) and PCWP (9±1 versus 6±1 mmHg in ILD+PVD and ILD-PVD, respectively; p=0.039) at rest, but neither group was above the upper limit of the normal range. No differences were seen in Q'T, cardiac index, PaO₂ or So₂ at rest.

Aerobic capacity was more markedly reduced in ILD+PVD subjects based on an earlier anaerobic threshold (30±2% versus 38±2% of predicted peak V'O₂, p=0.025) and a mean peak V'O₂ of

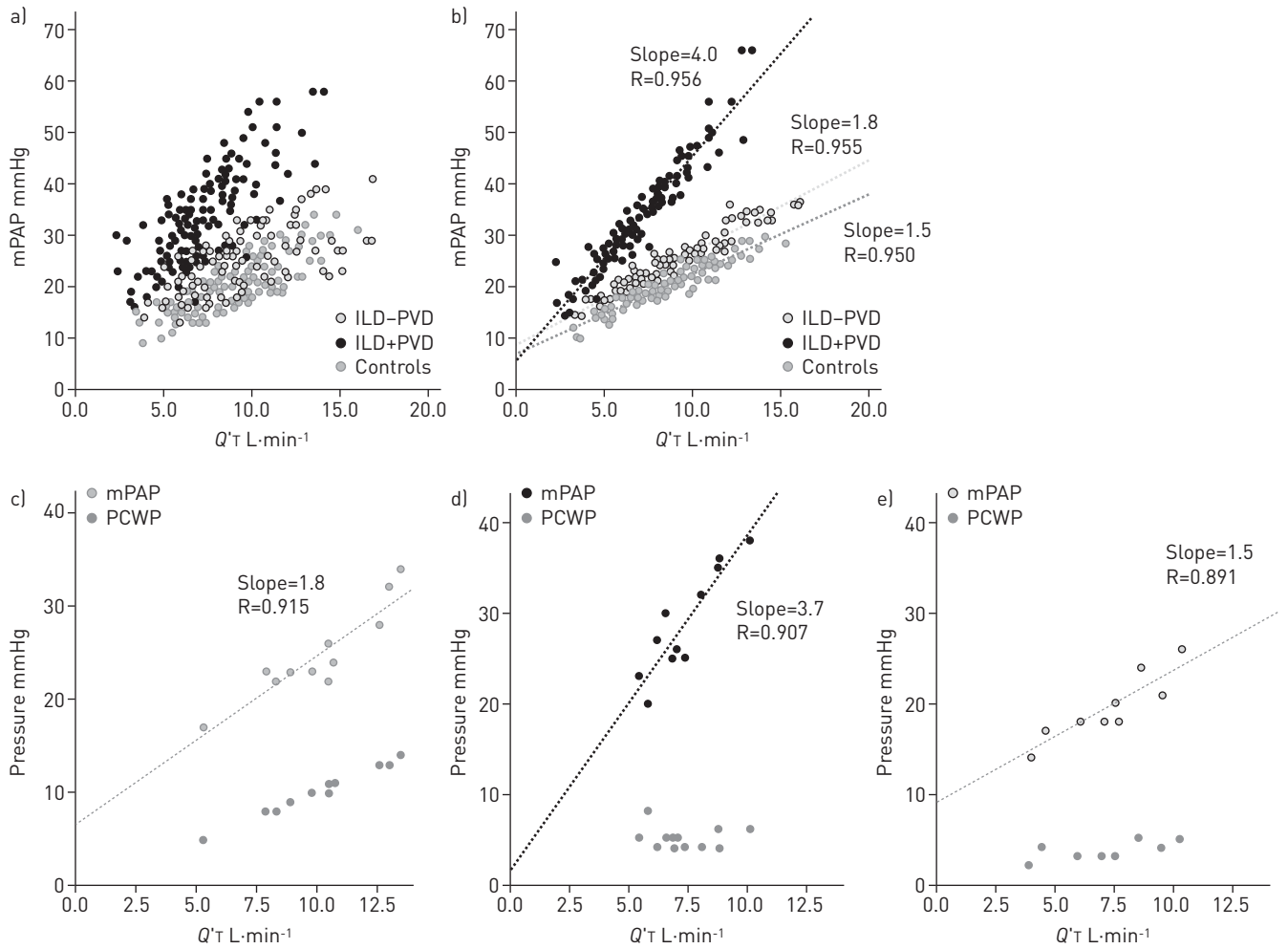


FIGURE 1 Pressure–flow relationships in interstitial lung disease (ILD) plus or minus pulmonary vascular dysfunction (PVD) and controls. a) Minute-by-minute mean pulmonary arterial pressure (mPAP) indexed to cardiac output ($Q'T$) in all subjects. b) Poon linear fit of the data points