A haemodynamic study of pulmonary hypertension in chronic hypersensitivity pneumonitis

Rudolf K.F. Oliveira[1], Carlos A.C. Pereira[1], Roberta P. Ramos[1], Eloara V.M. Ferreira[1], Carolina M.S. Messina[1], Lilian T. Kuranishi[1], Andrea Gimenez[1], Orlando Campos[2], Célia M.C. Silva[2] and Jaquelina S. Ota-Arakaki[1]

Affiliations: [1]Division of Respiratory Diseases, Dept of Medicine, Federal University of São Paulo (UNIFESP), Brazil. [2]Division of Cardiology, Dept of Medicine, UNIFESP, Brazil.

Correspondence: Carlos A.C. Pereira, Division of Respiratory Diseases, Dept of Medicine, UNIFESP, Rua Botucatu 740, 3°andar, São Paulo, SP 04023-062, Brazil. E-mail: pereirac@uol.com.br

ABSTRACT Chronic hypersensitivity pneumonitis is a common fibrotic interstitial lung disease. The prevalence of pulmonary hypertension diagnosed by right heart catheterisation and its cardiopulmonary function findings in patients with chronic hypersensitivity pneumonitis are unknown.

Consecutive symptomatic patients with chronic hypersensitivity pneumonitis were prospectively evaluated. All patients were submitted to right heart catheterisation, pulmonary function testing, a 6-min walk test, echocardiography, blood gas determination and N-terminal pro-brain natriuretic peptide analyses. Nonhypoxaemic patients also underwent incremental cardiopulmonary exercise testing.

50 patients underwent right heart catheterisation; 25 (50%) of these had pulmonary hypertension and 22 (44%) had a pre-capillary haemodynamic pattern. The patients with pre-capillary pulmonary hypertension had lower forced vital capacity (mean ± SD 50 ± 17% *versus* 69 ± 22% predicted, $p<0.01$), carbon monoxide diffusing capacity (37 ± 12% *versus* 47 ± 14% predicted, $p<0.01$), arterial oxygen tension (median (interquartile range) 59.0 (47.8–69.3) *versus* 73.0 (62.2–78.5) mmHg, $p<0.01$) and saturation after the 6-min walk test (78 ± 8% *versus* 86 ± 7%, $p<0.01$). In pre-capillary pulmonary hypertension, oxygen uptake was also lower at the anaerobic threshold (41 ± 11% *versus* 50 ± 8% predicted, $p=0.04$) and at peak exercise (12.8 ± 1.6 *versus* 15.0 ± 2.5 $mL \cdot kg^{-1} \cdot min^{-1}$, $p=0.02$).

Pre-capillary pulmonary hypertension is common in symptomatic chronic hypersensitivity pneumonitis and is related to interstitial lung disease severity. Additionally, pulmonary hypertension is more prevalent in hypoxaemic patients with impaired lung function and exercise capacity.

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Introduction

Interstitial lung diseases (ILDs) are common causes of pre-capillary pulmonary hypertension (PH) and are classified into group III of the international aetiological classification of PH [1, 2]. Pre-capillary PH is defined by mean pulmonary arterial pressure (mPAP) $\geqslant$25 mmHg and pulmonary arterial wedge pressure (PAWP) $\leqslant$15 mmHg on right heart catheterisation (RHC) [2]. When present in patients with ILD, pre-capillary PH is associated with a significantly poorer prognosis [3–6].

The prevalence of PH varies widely among the different forms of ILD, depending on the diagnostic algorithm, the PH definition used and the severity of the underlying parenchymal impairment [7]. Haemodynamic data are mainly available from patients in lung transplantation programmes, in whom a high prevalence of PH is likely because of their ILD severity. In an outpatient setting, echocardiography is frequently used to identify PH. However, this method is commonly inaccurate and can lead to considerable misdiagnosis [8, 9], particularly among group III patients [10, 11].

Among patients with ILD, hypersensitivity pneumonitis (HP) is a common condition [12]. HP is a pulmonary disease caused by the inhalation of one of various antigens that trigger a diffuse inflammatory response in the small airways and pulmonary parenchyma in susceptible individuals [13]. The causative antigens include bacteria, fungi, protozoa, low-molecular-weight chemical compounds, and animal and insect proteins present in different environments [14]. The spectrum of clinical presentation may vary with the frequency and intensity of antigen exposure and the host immune response [13]. HP can develop into a chronic disease, leading to irreversible lung fibrosis, which characterises chronic HP.

With the exception of two case-series studies [15, 16] and one retrospective study based on echocardiographic diagnosis [17], the literature on PH in chronic HP is scarce. In particular, there are no published data concerning the prevalence of invasively diagnosed PH in patients with chronic HP. Therefore, we sought to determine the prevalence of PH at RHC in symptomatic patients with chronic HP, and to compare cardiopulmonary function findings between cases with and without PH.

