Prevalence and Characteristics of Moderate to Severe Pulmonary Hypertension in Systemic Sclerosis with and without Interstitial Lung Disease

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ABSTRACT. ***Objective.*** To determine the prevalence and characteristics of moderate to severe pulmonary hypertension (PH) in patients with systemic sclerosis (SSc) with and without interstitial lung disease (ILD).

Methods. We retrospectively studied clinical and functional characteristics of 197 consecutive patients with SSc who had undergone a screening echocardiography to detect PH.

Results. Moderate to severe PH was suspected in 36 patients (18.3%) and confirmed in 32 who underwent right heart catheterization. The prevalence of PH did not differ between patients with limited and patients with diffuse cutaneous SSc. PH was detected in 12/67 (17.9%) patients without ILD vs 24/110 (21.8%) patients with ILD (p not significant). In patients with ILD, a lower PaO_2 appeared as the unique independent factor significantly associated with PH, regardless of the extent of fibrosis. In 3 patients out of 9 (33.3%) with ILD and significantly restrictive disease, PH was out of proportion to the degree of fibrosis. In patients with no ILD, a higher grade of dyspnea appeared as the unique independent factor associated with PH. In patients with no ILD, altered DLCO was the sole indicator of the pulmonary function tests associated with PH (best cutoff value 72%). DLCO correlated with systolic pulmonary arterial pressure only in patients with no ILD.

Conclusion. Prevalence of moderate to severe PH was similar in SSc patients with and those without ILD. In patients with ILD, a lower PaO_2 was the unique independent indicator associated with PH. In some patients with severe ILD, PH was out of proportion to the degree of fibrosis. A linear correlation between DLCO and systolic pulmonary arterial pressure was observed only in patients without ILD. All these indicators should assist identification of patients with or without ILD requiring diagnostic procedures for PH before annual screening. (First Release April 15 2007; J Rheumatol 2007;34:1005–11)

Key Indexing Terms:
ECHOCARDIOGRAPHY INTERSTITIAL LUNG DISEASE PaO_2
PULMONARY HYPERTENSION SYSTEMIC SCLEROSIS

Pulmonary hypertension (PH) is the major cause of morbidity and mortality in systemic sclerosis (SSc)[1-5]. Following the most recent classification[6], PH in SSc (SSc-PH) is primarily an isolated precapillary pulmonary arterial hypertension (PAH) or is associated with interstitial lung disease (ILD), especially in diffuse cutaneous SSc[7,8]. The exact prevalence of SSc-PH is estimated at between 7% and 15%[9-11]. The severe outlook for patients with SSc-PH led authorities to recommend repeated noninvasive testing to screen patients every year[12]. However, moderate to severe PH can develop rapidly between 2 screening evaluations. Moreover, patients with ILD are often evaluated every 6 months by clinical and pulmonary function testing (PFT). Therefore physicians caring for patients with SSc must be able to recognize clinical and functional presentations suggestive of PH in order to identify patients who require rapid referral and diagnostic procedures for PH before the annual screening[13].

The utility of carbon monoxide diffusing capacity (DLCO) used as a marker of SSc-PH is still a matter of debate[14-16]. Mukerjee, *et al* found only a weak correlation between DLCO and mean pulmonary arterial pressure (PAP)[9,17]. Moreover, the exact prevalence of PH in SSc patients with ILD as well as the effect of ILD and its severity in the predicting value of

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DLCO or other measures of PFT to detect PH are not well established[16], since severe ILD (as defined by forced vital capacity < 60% of predicted) was an exclusion criterion in one of the largest studies[11], and was not extensively described in another report[17].

Our aim was to determine the prevalence and the characteristics of moderate to severe PH in SSc patients with ILD, according to its severity, and in those without ILD.

MATERIALS AND METHODS

We retrospectively reviewed the medical files of 197 consecutive patients with SSc who had undergone baseline screening echocardiography to detect PH. Echocardiography was part of a systematic screening of PH whatever the clinical presentation, according to the international guidelines[12]. There was no followup assessment.