yielded similar slopes in each group. Minute-by-minute mPAP and pulmonary capillary wedge pressure (PCWP) indexed to $Q'T$ in representative subjects of each group: c) controls; d) ILD+PVD; e) ILD–PVD.

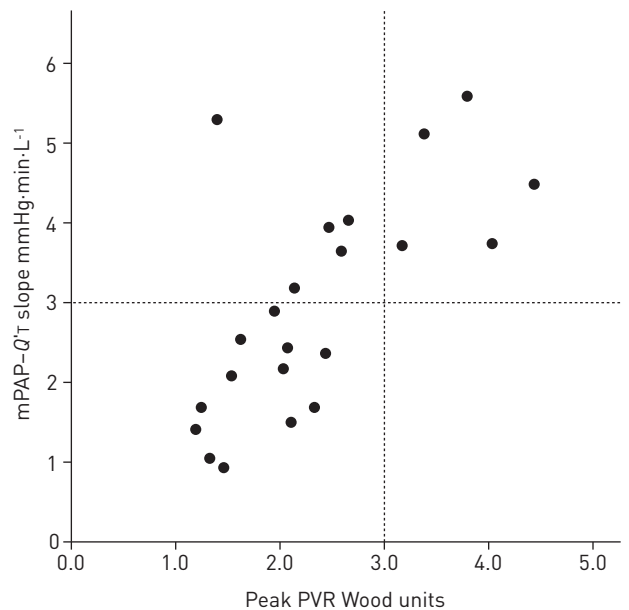


FIGURE 2 Relationship between peak pulmonary vascular resistance (PVR) and mean pulmonary arterial pressure (mPAP)–cardiac output ($Q'T$) slope.

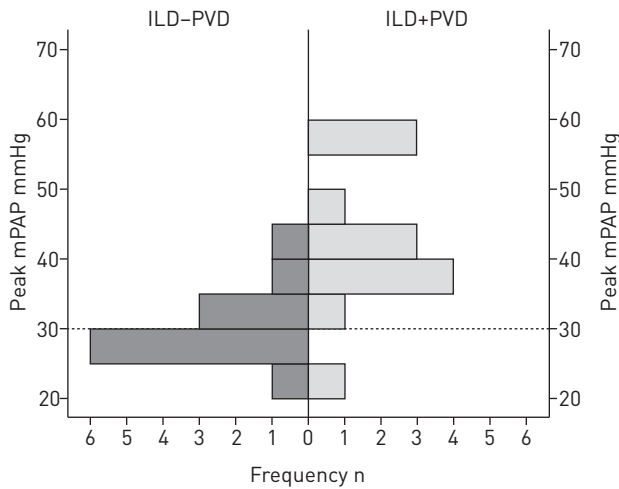


FIGURE 3 Mean pulmonary arterial pressure (mPAP) at peak exercise in interstitial lung disease (ILD) patients plus or minus abnormal pulmonary vascular response to exercise based on the mean pulmonary arterial pressure (mPAP)-cardiac output slope definition of exercise-induced pulmonary hypertension.