Material and methods

Study design and patients

This prospective, cross-sectional study was performed between August 2011 and February 2013 at the ILD Outpatient Clinic of the Federal University of São Paulo, Brazil. We evaluated 1023 consecutive outpatients with ILD who came for a routine consultation during this period. All symptomatic patients from 18–80 years of age with chronic HP were recruited for a standardised PH assessment. Patients with comorbidities that could lead to PH were excluded (fig. 1). All patients provided written informed consent, and the study protocol was approved by the Institutional Medical Ethics Committee.

Symptomatic patients were defined as patients with a baseline dyspnoea index $<$9 points at the time of evaluation [18] and stable disease, characterised by the absence of exacerbations and no change in baseline therapy during the 30 days before study enrolment.

Patients with chronic HP were defined as patients with relevant exposure preceding respiratory symptoms [19] and fibrotic disease visible on high-resolution computed tomography (HRCT) scans of the lungs, without another identifiable cause of ILD, in addition to at least one of the following findings. 1) Improvement of symptoms upon the withdrawal of exposure or clinical/functional deterioration upon re-exposure [20]. 2) At least two of the following HRCT-consistent HP findings: bilateral ground-glass opacity, poorly defined centrilobular nodules and mosaic patterns [21]. 3) A classic histological triad characterised by chronic interstitial pneumonia with peribronchiolar accentuation, bronchiolitis and non-necrotising granulomas or giant cells [22]. 4) Other consistent histological findings, including bronchiolocentric interstitial pneumonia, nonspecific interstitial pneumonia (NSIP) or usual interstitial pneumonia (UIP)-like findings [22].

Measurements

All patients were submitted to RHC, pulmonary function testing (PFT), a 6-min walk test (6MWT), echocardiography, blood gas analysis and serum N-terminal pro-brain natriuretic peptide level determination. Nonhypoxaemic patients (arterial oxygen saturation (S_{aO_2}) $>$90% at rest) without musculoskeletal limitations were also submitted to incremental cardiopulmonary exercise testing (CPET).

RHC was performed using a Swan–Ganz catheter inserted percutaneously *via* the internal jugular vein. Cardiac output was measured using the thermodilution technique. Pre-capillary PH was defined as mPAP $\geqslant$25 mmHg and PAWP $\leqslant$15 mmHg at rest [2].

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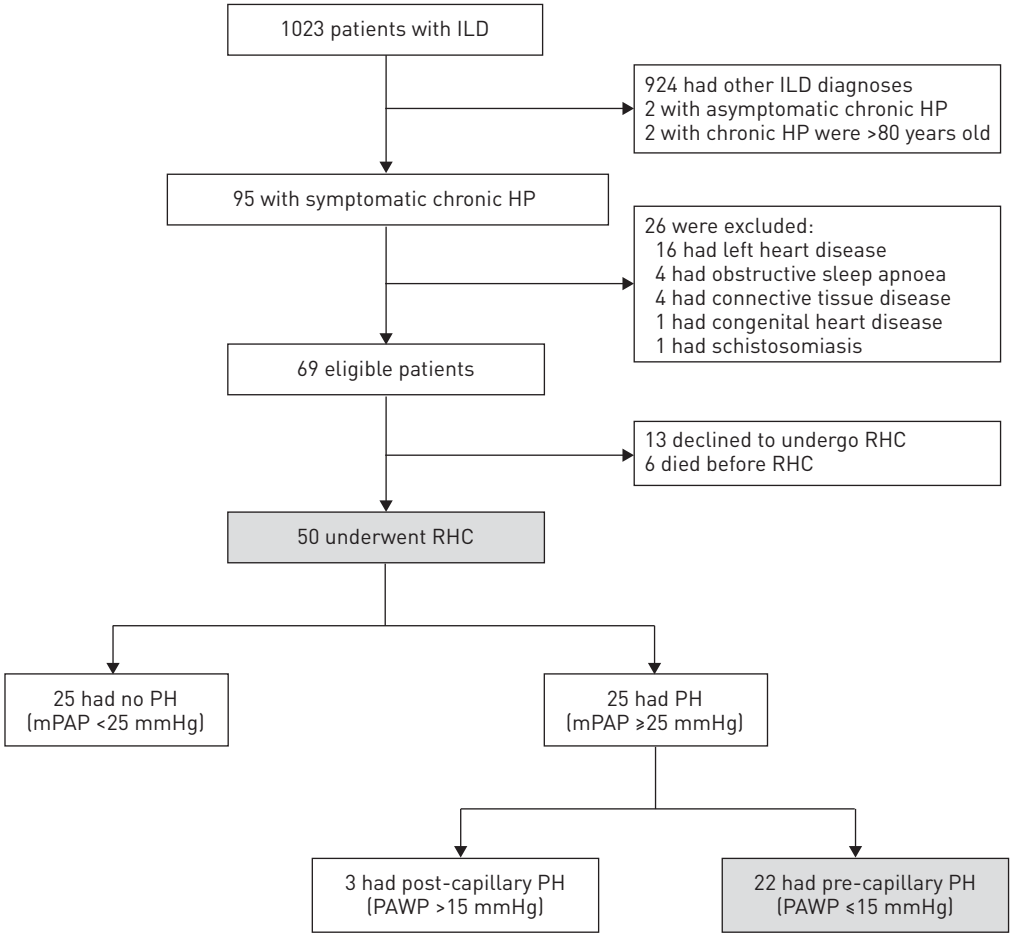