Clinical assessment included data on age at diagnosis of SSc, age at onset of Raynaud's phenomenon, sex, dyspnea graded according to the New York Heart Association (NYHA) (clearly apparent in 164 patients) at the time of echocardiography, and cutaneous extent graded according to the LeRoy classification system, i.e., limited cutaneous (lcSSc) or diffuse cutaneous (dcSSc)[18].

All patients had undergone screening echocardiography (Vingmed, System Five, GE Healthcare, USA) for the initial disease evaluation. Peak velocity of tricuspid regurgitation was assessed in continuous wave mode at the apex and tricuspid gradient was calculated using the simplified Bernoulli equation. Using Mukerjee's recent publication[9], we chose a tricuspid gradient of 40 mm Hg (i.e., an estimated systolic PAP ≥ 40 + 10 = 50 mm Hg) to suspect moderate to severe PH and to suggest right heart catheterization to confirm PH. PH was defined as mean PAP ≥ 25 mm Hg at rest. Right heart catheterization was not proposed in patients with tricuspid gradient < 40 mm Hg.

One hundred eighty-two patients had undergone PFT within 3 months before or after echocardiography, following standard protocols. Forced expiratory volume in 1 second (FEV_1), forced vital capacity (VC), total lung capacity (TLC), DLCO, and DLCO adjusted for alveolar volume (KCO) were measured. The predictive values for each subject, based on sex, age, and height, were obtained from standard tables[19]. Data were expressed as percentages of predicted values (e.g., %DLCO). Measurement of arterial blood gases was performed in 148 patients on air at rest to determine PaO_2 either by radial puncture or by arterial capillary samples taken from the earlobe in patients with severe Raynaud's phenomenon, as recently recommended[20]. No ischemia was observed in our patients due to radial puncture. Arterial blood gases were not analyzed in 23 patients because of technical failures (n = 13) or patient's refusal (n = 10), whereas in 11 other patients, blood gases were measured but results were not available for analysis. One hundred seventy-seven patients had undergone high-resolution computed tomography (HRCT) of the chest within 3 months before or after echocardiography to examine for ILD associated with scleroderma. We did not score the extent of ILD on HRCT. All patients with HRCT had PFT. To compensate for the lack of assessment of extent of ILD on HRCT, we studied 2 groups separately, i.e., patients with ILD and significant restrictive disease (%VC < 70%) and patients with ILD without significant restrictive disease (%VC ≥ 70%).

Antinuclear antibodies (ANA) were investigated by indirect immunofluorescence on HEp-2 cells. Fluorescence was considered positive at dilution ≥ 1:80. At the same time, anticentromere antibodies (ACA) were characterized by a pattern of discrete dots in cells lined up on the metaphase plate in dividing interphase cells. Antitopoisomerase-1 autoantibodies were detected by counter-immunoelectrophoresis using rabbit thymus extract as antigenic substrate.

Statistical analysis. Statistical analysis was performed using Statistica software (StatSoft, Tulsa, OK, USA). P values < 0.05 were considered statistically significant. Results were expressed as frequencies and percentages for binary and categorical variables and as mean ± standard deviation (SD) for continuous data. Comparative analyses were performed using chi-square or Fisher exact tests for categorical data. Unpaired bilateral Student's t test was used for continuous data when the number of subjects in each group was greater than 30 and by unpaired Wilcoxon rank-sum test otherwise. The parameters were subjected to post-hoc multivariate analysis to assess their potential association with PH.

Relationship between systolic PAP measured by echocardiography and %DLCO was established using Pearson's correlation coefficient.

Receiver-operator characteristic (ROC) curve analysis[21] was performed to find the optimal threshold of significant parameters for identification of PH.

RESULTS

SSc patient population. Among the 197 patients, 162 (82.2%) were female. The mean age at diagnosis of SSc was 48.0 ± 14.0 years. Mean disease duration from the onset of Raynaud's phenomenon (the first symptom attributable to SSc in all cases) to time of echocardiography was 8.4 ± 10.1 years for patients with lcSSc and 3.9 ± 7.6 years for patients with dcSSc. Eighty-six patients (43.6%) had lcSSc and 111 (56.4%) dcSSc. Among the 177 SSc patients who had undergone HRCT, 110 (62.1%) had ILD. Among them, 37/110 (33.6%) patients had significant reduction of lung volumes, i.e., %VC < 70%. ANA status was available for 188 patients: all except 16 had positive ANA. ACA were detected in 70 patients (37.2%), and 11 patients (5.8%) had ANA of nucleolar pattern. Anti-topoisomerase 1 antibodies were detected in 59 patients (31.4%), and other anti-soluble nuclear antigen antibodies (anti-RNP and anti-SSA antibodies) were detected in 32 patients (17.0%).