13±1 mL.kg⁻¹.min⁻¹ compared to 17±1 mL.kg⁻¹.min⁻¹ in the ILD-PVD group (p=0.012) (table 4). % predicted peak V[˙]O₂ was also lower in ILD+PVD patients and, even though this difference did not reach statistical significance, there was a negative correlation between mPAP-Q[˙]T slope and % predicted peak V[˙]O₂ (R=-0.444, p=0.023) in our study sample. Moreover, stroke volume, Q[˙]T and cardiac index at peak exercise were lower in ILD+PVD than in ILD-PVD, and it is interesting to note that the differences seen in V[˙]O₂ at the anaerobic threshold and peak exercise were proportional to the between-group differences in stroke volume, Q[˙]T and cardiac index (table 4). As expected, the ILD+PVD group had higher mPAP and PVR at peak exercise (p<0.05). The peak PCWP, however, did not differ between the ILD-PVD and ILD+PVD groups, and tended to remain normal in the patient population studied, with only three subjects exceeding 18 mmHg during exercise, which points to the predominantly pre-capillary mechanism of the hypertensive pulmonary vascular response to exercise in our sample (figs 1c-e and 4a-c).

ILD+PVD subjects showed increased dead space ventilation as evidenced by the higher dead space volume (V_D)/tidal volume (V_T) both at rest and peak exercise. Higher fractional dead space resulted in more

TABLE 3 Baseline characteristics of interstitial lung disease (ILD) patients plus or minus pulmonary vascular dysfunction (PVD)

	ILD+PVD	ILD-PVD	p-value
Patients n	15	12	
Age years	68±3	61±3	0.147
Female %	53	50	0.863
UIP n	9	8	0.653
BMI kg.m⁻²	27.5±1.3	26.1±1.3	0.456
Positive smoking history %	73.3	41.7	0.096
Smoking history pack-years	37±16	31±13	0.779
FVC % predicted	70±3	66±6	0.573
TLC % predicted	72±4	64±6	0.261
D_{LC_{ohb}} % predicted	40±3	46±6	0.392
P_{aO₂} mmHg	81±4	82±3	0.877
S_{O₂} %	96±1	96±1	0.380
GGO n	10	4	0.213
Reticulation n	12	10	0.912
Honeycombing n	8	6	0.978
Bronchiectasis n	10	10	0.476

Data are presented as mean±SEM, unless otherwise stated. UIP: usual interstitial pneumonia; BMI: body mass index; FVC: forced vital capacity; TLC: total lung capacity; D_{LC_{ohb}}: diffusing capacity of the lung for carbon monoxide corrected for haemoglobin; P_{aO₂}: arterial oxygen tension; S_{O₂}: oxygen saturation; GGO: ground-glass opacity.

TABLE 4 Cardiopulmonary exercise testing parameters in interstitial lung disease (ILD) patients plus or minus pulmonary vascular dysfunction (PVD)

	ILD+PVD [#]		ILD-PVD [¶]		p-value	
	Rest	Peak exercise	Rest	Peak exercise	Rest	Peak exercise
mPAP-Q'T slope mmHg·min·L ⁻¹		4.1±0.3		1.9±0.2		<0.001
Maximum workload W		75±9		94±12		0.223
V'O ₂ at AT %		30±2		38±2		0.025
Peak V'O ₂ mL·kg ⁻¹ ·min ⁻¹		13±1		17±1		0.012
Peak V'O ₂ % predicted		56±2		66±5		0.075
Q'T L·min ⁻¹	4.5±0.4	9.3±0.6	5.4±0.3	12.5±0.8	0.103	0.006
CI L·min ⁻¹ ·m ⁻²	2.4±0.2	4.9±0.3	2.9±0.2	6.6±0.3	0.082	0.001
SV mL	59±4	73±5	73±6	96±6	0.057	0.007
HR beats·min ⁻¹	78±4	131±7	75±3	132±5	0.575	0.912
O ₂ pulse		7.9±0.6		9.7±0.7		0.078
mPAP mmHg	23±1	43±3	17±1	31±2	0.001	0.001
mPCWP mmHg	7±1	13±3	4±1	9±1	0.015	0.252
PVR Wood units		3.2±0.4		1.8±0.1		0.001
V'E _{max} /MVV %		84±5		83±6		0.952
V _d /V _T %	41±2	39±2	34±2	30±2	0.035	0.008
V'E/V'CO ₂ at AT		45±2		38±1		0.015
PETCO ₂ at AT		31±1		35±1		0.085
SO ₂ %	96±1	89±2	96±1	89±2		0.820
PaO ₂ mmHg	81±4	62±5	82±3	63±5		0.906
PA-aO ₂ mmHg		61±8		50±5		0.287