FIGURE 1 Study flow diagram. ILD: interstitial lung disease; HP: hypersensitivity pneumonitis; RHC: right heart catheterisation; PH: pulmonary hypertension; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure.

Echocardiography was performed according to the American Society of Echocardiography guidelines [23] using the modified Bernoulli equation and the right atrial pressure to estimate the systolic pulmonary arterial pressure (sPAP).

Patients on continuous home oxygen therapy underwent RHC, the 6MWT and echocardiography under their usual oxygen supplementation. RHC was performed 7–21 days after study enrolment and dyspnoea quantification. All examinations were performed 1–14 days after RHC under stable clinical conditions.

Detailed methods are provided in the online supplementary material.

Statistical analysis

Data are presented as mean $\pm$ SD or median (interquartile range), unless otherwise stated. The distribution of continuous variables was evaluated using Kolmogorov–Smirnov and Shapiro–Wilk tests. Comparisons between patients with and without PH were made using a t-test or Mann–Whitney test, where appropriate. Categorical variables were compared using Chi-squared and Fisher's exact tests. Between-group comparisons across different mPAP ranges were performed using ANOVA with Tukey's *post hoc* analysis. Correlations between variables were calculated using Pearson's correlation coefficient. Receiver operating characteristic (ROC) curves for forced vital capacity (FVC), diffusing capacity of the lung for carbon monoxide (D_{LCO}) and arterial oxygen tension (P_{aO_2}) at rest were derived while accounting for the presence or absence of PH. The thresholds for each ROC curve were obtained from the points with the greatest sum of sensitivity and specificity. Variables that were statistically significant in the univariate analysis ($p<0.05$) were transformed into categorical variables based on the ROC analysis and included in a logistic regression model to estimate the probability of PH. To avoid multicollinearity, only one of the highly correlated

variables ($r \geqslant 0.6$) was included in the model. $p<0.05$ was considered significant. The statistical analyses were performed using SPSS software, version 19 (IBM Company, Armonk, NY, USA).

Results

Prevalence of PH and overall cohort description

A total of 95 consecutive symptomatic patients with chronic HP were evaluated. 26 were excluded because of significant comorbidities, six died before RHC and 13 declined to participate. 50 patients underwent RHC; 25 (50%) had PH and 22 (44%) demonstrated a pre-capillary pattern (fig. 1). Most patients had mild PH, with mPAP $\leqslant$35 mmHg (fig. 2).

The main exposures were to moulds (n=24), birds (n=8) or both (n=17), and one patient had hot-tub lung. Lung biopsies were performed in 33 (66%) patients. Of these, 12 showed the classic histological triad, 16 showed bronchiolocentric interstitial pneumonia, three showed NSIP and two showed UIP-like findings. The diagnosis of 17 (34%) patients was based on clinical and radiological findings. In total, 32 patients were being treated with corticosteroids, with a median dose of 20 mg per day. The median disease duration from diagnosis was 23 months, with an interquartile range of 3–71 months. All patients were nonsmokers or ex-smokers and no patient had emphysema on HRCT. The patients' baseline characteristics are shown in table 1.

Comparisons of patients with and without pre-capillary PH at RHC

Patients with pre-capillary PH had significantly lower FVC, forced expiratory volume in the 1 s (FEV_1), D_{LCO}, P_{aO_2} and oxygen saturation values at the end of the 6MWT compared with patients without PH (table 1). In contrast, the absence of anti-inflammatory therapy, the histological pattern and the disease duration from diagnosis were not associated with PH (data not shown). Haemodynamic, pulmonary function and echocardiographic characteristics across different mPAP ranges, as assessed by RHC, are shown in table 2.

FVC and FEV_1 values could not be obtained in two patients. D_{LCO} values could not be obtained in nine patients; in seven of these patients, this was because their FVC was <1 L. Moreover, sPAP could not be estimated for 17 patients (eight from the pre-capillary PH group) because of a lack of a detectable tricuspid regurgitant jet.