Prevalence of pulmonary hypertension. A tricuspid gradient ≥ 40 mm Hg was found in 36/197 (18.3%) patients. According to a reference classification[22], 12 patients had moderate PH (systolic PAP between 46 and 55 mm Hg) and 24 had severe PH (systolic PAP > 55 mm Hg). Among these 36 patients, 32 (88.9%) underwent right heart catheterization, which confirmed the diagnosis of precapillary PH in all of them (mean PAP 41.5 ± 10.4 mm Hg, mean cardiac index 2.8 ± 0.6 l/min/m^2), whereas 4 patients declined the right heart catheterization procedure. Echocardiography of these 4 patients showed either a marked (n = 2) or moderate right heart chamber enlargement (n = 2) and no evidence of systolic or diastolic left ventricular dysfunction. According to other authors[22], we included these patients in the group with moderate or severe PH. No patient with estimated tricuspid gradient < 40 mm Hg underwent a right heart catheterization, thus mild PH could not be detected.

Moderate to severe PH was detected in 16/86 (18.6%) patients with lcSSc and 20/111 (18.0%) patients with dcSSc (p not significant).

Among the 67 patients without ILD, 12 (17.9%) had moderate to severe PAH. Among the 37 patients with ILD and significant reduction in lung volumes, 9 (24.3%) had moderate to severe PH. Among the 73 patients with ILD but with no significant reduction in lung volumes, 15 (20.5%) had moderate to severe PH. These frequencies did not differ significantly between subgroups. The mean systolic PAP was higher in

patients with moderate to severe PAH and no ILD than in patients with moderate to severe PH associated with ILD and %VC < 70% (76.3 ± 23.2 vs 60.1 ± 11.4, respectively; p = 0.03). There was no statistically significant difference (only a tendency) in mean systolic PAP between patients with PAH and no ILD and patients with PH, ILD, and %VC ≥ 70% (76.3 ± 23.2 vs 65.0 ± 13.8 mm Hg, respectively; p = 0.06). When patients with ILD and %VC < 70% and %VC ≥ 70% were compared, the mean systolic PAP did not differ significantly (60.1 ± 11.4 vs 65.0 ± 13.8 mm Hg, respectively; p = 0.8).

Three among the 9 (33.3%) patients with PH, ILD, and significant reduction in lung volumes had severe PH, with a mean PAP > 40 mm Hg on right heart catheterization.

Comparison of patients without ILD according to presence (n = 12) or absence (n = 55) of moderate to severe PAH. Table 1 summarizes these results. Significant differences were observed in the grade of dyspnea, the frequency of ACA, and the %DLCO and %KCO. Grade of dyspnea according to the NYHA classification was available for 47 patients without moderate to severe PAH and for all patients with moderate to severe PAH. Patients with moderate to severe PAH had significantly more severe dyspnea than patients without moderate to severe PAH. The numbers of patients with grade IV, III, II, and I dyspnea, respectively, were 2 (16.7%), 4 (33.3%), 5 (41.7%), and 1 (8.3%) in the group with moderate to severe PAH, compared to 0 (0%), 2 (4.3%), 13 (27.6%), and 32 (68.1%) in the group without moderate to severe PAH (p = 0.0002). ACA were significantly more frequent in patients without PAH: 36/55 (65.4%) versus 4/12 (33.3%) (p = 0.04). %DLCO and %KCO were significantly lower in patients with moderate to severe PAH: 62.8 ± 29.9% versus 87.1 ± 31.3% (p = 0.02) and 63.0 ± 25.5% vs 78.1 ± 16.1% (p = 0.02), respectively. In multivariate analysis including the grade of dyspnea and %DLCO, only the grade of dyspnea appeared to be independently and significantly different between patients without ILD according to the presence or the absence of moderate to severe PAH (p = 0.0001).

