

# The Three-Year Incidence of Pulmonary Arterial Hypertension Associated With Systemic Sclerosis in a Multicenter Nationwide Longitudinal Study in France

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**Objective.** An algorithm for the detection of pulmonary arterial hypertension (PAH), based on the

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presence of dyspnea and the findings of Doppler echocardiographic evaluation of the velocity of tricuspid regurgitation (VTR) and right-sided heart catheterization (RHC), which was applied in a large multicenter systemic sclerosis (SSc) population, estimated the prevalence of PAH to be 7.85%. The aim of this observational study was to investigate the incidence of PAH and pulmonary hypertension (PH) during a 3-year followup of patients from the same cohort (the ItinérAIR-Sclérodermie Study).

**Methods.** Patients with SSc and without evidence of PAH underwent evaluation for dyspnea and VTR at study entry and during subsequent visits. Patients in whom PAH was suspected because of a VTR of 2.8–3.0 meters/second and unexplained dyspnea or a VTR of >3.0 meters/second underwent RHC to confirm the diagnosis.

**Results.** A total of 384 patients were followed up for a mean  $\pm$  SD of  $41.03 \pm 5.66$  months (median 40.92 months). At baseline, 86.7% of the patients were women, and the mean  $\pm$  SD age of the patients was  $53.1 \pm 12.0$  years. The mean  $\pm$  SD duration of SSc at study entry was  $8.7 \pm 7.6$  years. After RHC, PAH was diagnosed in 8 patients, postcapillary PH in 8 patients, and PH associated with severe pulmonary fibrosis in 2 patients. The incidence of PAH was estimated to be 0.61 cases per

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**100 patient-years. Two patients who exhibited a mean pulmonary artery pressure of 20–25 mm Hg at baseline subsequently developed PAH.**

**Conclusion.** The estimated incidence of PAH among patients with SSc was 0.61 cases per 100 patient-years. The high incidence of postcapillary PH highlights the value of RHC in investigating suspected PAH.

Within the last 2 decades, pulmonary fibrosis and pulmonary arterial hypertension (PAH) have become the leading causes of death in patients with systemic sclerosis (SSc) (1). According to the most recent case series, the estimated 3-year survival in PAH associated with SSc is ~50% (2). Right-sided heart catheterization (RHC) is the gold standard technique for the diagnosis of PAH and is necessary for the differentiation between different forms of pulmonary hypertension (PH) in SSc.

We have previously demonstrated that a screening algorithm that combines Doppler echocardiographic measurement of the peak velocity of tricuspid regurgitation (VTR) with the evaluation of dyspnea and with RHC for confirmation of the diagnosis of PAH can be applied to SSc patients in a multicenter setting and in routine practice (3). Using this method, we found that the prevalence of PAH in a multicenter cohort of SSc patients in France was 7.85% when patients with severe pulmonary fibrosis and known severe disease of the left side of the heart were excluded (3).

There is currently little published literature reporting the incidence of PAH associated with SSc. Therefore, we investigated the incidence of PAH in patients with SSc during a 3-year followup of the previously described large multicenter cohort of patients with SSc in France.

## PATIENTS AND METHODS

**Study centers and study population.** The prospective ItinérAIR-Sclérodermie Study was conducted at 21 French university hospitals experienced in the management of SSc (3). One center did not participate in the collection of the 3-year followup data; therefore, the present study involved 20 centers. The ItinérAIR-Sclérodermie Study Group participating investigators and study centers are listed in Appendix A.

Adult patients with SSc who visited each participating center between September 2002 and July 2003 for their regular followup visits were invited to enter the study. Patients were required to fulfill the American College of Rheumatology (formerly, the American Rheumatism Association) criteria for SSc (4) and were classified as having limited cutaneous SSc (lcSSc) or diffuse cutaneous SSc (dcSSc) according to the criteria described by LeRoy et al (5).