There were significant inverse correlations between mPAP and P_{aO_2} ($r=0.57$, $p<0.01$), FVC ($r=0.44$, $p<0.01$) and D_{LCO} ($r=0.37$, $p=0.02$). ROC analysis (fig. 3) demonstrated an area under the curve of 0.78 for P_{aO_2} (95% CI 0.63–0.92, $p<0.01$), 0.73 for FVC (95% CI 0.57–0.89, $p=0.01$) and 0.69 for D_{LCO} (95% CI 0.52–0.86, $p=0.05$). Based on the ROC analysis, an FVC of 60%, P_{aO_2} of 70 mmHg and D_{LCO} of 50% were the optimal cut-offs in the presence of pre-capillary PH. In the multivariate analysis, these FVC (hazard ratio (HR) 4.18, 95% CI 1.10–17.54; $p=0.04$) and P_{aO_2} (HR 7.04, 95% CI 1.66–30.30; $p<0.01$) cut-offs were shown to be independent predictors of pre-capillary PH.

Cardiopulmonary exercise testing

In total, 33 nonhypoxaemic patients (S_{aO_2} >90%) were enrolled for CPET. Four patients could not undergo CPET because of musculoskeletal limitations, so 29 patients were evaluated. These patients had less severe ILD than did the patients who did not undergo CPET, as indicated by higher FVC (mean$\pm$SD 65$\pm$21%

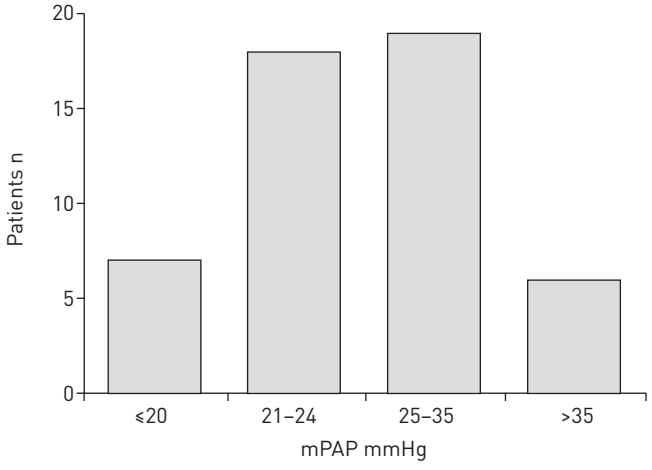

FIGURE 2 Patients' frequency distribution across mean pulmonary arterial pressure (mPAP) ranges. Patients with a post-capillary haemodynamic pattern had an mPAP of 25–35 mmHg (n=2) or >35 mmHg (n=1).

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TABLE 1 Baseline characteristics of patients with symptomatic chronic hypersensitivity pneumonitis

	Total	Non-PH	Pre-capillary PH	p-value[#]
Patients	50	25	22	
Females	39 (78)	21 (84)	15 (68)	0.18
Age years	61±11	61±12	60±11	0.80
Body mass index kg·m^{-2}	28±5	28±5	28±6	0.59
Baseline dyspnoea index	6±2	6±2	5±2	0.07
NYHA functional class II/III/IV	18/27/2	10/15/0	8/12/2	0.31
Pulmonary function testing[¶]				
FVC % predicted	59±22	69±22	50±17	<0.01
FEV1 % predicted	65±24	75±23	54±17	<0.01
*D*LCO % predicted	44±15	47±14	37±12	0.03
FVC/*D*LCO % predicted	1.5 (1.4–1.7)	1.5 (1.3–1.7)	1.6 (1.4–1.8)	0.68
Blood gas analysis				
P_{aO_2} at rest mmHg	68.5 (54.5–75.0)	73.0 (62.2–78.5)	59.0 (47.8–69.3)	<0.01
P_{aCO_2} at rest mmHg	37.9±4.7	37.5±3.8	38.1±5.4	0.68
6-min walk test				
Distance m	338±105	365±99	321±108	0.15
Final S_{pO_2} %	82±9	86±7	78±8	<0.01
Echocardiography[+]				
TRV m·s^{-1}	2.8±0.6	2.6±0.3	3.1±0.8	0.08
sPAP mmHg	35 (30–40)	34 (30–36)	38 (29–49)	0.31
NT-proBNP pg·mL^{-1}	78.7 (44.9–143.1)	78.7 (49.7–128.4)	68.8 (34.8–145.8)	0.71
Right heart catheterisation				
RAP mmHg	8±4	7±3	7±4	0.72
mPAP mmHg	25 (21–30)	21 (20–23)	30 (27–35)	<0.01
PAWP mmHg	10±4	10±3	10±4	0.74
TPG mmHg	15 (11–19)	11 (10–14)	19 (17–25)	<0.01
PVR Wood units	3.2 (2.3–3.8)	2.3 (1.9–2.8)	4.0 (3.5–4.9)	<0.01
Cardiac index L·min^{-1}·m^{-2}	2.8 (2.4–3.0)	2.8 (2.4–3.2)	2.7 (2.4–2.9)	0.59