By ROC analysis, the best cutoff value of %DLCO to distinguish patients with and without moderate to severe PAH was 72% (Figure 1). There was a linear correlation between %DLCO and systolic PAP ($R^2 = 0.52$, p = 0.01).

Comparison of patients with ILD according to presence or absence of moderate to severe pulmonary hypertension

Patients with ILD and no significant restrictive disease (%VC ≥ 70%; n = 73). Table 2 summarizes these results. Significant differences were observed in the grade of dyspnea, the %VC, %TLC, %DLCO, %KCO, and PaO_2 and SaO_2 values between patients with (n = 15) and those without PH (n = 58). In multivariate analysis with grade of dyspnea, %DLCO, and PaO_2, only PaO_2 appeared to be independently and significantly different between patients with ILD according to the presence or absence of moderate to severe PH (p = 0.01). By ROC analysis (Figure 2), the best cutoff value of PaO_2 to distinguish patients with and without moderate to severe PH was 85 mm Hg, with a sensitivity of 92.9% and specificity 74.5% for the

Table 1. Comparison of patients without ILD according to presence or absence of pulmonary arterial hypertension (PAH).

	Patients with PAH, n = 12	Patients without PAH, n = 55	p
Female/male, n	10/2	49/6	NS
Limited/diffuse SSc, n (%)	10 (83.3)/2 (16.7)	42 (76.3/13 (23.7)	NS
Age at occurrence of RP, yrs, mean ± SD	42.1 ± 16.4	40.8 ± 16.2	NS
Age at diagnosis of SSc, yrs, mean ± SD	54.5 ± 11.4	48.2 ± 15.7	NS
Duration of SSc yrs, mean ± SD	5.3 ± 15.8	6.7 ± 9.1	NS
Dyspnea class, n (%)			
IV	2 (16.7)	0 (0)	0.0002
III	4 (33.3)	2 (4.3)	
II	5 (41.7)	13 (27.6)	
I	1 (8.3)	32 (68.1)	
Anticentromere, n (%)	4 (33.3)	36 (65.4)	0.04
Anti-topoisomerase 1, n (%)	1 (8.3)	5 (9.1)	NS
Antinucleolar, n (%)	1 (8.3)	4 (7.2)	NS
VC %, mean ± SD	96.2 ± 16.6	100.3 ± 19.9	NS
FEV_1/VC %, mean ± SD	79.5 ± 17.8	81.5 ± 9.1	NS
TLC %, mean ± SD	100.0 ± 17.0	102.5 ± 19.5	NS
DLCO %, mean ± SD	62.8 ± 29.9	87.1 ± 31.3	0.02
% VC/% DLCO	1.9 ± 0.8	1.3 ± 0.4	0.005
KCO %, mean ± SD	63.0 ± 25.5	78.1 ± 16.1	0.02
PaO_2, mmHg, mean ± SD	86.4 ± 15.5	92.3 ± 9.8	NS
SaO_2 %, mean ± SD	95.2 ± 4.2	93.9 ± 12.0	NS

VC: vital capacity, FEV: forced expiratory volume, TLC: total lung capacity; RP: Raynaud's phenomenon.