Data are presented as mean±SEM, unless otherwise stated. mPAP: mean pulmonary arterial pressure; Q'T: cardiac output; V'O₂: oxygen consumption; AT: anaerobic threshold; CI: cardiac index; SV: stroke volume; HR: heart rate; mPCWP: mean pulmonary capillary wedge pressure; V'E_{max}: maximum minute ventilation at peak exercise; MVV: maximum voluntary ventilation; V_d: dead space volume; V_T: tidal volume; V'E: minute ventilation; V'CO₂: carbon dioxide production; PETCO₂: end-tidal carbon dioxide tension; SO₂: oxygen saturation; PaO₂: arterial oxygen tension; PA-aO₂: alveolar-arterial oxygen tension difference. #: n=15; ¶: n=12. Bold indicates statistical significance.

inefficient ventilation (*i.e.* higher minute ventilation (V'E)/carbon dioxide production (V'CO₂) at the anaerobic threshold) in ILD+PVD (fig. 4d and e). However, the ventilatory inefficiency and haemodynamic impairment did not impact on the magnitude of oxygen desaturation in ILD+PVD patients, as both ILD+PVD and ILD-PVD showed an average drop of 7 units in SO₂ from rest to peak exercise and reached a mean value of 89% at the end of the test.

Classification of Ei-PH by mPAP ≥30 or <30 mmHg does not result in between group differences in peak Q'T, peak cardiac index, V'E/V'CO₂ at the anaerobic threshold or peak V_d/V_T.

Discussion

In the present study, we found a 24% prevalence of pulmonary hypertension at rest (n=7), as well as an additional 28% (n=8) prevalence of abnormal pulmonary vascular response patterns during exercise based on a mPAP-Q'T slope ≥3 mmHg·min·L⁻¹ at peak exercise. By integrating pathophysiological responses to exercise into assessment of the pulmonary vasculature in ILD, we reclassified 28% of the patients by defining an Ei-PH phenotype. Despite similar demographic variables, PFT and radiographic results, the ILD+PVD group demonstrated impairment in several measurements associated with functional capacity and prognosis in pulmonary hypertension, including V'O₂ at the anaerobic threshold, peak V'O₂ and V'E/V'CO₂ at the anaerobic threshold. These findings suggest that PAP responses to exercise may help to refine resting phenotypes related to pulmonary vascular dysfunction in ILD.

Pulmonary hypertension in the setting of ILD

In a recent cohort of 212 subjects with ILD of mixed aetiologies (IPF, NSIP, sarcoidosis, hypersensitivity pneumonitis and CTD-related ILD), the prevalence of pulmonary hypertension was 14%, where pulmonary hypertension was defined by systolic pulmonary arterial pressure (SPAP) >40 mmHg and tricuspid annular plane systolic excursion <1.8 or a dilated right ventricle on a resting echocardiogram [18]. We believe that the difference in the prevalence of resting pulmonary hypertension between our