SSc patients may develop various forms of PH, includ-

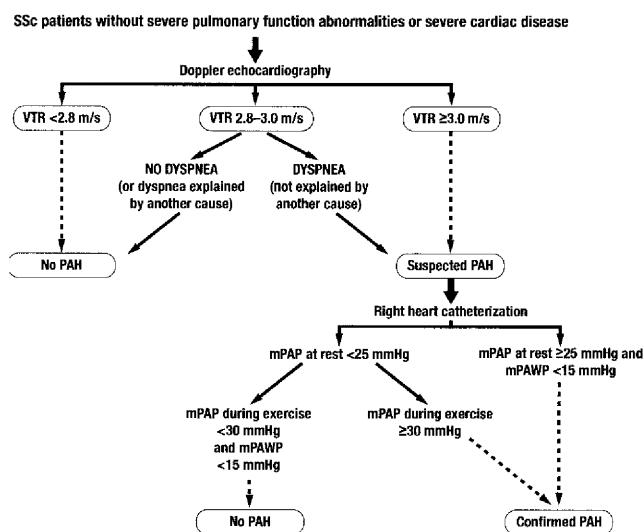
ing PH secondary to left ventricular diastolic disease, severe pulmonary fibrosis, pulmonary venoocclusive disease, or pulmonary vasculopathy. The ItinérAIR-Sclérodermie Study was primarily implemented for the investigation of PAH, and for the sake of homogeneity, patients who were considered to be more prone to developing other types of PH were not enrolled. These included patients with severe disease of the left side of the heart at baseline (defined as left ventricular ejection fraction <45%, mitral or aortic regurgitation higher than grade 2, mitral area <1.5 cm<sup>2</sup>, or aortic area <1 cm<sup>2</sup>) who were considered to be at risk of developing postcapillary PH. Patients with severe restrictive lung disease at baseline (defined as a forced vital capacity [FVC] or a total lung capacity [TLC] <60% of predicted) who were considered to be at risk of developing PH associated with severe pulmonary fibrosis were also excluded.

The primary objective of this study was to define the incidence of PAH in this large cohort of SSc patients during a 3-year period using our previously reported screening algorithm for diagnosis of PAH in patients with SSc (3). The study protocol was approved by an independent Ethics Review Board (Comité de Protection des Personnes, Lille, France). Informed consent was obtained from each patient at study entry and at each followup visit.

**Assessment of patients.** It is recommended that SSc patients be screened for the presence of PAH on a regular basis (6). Our patients were therefore screened for PAH according to the VTR value at entry into the present study and at intervals during the 3-year followup period. Due to the observational nature of the study, a specific schedule for the followup visits was not imposed.

A detailed description of the screening algorithm for the diagnosis of PAH that was used in this investigation has previously been published (3). The algorithm included evaluation of the VTR using Doppler echocardiography and evaluation of dyspnea based on the New York Heart Association (NYHA) functional class (7). Although the NYHA classification has not been specifically validated in SSc patients as a tool for the quantification of dyspnea, it is frequently used in the assessment of many cardiopulmonary diseases. All patients, regardless of the presence or absence of dyspnea, were referred to an expert cardiologist in each center who performed a complete time-motion bidimensional and Doppler echocardiographic examination with standard views and procedures. After patients were positioned for the examination, a 20-minute rest period was observed before the Doppler examination was performed. VTR was measured using the continuous-wave Doppler and guided by color-flow Doppler.

During the cross-sectional phase of the study, in which the prevalence of PAH was previously described (3), we used either a VTR threshold of 3.0 meters/second or a VTR threshold of 2.5 meters/second (transtricuspid gradient 25 mm Hg) when combined with unexplained dyspnea to identify patients in whom PAH was suspected. Patients in whom PAH was suspected were referred for RHC to confirm the diagnosis. The observed rate of false-positive diagnosis of PAH by Doppler echocardiography using this VTR threshold was 36% (3). Only 2 of 20 SSc patients with dyspnea and a VTR of 2.5–2.7 meters/second had the diagnosis of PAH confirmed by RHC. Both of these patients exhibited PAH of mild severity (mean pulmonary artery pressure [mPAP] 25 mm Hg and 26



**Figure 1.** Modified screening algorithm for the diagnosis of pulmonary arterial hypertension (PAH) in patients with systemic sclerosis (SSc) without severe pulmonary function abnormalities and without severe cardiac disease. VTR = peak velocity of tricuspid regurgitation; mPAP = mean pulmonary artery pressure; mPAWP = mean pulmonary artery wedge pressure.

mm Hg, respectively; pulmonary vascular resistance [PVR] 242 dynes · seconds/cm<sup>5</sup> and 149 dynes · seconds/cm<sup>5</sup>, respectively) (3).