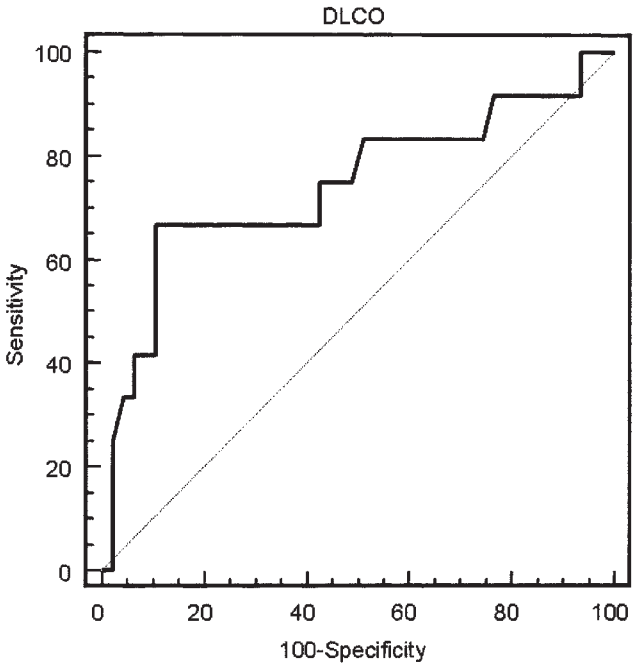

Figure 1. ROC analysis of %DLCO values according to the presence or absence of pulmonary hypertension (PH) in patients without interstitial lung disease. The best cutoff value of %DLCO to distinguish patients with and without PH was 72%.

diagnosis of PH. Among the 7 patients with $PaO_2 \leq$ 69 mm Hg, 6 (85.7%) had moderate to severe PH. There was no linear correlation between %VC, %TLC, %DLCO, or PaO_2 and systolic PAP.

Patients with ILD and significant restrictive disease (%VC < 70%; n = 37). Table 3 summarizes these results. Significant differences were observed in the grade of dyspnea and PaO_2 values between patients with (n = 9) and those without PH (n = 28). In multivariate analysis with grade of dyspnea and PaO_2, only PaO_2 appeared to be independently and significantly different between patients with ILD according to the presence or absence of moderate to severe PH (p = 0.03). ROC analysis was not significant. Among the 4 patients with $PaO_2 \leq$ 62 mm Hg, 3 (75%) had moderate to severe PH. There was no linear correlation between %VC, %TLC, %DLCO, or PaO_2 and systolic PAP.

DISCUSSION

The prevalence of moderate to severe PH in our population was 18.3% when we used a cutoff value of 40 mm Hg for the echographic tricuspid gradient to define PH. In the literature, there is a wide range in the reported frequency of SSc-PH (5%–35%) because of the different methods and diagnostic criteria used to screen patients[10,11,17,23-29]. The mean from several studies is 16% (300 of 1837 patients)[30]. In the largest cohort of SSc patients screened for PH (n = 722), tricuspid gradient > 35 mm Hg on echocardiography was used as a cutoff point to proceed with right heart catheterization[17]. Using this strategy, the prevalence of SSc-PH was 12%[17]. In the second largest study, there was an estimate of PH prevalence of 7.85% (95% confidence interval 5.70–10.00%), but that study excluded patients with significant ILD (%VC < 60%)[11]. The prevalence of PH was probably underestimated in our population using a threshold of 40 mm Hg because we selected

Table 2. Comparison of patients with ILD but no significant restrictive disease (% VC ≥ 70%) according to presence or absence of pulmonary hypertension (PH).

	Patients with PH, n = 15	Patients without PH, n = 58	p
Female/male, n	10/5	48/10	NS
Limited/diffuse SSc, n (%)	5 (33.3)/10 (66.7)	15 (25.9)/43 (74.1)	NS
Age at occurrence of RP, yrs, mean ± SD	43.8 ± 17.1	43.2 ± 14.0	NS
Age at diagnosis of SSc, yrs, mean ± SD	53.5 ± 13.1	49.7 ± 12.8	NS
Duration of SSc yrs, mean ± SD	6.3 ± 10.4	5.5 ± 7.7	NS
Dyspnea class, n (%)			
IV	4 (26.7)	1 (1.71)	0.001
III	5 (33.3)	6 (10.3)	
II	5 (33.3)	25 (43.1)	
I	1 (6.7)	21 (36.2)	
Anticentromere, n (%)	4 (26.7)	12 (20.7)	NS
Anti-topoisomerase 1, n (%)	7 (46.7)	20 (34.5)	NS
Antinucleolar, n (%)	0 (0.0)	3 (5.2)	NS
VC %, mean ± SD	83.4 ± 7.2	93.9 ± 22.1	0.03
FEV_1/VC %, mean ± SD	77.4 ± 9.6	80.4 ± 11.5	NS
TLC %, mean ± SD	76.2 ± 12.4	93.1 ± 16.1	0.0007
DLCO %, mean ± SD	52.4 ± 21.9	74.9 ± 26.1	0.003
% VC/% DLCO	1.87 ± 0.85	1.41 ± 0.93	0.06
KCO %, mean ± SD	54.9 ± 10.9	74.1 ± 16.2	0.0007
PaO_2, mmHg, mean ± SD	74.0 ± 11.4	90.1 ± 11.0	0.00005
SaO_2 %, mean ± SD	93.2 ± 4.4	94.6 ± 8.9	0.02