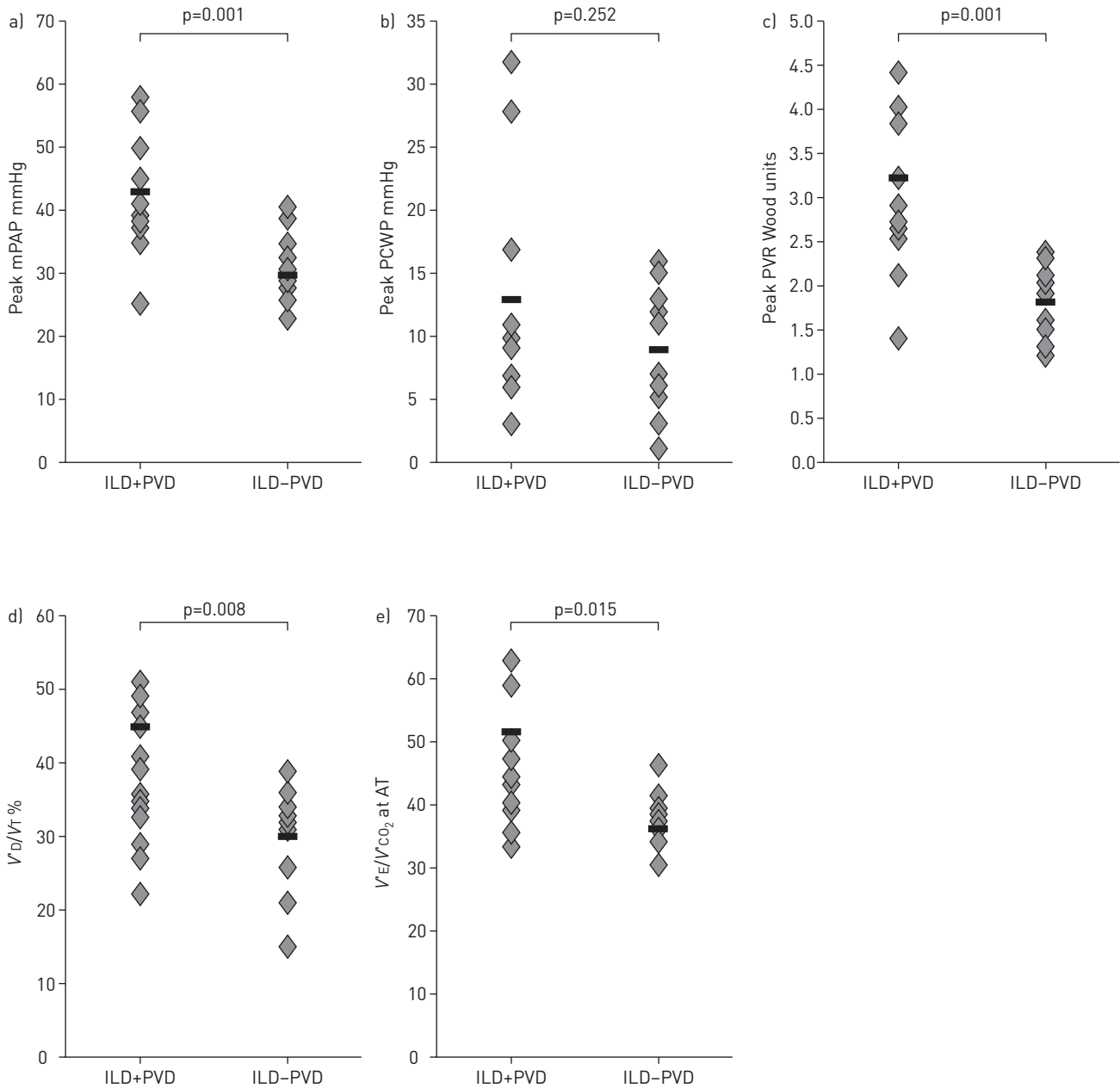


FIGURE 4 Exercise parameters in interstitial lung disease (ILD) plus or minus pulmonary vascular dysfunction (PVD). a) Mean pulmonary arterial pressure (mPAP). b) Pulmonary capillary wedge pressure (PCWP). c) Pulmonary vascular resistance (PVR). d) Dead space ventilation (V_d)/tidal volume (V_T). e) Minute ventilation (V_E)/carbon dioxide production (V_{CO_2}) at the anaerobic threshold (AT).

study and that of ANDERSEN *et al.* [18] could be at least partially attributed to a reduced sensitivity of the echocardiographic criteria for pulmonary hypertension diagnosis. However, the high prevalence of pulmonary hypertension in our study could have resulted from a potential selection bias, since the most symptomatic patients are the ones who tend to be sent for iCPET.

Previous studies have been able to show a relationship between reduced DLCO and increased prevalence of pulmonary hypertension in patients with ILD [10, 18–20]. In the present study, even though mean group DLCO was lower in ILD+PVD compared with ILD–PVD, this difference was not statistically significant. In line with previous reports [19, 21], the presence of pulmonary hypertension did not correlate with the severity of the restrictive ventilatory defect or the degree of desaturation on exertion. Age, sex, BMI and radiographic findings were also similar between ILD+PVD and ILD–PVD.