Data are presented as n, n (%), mean±SD or median (interquartile range), unless otherwise stated. PH: pulmonary hypertension; NYHA: New York Heart Association; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 s; *D*LCO: diffusing capacity of the lung for carbon monoxide; P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; TRV: tricuspid regurgitant jet velocity; sPAP: systolic pulmonary arterial pressure; NT-proBNP: N-terminal pro-brain natriuretic peptide; RAP: right atrial pressure; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; TPG: transpulmonary gradient; PVR: pulmonary vascular resistance. [#]: comparing pre-capillary PH patients with non-PH patients. [¶]: FVC and FEV1 values could not be obtained in two patients (one from each group); *D*LCO values could not be obtained in nine patients (six from the pre-capillary PH group). [+]: 17 patients had no detectable tricuspid regurgitant jet (eight from the pre-capillary PH group).

versus 50±20% predicted, p=0.03) and P_{aO_2} (72.8±7.5 *versus* 51.9±10.6 mmHg, p<0.01) values. None of the patients with mPAP >35 mmHg underwent CPET because of low S_{aO_2} at rest. Oxygen uptake (V'_{O_2}) at peak exercise and at the anaerobic threshold (AT) was significantly lower in the PH group (table 3). However, no significant differences were found for the other CPET parameters. Among the 29 patients who underwent CPET, the patients with pre-capillary PH (n=10) had lower values than did the patients without PH (n=19) for FVC (55±10% *versus* 70±23% predicted, p=0.02), *D*LCO (37±10% *versus* 49±15% predicted, p=0.03) and P_{aO_2} (68.5±5.8 *versus* 75.1±7.5 mmHg, p=0.02).

Echocardiography

Nearly all patients for whom echocardiography indicated sPAP ⩾40 mmHg had pre-capillary PH, as confirmed by RHC (fig. S1). However, patients with pre-capillary PH had the greatest differences between the sPAP values estimated by echocardiography and values measured by RHC (fig. 4). In this patient subgroup, echocardiography underestimated the value provided by invasive measurement by up to 23 mmHg and overestimated by up to 38 mmHg. In the group without PH, most patients presented a difference of ±10 mmHg between the two measurements.

PH risk assessment score

We found that at least two of the following findings were present in 76% of patients with chronic HP and pre-capillary PH: FVC ⩽60% predicted, P_{aO_2} ⩽70 mmHg and sPAP ⩾40 mmHg on echocardiography. There were no cases of PH among patients with none of these findings. Based on this observation, we

TABLE 2 Haemodynamic, pulmonary functional and echocardiographic characteristics across different mean pulmonary arterial pressure (mPAP) ranges

	mPAP ⩽20 mmHg	mPAP 21–24 mmHg	mPAP 25–35 mmHg	mPAP >35 mmHg	p-value#
Patients n	7	18	17	5	
PVR Wood units	2.2±0.7	2.5±0.5	4.2±1.1*,§	6.0±1.4*,§,ƒ	<0.01
Cardiac index L·min^{-1}·m^{-2}	2.6±0.5	2.9±0.5	2.7±0.3	2.7±0.2	0.51
FVC¶ % predicted	65±16	70±24	52±17§	38±14§	0.01
***P*aO_2 at rest mmHg**	75.9±8.3	68.8±11.9	61.6±11.2*	45.4±9.4*,§,ƒ	<0.01
6MWT final *S*pO_2 %	87±6	85±8	81±7	69±5*,§,ƒ	<0.01
TRV+ m·s^{-1}	2.5±0.3	2.7±0.3	2.7±0.5	3.8±0.8*,§,ƒ	<0.01
sPAP on echocardiography+ mmHg	33±3	33±6	34±11	38±16*,§,ƒ	<0.01

Data are presented as mean±SD unless otherwise stated. PVR: pulmonary vascular resistance; FVC: forced vital capacity; *P*aO_2: arterial oxygen tension; 6MWT: 6-min walk test; *S*pO_2: arterial oxygen saturation measured by pulse oximetry; TRV: tricuspid regurgitant jet velocity; sPAP: systolic pulmonary arterial pressure. #: intergroup comparison by ANOVA; ¶: could not be obtained in two patients (one had an mPAP of 21–24 mmHg and one had mPAP >35 mmHg); +: 17 patients had no detectable tricuspid regurgitant jet (three had mPAP ⩽20 mmHg, six had an mPAP of 21–24 mmHg, seven had an mPAP of 25–35 mmHg and one had mPAP >35 mmHg). *: p<0.05 compared with mPAP ⩽20 mmHg; §: p<0.05 compared with an mPAP of 21–24 mmHg; ƒ: p<0.05 compared with an mPAP of 25–35 mmHg.

developed a risk assessment score for PH. One point was given for each of the following findings: sPAP ⩾40 mmHg on echocardiography, FVC ⩽60% predicted and *P*aO_2 ⩽70 mmHg. The absence of a detectable tricuspid regurgitant jet was assigned zero points. The distribution of patients with and without PH according to risk assessment scores is shown in table 4.