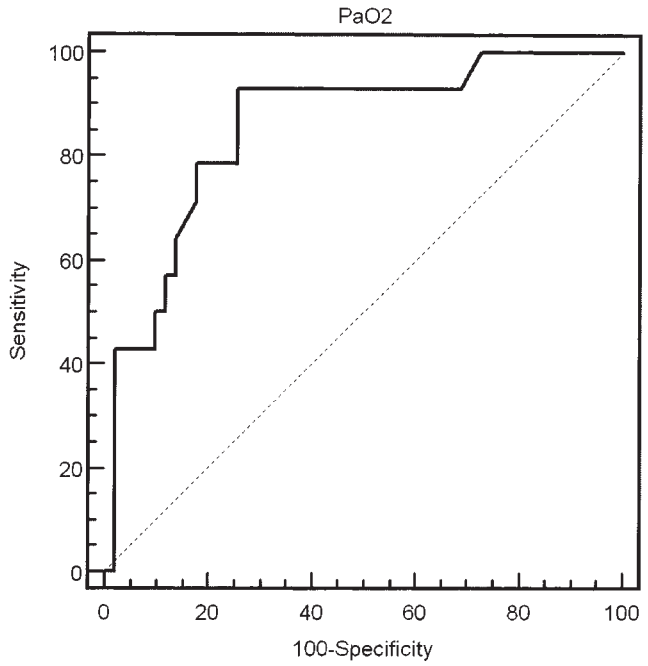

Figure 2. ROC analysis of PaO_2 values according to the presence or absence of pulmonary hypertension (PH) in patients with interstitial lung disease and %VC ≥ 70%. The best cutoff value of PaO_2 to distinguish patients with and without PH was 85 mm Hg.

patients with moderate to severe PH and did not detect patients with mild PH. This is reinforced by the fact that all 32 patients who underwent right heart catheterization had PH (there was no false-positive) and that the majority (63.9%) of these patients with PH already had a dyspnea of grade III-IV of the NYHA classification, which is similar to the frequencies of 55%–75% reported in the literature[10,13,17]. However, we found a relatively high frequency of PH. The most probable explanation for this is that the patients were evaluated in 2 tertiary referral centers and could therefore have had a more severe form of SSc and in particular a more severe dyspnea and thus a higher risk of having PH. By choosing a cutoff value of 35 mm Hg for tricuspid gradient, 13 additional cases of suspected PH would have been identified. Unfortunately, as reported by Mukerjee, *et al*[9], this cutoff value has a low specificity (66%), indicating that a significant proportion of patients with a tricuspid gradient ≥ 35 mm Hg do not have PH as assessed by right heart catheterization, which is the gold standard. As we did not perform right heart catheterization in patients with a gradient < 40 mm Hg, we decided not to include these 13 additional cases of suspected PAH in the final analysis.

The pathophysiology of SSc-PH is probably different depending on the presence and severity or the absence of ILD[7]. In SSc with ILD, PH can be a direct consequence of the ILD, probably due in part to hypoxemia in cases of extensive tissue destruction. In patients with ILD but no severe restrictive disease, vasculopathy could play a major role. Moreover, ILD can influence PFT and clinical characteristics[16]. Therefore, as described by Mukerjee, *et al*[9], we decided to analyze patients with and without ILD separately. Among patients with ILD we also separated those with a significant restrictive pattern (%VC < 70%) from those without such evidence (%VC ≥ 70%).

In patients without ILD, the grade of dyspnea was higher

Table 3. Comparison of patients with ILD and significant restrictive disease (% VC < 70%) according to presence or absence of pulmonary hypertension (PH).