Finally, even though it has been previously suggested that patients with UIP are at higher risk of developing pulmonary hypertension [18], in our study, subjects with UIP were equally distributed between

the groups. In addition, because PVD is known to arise with CTD and sarcoidosis, we examined whether the seven subjects with CTD had a differential mPAP– \dot{Q}'_T response pattern. No differences were observed between ILD patients with and without CTD (3.1 ± 0.6 versus 2.8 ± 0.3 mmHg·L·min⁻¹, respectively; $p=0.62$)

CPET in ILD

A number of studies have demonstrated that ILD patients with overt pulmonary hypertension have poorer aerobic capacity and gas exchange than those without pulmonary hypertension. In the study by BOUTOU *et al.* [1], SPAP correlated with peak \dot{V}'_{O_2} , anaerobic threshold, peak oxygen pulse, end-tidal carbon dioxide tension (P_{ETCO_2}) at the anaerobic threshold and during peak exercise, as well as $\dot{V}'_E/\dot{V}'_{CO_2}$ at the anaerobic threshold, but only the latter was able to independently predict the presence of pulmonary hypertension. ARMSTRONG *et al.* [19] showed that ILD subjects with pulmonary hypertension ($n=25$) have higher $\dot{V}'_E/\dot{V}'_{CO_2}$ as well as lower expiratory carbon dioxide tension and P_{ETCO_2} , both at the anaerobic threshold and during peak exercise, compared with ILD patients without pulmonary vascular disease ($n=50$). The fact that between-group difference in V_D/V_T was not statistically significant was considered to be further evidence that the worse gas exchange pattern in ILD+PVD resulted mainly from perfusion abnormalities.

In our study, the presence of abnormal pulmonary vascular responses to exercise was associated with increased peak V_D/V_T and $\dot{V}'_E/\dot{V}'_{CO_2}$ at the anaerobic threshold, and translated into poorer aerobic capacity (earlier anaerobic threshold, lower peak \dot{V}'_{O_2} and maximum workload) in the ILD+PVD group compared to ILD–PVD group and controls. There was also a trend towards lower P_{ETCO_2} at anaerobic threshold in the ILD+PVD group. The trend towards lower P_{ETCO_2} in ILD+PVD and the fact that both groups had similar impairment in lung function speaks in favour of the differences in gas exchange being driven by the pulmonary vascular disease in the group ILD+PVD.

iCPET to define abnormal pulmonary vascular responses to exercise

Since $mPAP = PVR \times \dot{Q}'_T + mPCWP$, it is clear that the absolute value of mPAP at peak exercise depends not only on the ability to appropriately decrease PVR by mechanisms of pulmonary vascular recruitment and distensibility but also on the peak \dot{Q}'_T and the presence or absence of left heart disease. Therefore, establishing a rigid cut-off for the absolute value of mPAP ignores the impact of the increased \dot{Q}'_T and leads to a high percentage of false-positive results, one of the reasons why the definition of pulmonary hypertension based on $mPAP > 30$ mmHg during exercise was eventually removed from the pulmonary hypertension guidelines [22]. This observation is further confirmed in our study by the fact that 42% of the patients in the ILD–PVD group and 36% of control subjects would have been considered to have Ei-PH had we adopted this definition. These control patients reached mPAP values > 30 mmHg on account of increased \dot{Q}'_T and not because of abnormally high left atrial pressure (LAP) or PVR.

Ideally, assessment of exercise-induced increases in mPAP should be interpreted relative to increases in \dot{Q}'_T [2, 3, 23]. The ability of the pulmonary vasculature to distend in response to increased \dot{Q}'_T appears to be higher in women than in men and decreases with age [24], but the limits of normal of mPAP– \dot{Q}'_T relationships range from 0.5 to 3.0 mmHg·min·L⁻¹, as defined in heterogeneous populations. Therefore, a mPAP– \dot{Q}'_T slope ≥ 3 mmHg·min·L⁻¹ appears to be a reasonable cut-off for the diagnosis of Ei-PH [23]. Central pulmonary pressures have been traditionally measured at end-expiration on resting right heart catheterisation under the argument that at functional residual capacity, the impact of pleural pressure on the value of pulmonary pressures would be minimised [25]. However, it has been recently shown that large intrathoracic pressure swings during exercise may result in overestimation of central pulmonary pressures in COPD patients when measurements are taken at end-expiration [26] and potentially opposite effects in ILD; therefore, we used an average over the breathing cycle in this study. Another distinct advantage of looking at change in PAP versus change in flow is that it renders the zero level irrelevant. Similarly, differences in where PAP is measured in the respiratory cycle compared to an absolute value cut-point are no longer a concern.