Discussion

In this study, we found that pre-capillary PH is common in symptomatic patients with chronic HP, with a prevalence of 44%, as assessed by RHC. Additionally, we found that pre-capillary PH is related to ILD severity, as indicated by its greater frequency in hypoxaemic patients with reduced lung function and exercise capacity.

Data on PH in chronic HP are scarce. Our study is the first to systematically evaluate PH using RHC in a large cohort of patients with chronic HP. Two case-series studies have also been reported [15, 16]. LUPI-HERRERA *et al.* [15] described 10 patients with invasively diagnosed HP whose mPAP was 22±2 mmHg. All of these patients were hypoxaemic. However, the study was conducted 2240 m above sea level, which raises doubts about whether the PH and hypoxaemia were produced by ILD or high altitude [15]. In the second study, COSTABEL *et al.* [16] reported nine cases of invasively studied HP, seven of which had mild PH (mPAP 20±7 mmHg).

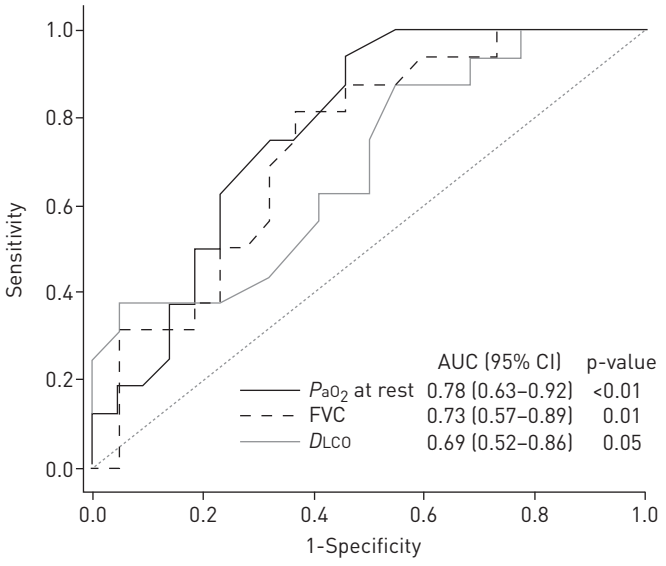

FIGURE 3 Receiver operating characteristic curves for arterial oxygen tension (*P*aO_2) at rest, forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (*D*LCO) for the diagnosis of pre-capillary pulmonary hypertension. AUC: area under the curve.

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TABLE 3 Cardiopulmonary exercise testing in nonhypoxaemic patients with symptomatic chronic hypersensitivity pneumonitis[#]

	Non-PH	Pre-capillary PH	p-value
Patients n	19	10	
Peak WR W	49 (38–55)	45 (30–64)	0.70
Metabolic responses			
Peak V'_{O_2} % predicted	80±13	68±20	0.06
Peak V'_{O_2} mL·kg^{-1}·min^{-1}	15.0±2.5	12.8±1.6	0.02
V'_{O_2} at AT[¶] % $V'_{O_{2max}}$ predicted	50±8	41±11	0.04
$\Delta V'_{O_2}/\Delta$WR mL·min^{-1}·W^{-1}	8.8±1.6	9.9±2.9	0.24
Cardiovascular responses			
Peak heart rate beats·min^{-1}	124±22	121±14	0.72
Peak heart rate % predicted	77±15	76±5	0.75
Δheart rate/$\Delta V'_{O_2}$ beats·L^{-1}	69±27	62±24	0.27
Peak V'_{O_2}/heart rate % predicted	97 (85–117)	99 (62–110)	0.51
Peak SBP mmHg	170 (160–170)	155 (150–163)	0.05
Ventilatory responses			
V'_E/MVV	0.61 (0.51–0.92)	0.66 (0.60–0.86)	0.65
$\Delta V'_E/\Delta V'_{CO_2}$	40±5	42±6	0.78
V'_E/V'_{CO_2} at AT[¶]	37±7	38±7	0.67
Peak P_{ETCO_2} mmHg	35±4	36±5	0.61
P_{ETCO_2} at AT[¶] mmHg	37±4	38±5	0.79
Peak S_{pO_2} %	93 (86–95)	87 (84–90)	0.06
Subjective responses			
Peak dyspnoea Borg score	5±2	6±2	0.51
Peak leg effort Borg score	6±2	5±3	0.31

Data are presented as median (interquartile range) or mean±SD, unless otherwise stated. PH: pulmonary hypertension; WR: work rate; V'_{O_2}: oxygen uptake; AT: anaerobic threshold; Δ: change in; SBP; systolic blood pressure; V'_E: minute ventilation; MVV: maximal voluntary ventilation; V'_{CO_2}: carbon dioxide production; P_{ETCO_2}: end-tidal carbon dioxide tension; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry. [#]: n=29; [¶]: we were not able to determine the AT in eight patients (three from the pre-capillary PH group).