	Patients with PH, n = 9	Patients without PH, n = 28	p
Female/male, n	7/2	22/6	NS
Limited/diffuse SSc, n (%)	1 (11.1)/8 (88.9)	1 (3.6)/27 (96.4)	NS
Age at occurrence of RP, yrs, mean ± SD	45.1 ± 13.6	37.2 ± 13.5	NS
Age at diagnosis of SSc, yrs, mean ± SD	48.3 ± 13.6	40.9 ± 12.4	NS
Duration of SSc yrs, mean ± SD	3.2 ± 3.7	4.6 ± 6.7	NS
Dypsnea class, n (%)			
IV	3 (33.3)	0 (0.0)	0.001
III	5 (55.6)	15 (53.6)	
II	1 (11.1)	10 (35.7)	
I	0 (0.0)	3 (10.7)	
Anticentromere, n (%)	1 (11.1)	3 (10.7)	NS
Anti-topoisomerase 1, n (%)	4 (44.4)	14 (50.0)	NS
Antinucleolar, n (%)	1 (11.1)	1 (3.6)	NS
VC %, mean ± SD	56.0 ± 10.3	57.0 ± 8.7	NS
FEV_1/VC %, mean ± SD	88.3 ± 14.2	91.7 ± 8.0	NS
TLC %, mean ± SD	60.3 ± 13.0	62.6 ± 11.7	NS
DLCO %, mean ± SD	36.4 ± 12.6	44.0 ± 15.5	NS
% VC/% DLCO	1.62 ± 0.59	1.42 ± 0.50	NS
KCO %, mean ± SD	58.6 ± 17.2	72.2 ± 22.2	NS
PaO_2, mmHg, mean ± SD	70.9 ± 12.3	86.1 ± 13.1	0.01
SaO_2 %, mean ± SD	93.1 ± 3.6	95.6 ± 1.7	0.06

in the presence of moderate to severe PAH than in the absence of detectable PAH. It is well known that dyspnea is one of the most important symptoms of PAH, and that in each SSc patient with unexplained dyspnea investigation is mandatory to rule out PAH[7,9]. Despite the possible subjectivity of dyspnea grading, our study emphasizes that grade III or IV dyspnea is associated with moderate to severe PAH in SSc without ILD. Concerning PFT, only %DLCO and %KCO were significantly reduced in patients with moderate to severe PAH, with a best cutoff value of 72% for %DLCO to identify patients with moderate to severe PAH. Actually, this value is higher than reported in the literature. This higher DLCO cutoff could be related in part to the formula used for calculating the percentage predicted in our laboratory, using European Respiratory Society values. Mukerjee, *et al*[9] found that sensitivity, specificity, positive predictive value, and negative predictive value with a cutoff value of 60% for %DLCO were 74%, 45%, 70%, and 50%, respectively. Chang, *et al* showed that DLCO < 50% was a factor predicting development of severe SSc-PH[31]. Our results favor the value of %DLCO > 72% as an important argument against the presence of moderate to severe PAH in patients without ILD, as suggested by the high negative predictive value (near 92%). In our study, patients with PAH and no ILD had higher %VC/%DLCO values than those without PH. This had been reported by Stupi, *et al*, suggesting that a low %DLCO with normal lung volumes (resulting in a high %VC/%DLCO) was suggestive of PH[32]. Mukerjee, *et al* showed that %DLCO and mean PAP (r^2 = 0.09) were weakly correlated only in patients without significant ILD[9]. We identified a more robust linear correlation between %DLCO and systolic PAP only in the subgroup of patients with no ILD (R^2 = 0.52). The explanation for this is unclear. ILD can alter %DLCO independently of the presence of PAH and could disrupt the linear correlation between %DLCO and systolic PAP[16].