The mPAP– \dot{Q}'_T slope integrates LAP and PVR throughout exercise, which fails to fall appropriately and remains elevated at peak exercise in patients with pulmonary vascular disease. For that reason, some authors have suggested using $PVR > 3$ Wood units at peak exercise as an indicator of Ei-PH [27]. It is interesting to note, however, that applying this definition in our study population would have led to five patients being categorised as having normal pulmonary vascular response to exercise. Therefore, this reinforces the notion that the use of a single haemodynamic variable, such as mPAP or PVR, may be inadequate to define a normal versus abnormal pulmonary vascular response to exercise [28]. Further long-term outcomes studies are needed to evaluate the prognostic significance and natural history of abnormal pulmonary vascular responses to exercise in ILD.

Limitations

Assessment of mPAP–Q'T slope with iCPET in identifying pulmonary vascular disease has some limitations. First, it depends on the patient exercising for long enough to generate a reliable slope (preferably four or more measurements of PAP and Q'T). Second, a mPAP–Q'T slope ≥ 3 mmHg·min·L⁻¹, by itself, does not differentiate patients with exercise-induced pre-capillary PH from those with a predominantly post-capillary pressure elevation. We therefore performed PCWP measurements to quantify pre- and post-capillary components of the mPAP–Q'T response to exercise. When analysing the pattern of pulmonary vascular response in the ILD+PVD group according to the criteria proposed by SAGGAR *et al.* [29], there were five patients with a pre-capillary pattern (peak PCWP ≤ 18 mmHg mPAP–Q'T and transpulmonary gradient (TPG) ≥ 15 mmHg at peak exercise), one with a passive post-capillary pattern (peak PCWP > 18 mmHg and TPG < 15 mmHg at peak exercise) and two who developed exercise out-of-proportion pulmonary hypertension (PCWP > 18 mmHg and TPG ≥ 15 mmHg at peak exercise). While this classification remains under debate, it provides insight on the mechanisms behind the development of abnormal pulmonary vascular responses to exercise in patients with ILD.

Other limitations relate to the small sample size and, consequently, the reduced study power, which increases the chance of incurring on a Type II error in comparisons of ILD+PVD and ILD–PVD groups. Second, our subjects had surprisingly mild restrictive ventilatory defect compared with patients in previous studies in ILD where differences in CPET parameters between patients with and without pulmonary hypertension were investigated. Therefore, it is possible that, had our subjects shown more severe pulmonary function impairment, non-invasive CPET parameters could have been able to predict the presence of pulmonary vascular disease. In patients with advanced ILD, iCPET may not be able to be performed due to disease severity and the need for supplemental oxygen. Therefore, advanced ILD, in which PVD is likely to be even more prevalent, was underrepresented in our study. Finally, we cannot affirm, based on our data, that the radiographic severity of the ILD is or is not associated with the presence of pulmonary hypertension or exercise PVD because of the lack of a standard method to quantify radiographic abnormalities led to a simple categorisation of these variables into present or absent.

Conclusions

In ILD, a mPAP–Q'T slope ≥ 3 mmHg·min·L⁻¹ is associated with lower peak V'O₂ and Q'T, as well as increased dead space ventilation and inefficient ventilation during exercise. While noninvasive parameters, such as PFTs and oxygen desaturation pattern, were unable to predict those with abnormal pulmonary vascular responses to exercise, use of iCPET to derive mPAP–Q'T slope may aid in unmasking physiologically significant early pulmonary vascular disease in ILD. Further studies are needed in order to identify potential subgroups of ILD patients who could benefit from invasive assessment of pulmonary haemodynamics during exercise as well as to determine whether treatment of ILD–PVD with PAH-directed therapies will improve functional capacity and prognosis in this patient population.

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