One recent retrospective study based on echocardiographic diagnosis (sPAP ⩾50 mmHg) described 73 patients with chronic HP with a 19% prevalence of PH [17], which is well below our finding of 44%. The noninvasive diagnostic approach and retrospective design of the prior study may explain the lower prevalence of PH compared with our results. Despite this difference in the reported prevalence of PH, KOSCHEL *et al.* [17] found that P_{aO_2} and FVC correlated with PH, although only P_{aO_2} was significantly decreased among patients with sPAP ⩾50 mmHg.

Echocardiography is known to have certain limitations in PH diagnosis [8, 9], especially in parenchymal lung diseases [10, 11]. If our study were based on only echocardiographic findings, we would have missed

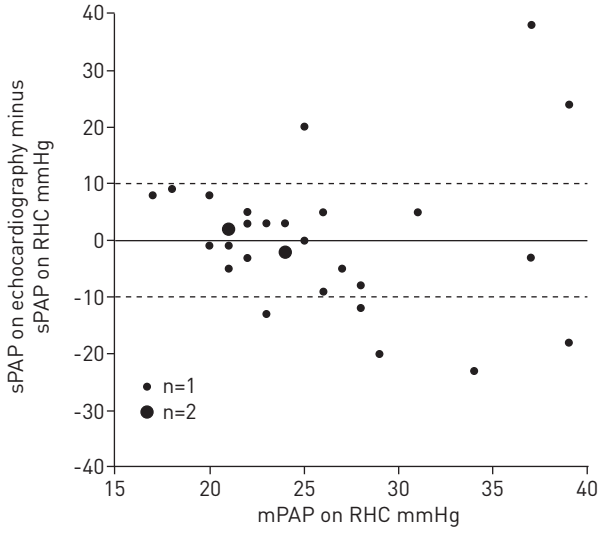

FIGURE 4 Patients' distribution according to the difference between the systolic pulmonary arterial pressure (sPAP) estimated by echocardiography and the sPAP measured by right heart catheterisation (RHC) in relation to the mean pulmonary artery pressure (mPAP). 17 patients had no detectable tricuspid regurgitant jet.

TABLE 4 Distribution of symptomatic patients with chronic hypersensitivity pneumonitis with and without pulmonary hypertension according to the risk assessment score for pulmonary hypertension

Points#	mPAP at right heart catheterisation		Total
	<25 mmHg	⩾25 mmHg	
0	11	0	11
1	9	8	17
⩾2	4	13	17
Total	24	21	45

Data are presented as n. Chi-squared 17.00, $p<0.01$ by Fisher's exact test. mPAP: mean pulmonary arterial pressure. #: one point was given for each of the following findings: systolic pulmonary arterial pressure ⩾40 mmHg on echocardiography, forced vital capacity ⩽60% predicted and arterial oxygen tension ⩽70 mmHg at rest. The absence of a detectable tricuspid regurgitant jet by echocardiography was assigned zero points. Forced vital capacity values could not be obtained in two patients.

17 (34%) patients because of the absence of tricuspid regurgitation and would have failed to diagnose three cases of post-capillary PH. Additionally, if the selection criteria for RHC were based on a tricuspid regurgitant jet velocity (TRV) ⩾2.5 $m \cdot s^{-1}$, 26 patients would have been deprived of invasive haemodynamic evaluation, including 11 patients with pre-capillary PH and two patients with post-capillary PH. Therefore, reliance solely on a PH suspicion threshold ⩾2.5 $m \cdot s^{-1}$ for TRV on echocardiography would have missed 50% of the patients with pre-capillary PH.

Among patients with ILD, PH has been more frequently studied in idiopathic pulmonary fibrosis (IPF) and sarcoidosis [24]. The prevalence of PH among patients with IPF ranges from 8% to 84% [3, 25, 26], with higher prevalence among patients in lung transplant programmes [26]. However, PH is also common among nonhypoxaemic patients with mild-to-moderate functional impairment, with a nearly 15% prevalence as assessed by RHC [5]. This finding suggests that PH may be related to remodelling of the pulmonary vascular bed, independent of the severity of lung fibrosis or hypoxaemia [27]. In sarcoidosis, the prevalence of PH ranges from 6% to 74% [4, 28, 29] and PH can occur even in the absence of ILD [30]. However, PH is more frequent in patients with advanced parenchymal fibrosis [31], in which the predominant mechanisms of PH are hypoxaemia, parenchymal destruction and distortion of the lung microcirculation [32].