In patients with ILD, moderate to severe PH was observed in nearly the same proportion among patients with reduced lung volumes (indicating a more severe ILD) than in others. The mean systolic PAP was also similar between these 2 subgroups. We did not quantify the extent of ILD on HRCT and did not make an extensive study of HRCT patterns; thus we cannot comment on the relationship between extent of ILD or characteristics of the patterns on HRCT and the characteristics of PH. Among patients with ILD, with or without a significant restrictive pattern, the presence of PH was associated with a higher degree of dyspnea. For example, among the 8 patients with grade IV dyspnea, 7 (87.5%) had PH. In our study, PaO_2 appeared to be the sole variable that was significantly and independently different between patients with ILD, regardless of its severity as assessed by %VC, according to the presence or absence of PH. Moreover, in patients with %VC < 70%, no PFT measure except PaO_2 was significantly different between patients with and those without PH. Recently, Hachulla, *et al* reported that PaO_2 + $PaCO_2$ was lower in patients with SSc-PH[11]. PFT is usually performed in followup of patients with ILD. In patients with more severe ILD (%VC < 70%), hypoxia could contribute to PH because it can cause vasoconstriction of pulmonary arterioles. Therefore, in this subgroup of patients hypoxic PH could be overrepresented. The mean PAP in hypoxic PH is usually not very high. For example, it is recognized that one of the main characteristics of PH in patients with chronic obstructive pulmonary disease is its mild to moderate degree, with resting mean PAP in a stable state of the disease usually ranging between 20 and 35 mm Hg[33]. This could explain our finding that systolic PAP was lower in patients with ILD and a significant restrictive pattern (probably having hypoxic PH) than in patients without ILD (having vasculopathic PAH). However, some patients with hypoxic PH can develop a more severe PH (mean PAP > 40 mm Hg), which is called "PH out of proportion." In our study, 3 among the 9 (33.3%) patients with PH, ILD, and significant reduction in lung volumes had a mean PAP > 40 mm Hg as measured by right heart catheterization, and who therefore had PH out of proportion to the degree of fibrosis. In these patients, a vasculopathic type of PH could be present, in addition to hypoxic PH. Chang, *et al* have shown that a proportion (between 15% and 30%) of patients with moderate to severe restrictive ventilatory defect (%VC < 65%) had severe PH defined by systolic PAP > 55 mm Hg[22]. In contrast to Chang, *et al* we used right heart catheterization, which is the gold standard for PH. These results suggest that a low PaO_2 value in patients with significant ILD should lead to a diagnostic procedure for PH, especially to identify those with PH out of proportion to the degree of fibrosis. These patients could represent a particular subgroup in SSc-related ILD that has not been extensively studied. It is probably important to identify these patients because specific antiproliferative PH treatment could represent a therapeutic option to improve their clinical status and perhaps improve survival. Indeed, Trad, *et al* recently demonstrated that PH was a major mortality factor in patients with ILD[5]. However, this needs to be confirmed in future studies — the low number of patients with this PH out of proportion to the degree of fibrosis in our study precludes any firm conclusion.

In patients with less severe ILD (VC ≥ 70%), patients with PH had lower %DLCO, lung volumes, and PaO_2 values than those without PH. Again, PaO_2 was the sole measure that was significantly and independently different between patients with and those without PH. In this subgroup, it could be hypothesized that PH itself may cause hypoxia. The best cutoff value for PaO_2 was 85 mm Hg. We acknowledge that 85 mm Hg is on the lower limit of normal value of PaO_2 for a patient population of about 50 years of age. To our knowledge, PaO_2 has not been reported previously as an independent marker of PH in patients with SSc and ILD, whatever the severity of the restrictive pattern, and further prospective studies are needed to confirm this finding. As PFT are usually used to follow patients with ILD at least every 6 months, our study suggests that PaO_2 is an important indicator for PH regardless

of the importance of the restrictive pattern. Interestingly, %DLCO was lower in patients with moderate to severe PH, suggesting that in this subgroup ILD was not the sole mechanism of impairment of DLCO.

The prevalence of moderate to severe PH was 18.3% in our population and was similar in SSc patients with and those without ILD. In patients with ILD, regardless of the importance of the restrictive pattern, low PaO_2 was the unique independent measure significantly associated with PH. A linear correlation between DLCO and systolic pulmonary arterial pressure was observed only in patients without ILD. All these measures should help to identify patients requiring rapid diagnostic procedures for PH, before their annual screening. We propose that PaO_2 should be evaluated in further studies screening for SSc-PH and that PFT is useful to identify moderate to severe PH in SSc.

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