In contrast to IPF and similar to advanced stages of sarcoidosis, our findings suggest that in chronic HP, PH severity is proportional to ILD severity. PH was more frequent among patients with lower lung function and hypoxaemia. The latter is a well-known cause of PH induction *via* pulmonary vasoconstriction and remodelling.

Beyond disease severity, the inflammatory response related to chronic HP [14] could represent another possible contributor to PH development. Inflammatory mechanisms play important roles in the pathogenesis of pulmonary arterial hypertension [33] and are, for example, assumed to contribute to altered pulmonary circulation in chronic obstructive pulmonary disease [34]. Recent studies suggest that allergen-induced lung inflammation is accompanied by significant pulmonary vascular hyperresponsiveness and pulmonary arterial muscularisation, which may contribute to vascular remodelling and PH development [35, 36]. However, in our study, anti-inflammatory therapy was not associated with an absence of PH.

PH has a significant impact on exercise capacity in patients with ILD [37]. CPET has already been shown to be effective in identifying PH in patients with IPF because of the remarkable ventilatory inefficiency present when these patients develop PH [38]. In our study, a dynamic exercise evaluation using CPET showed reduced exercise capacity in pre-capillary PH patients, as demonstrated by lower V'_{O_2} at peak exercise and at the AT than in patients without PH. We did not find any other ventilatory or metabolic PH predictors. Possible explanations for this finding include that few patients were enrolled for CPET (n=29) and that CPET was performed only in nonhypoxaemic patients, *i.e.* those with less severe ILD. Another possible explanation for our CPET findings is the likely different pathophysiologies of PH in IPF and PH in chronic HP. Patients with IPF who develop PH may have pulmonary vasculopathy independent of ILD severity, which could justify the presence of ventilatory inefficiency on CPET.

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Although the patients who underwent CPET had less severe pulmonary function impairment, the patients with pre-capillary PH (n=10) had lower FVC and P_{aO_2} values than did the patients without PH who also underwent CPET (n=19), which reinforces the observation that pre-capillary PH is related to the severity of chronic HP.

To help to identify patients with chronic HP and pre-capillary PH, we developed a risk assessment score for PH using variables routinely obtained in outpatient settings (FVC, P_{aO_2} and sPAP on echocardiography). We found that scores $\geqslant 2$ points were suggestive of PH and a score of zero indicated the absence of PH. This risk assessment score could help physicians to stratify patients to identify those who need invasive investigation by RHC. However, this score was derived from a small population, so further validation is needed in a larger population with chronic HP before clinical use.

The presence of PH represents a known marker for a poor prognosis in ILD [1]. In chronic HP, the prognosis is associated with the presence of fibrosis (especially a UIP-like pattern) but is not correlated with FVC [39, 40]. Another predictor of survival is oxygen desaturation during exercise [12]. Furthermore, PH seems to represent an adverse prognostic marker in patients with chronic HP [17]. Although the present study was not designed to evaluate survival, we intend to follow this patient cohort over an extended period to evaluate the utility of the presence of PH as a predictor of survival.

This study had certain limitations. It was a single-centre study, with potential bias in the patient selection process. Another potential limitation is that we evaluated only patients with HRCT-confirmed fibrosis. This population could have more severe ILD, which could affect the prevalence of PH. However, patients with chronic HP and fibrosis are of greater interest regarding PH development compared with acute/subacute HP cases that have potentially reversible disease. Additionally, we did not quantify fibrosis using HRCT. However, the PFT parameters are assumed to be physiological correlates of the extent of lung fibrosis and, therefore, could be sufficient to determine ILD severity.

Another limitation of our study is the number of patients in whom D_{LCO} values could not be obtained (n=9), seven because their FVC was <1 L. This may have influenced the correlation between D_{LCO} and mPAP, as HP was more frequent in patients with reduced FVC.

We did not evaluate serum precipitins because this test is not available in our country and we did not perform bronchoalveolar lavage in many patients. However, there are no standardised diagnostic criteria for chronic HP that require these two examinations. HP diagnosis depends on a high level of clinical suspicion, recognition of relevant antigen exposure preceding the onset of respiratory symptoms (which represents a key component of HP diagnosis), and the association of clinical, radiological, laboratory and pathological findings [14, 19], without another identifiable cause of ILD.

In conclusion, our study demonstrated that pre-capillary PH in symptomatic patients with chronic HP is common. The presence of PH is related to ILD severity, as indicated by the observation that PH was more prevalent in hypoxaemic patients with greater impairment in lung function and lower exercise capacity.

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