In order to decrease the rate of false-positive diagnosis by Doppler echocardiography, and therefore avoid unnecessary and invasive RHC procedures, our screening algorithm for the diagnosis of PAH was revised for the present study to include suspected PAH on Doppler echocardiography in patients with a VTR ≥ 2.8 meters/second (transtricuspid gradient 31 mm Hg) with unexplained dyspnea or a VTR ≥ 3.0 meters/second, which is consistent with international guidelines (8,9). These revisions were also consistent with those recently reported by Hsu et al to confer high specificity for the identification of PAH (10). The revised algorithm is illustrated in Figure 1.

In all patients in whom PAH was suspected following echocardiography, RHC was performed to confirm the diagnosis, unless they exhibited evidence of significant disease of the left side of the heart (3). In patients with elevated VTR but normal RHC parameters at baseline, RHC was repeated during the longitudinal period if their dyspnea worsened by at least 1 NYHA functional class or if their VTR increased by ≥20% from baseline. RHC was performed at specialized centers according to standard techniques, as previously reported (3). The mean right atrial pressure, systolic and diastolic arterial pressure, mPAP, mean pulmonary artery wedge pressure (mPAWP), cardiac index, cardiac output, PVR, and indexed PVR (PVRi) were quantified according to the methods described previously (3).

For patients with a resting mPAP < 25 mm Hg, hemodynamics during exercise were measured, if possible. This was

performed by asking the patient to move his or her legs to a level of exercise corresponding to 30–40W for 6–10 minutes.

Based on current guidelines, PAH was defined as an mPAP ≥ 25 mm Hg at rest or ≥ 30 mm Hg during exercise, with an mPAWP < 15 mm Hg (6,8,9). If the mPAWP exceeded 15 mm Hg, disease of the left side of the heart and postcapillary PH were diagnosed. PH associated with severe pulmonary fibrosis was diagnosed in patients with a significant reduction in lung volume (FVC < 60% and/or TLC < 60%) and a modest elevation in mPAP (< 35 mm Hg at rest) (8). We also characterized a subgroup of patients who had an mPAP above the normal range (20–25 mm Hg), as measured by RHC at study entry (11).

**Additional data collected at study entry.** Additional data collected at study entry consisted of demographic information, SSc characteristics (including disease history since first symptoms and Raynaud's phenomenon), Rodnan skin thickness score (12), and signs and symptoms suggestive of PAH. Pulmonary function tests were repeated, unless they had been performed within the previous 6 months. The TLC, FVC, forced expiratory volume in 1 second, diffusing capacity for carbon monoxide (DLCO), and levels of blood gases were quantified. The presence of antinuclear antibodies, including antitopoisomerase and anticentromere antibodies, was investigated.

**Data collected at followup visits.** At the followup visits, data pertaining to cardiovascular risk factors (including tobacco use or the presence of diabetes mellitus, hypertension, or hypercholesterolemia), the Rodnan skin thickness score, and the presence of digital ulcers were recorded. Laboratory data on hemoglobin and creatinine values were collected, if available. Pulmonary function tests were also repeated at each followup visit. If a patient had died since the last visit, the date and cause of death were recorded.

**Statistical analysis.** Data analysis was conducted on the population of patients who were identified according to, and completed all procedures within, the screening algorithm for the diagnosis of PAH in SSc. This comprised all patients without documented PAH or PH at baseline who agreed to participate in the followup segment of the study and who underwent all study procedures in accordance with the protocol requirements (i.e., at least 1 clinical examination, 1 Doppler echocardiographic examination, and referral for RHC if PAH was suspected based on the echocardiographic results). Patients with PAH diagnosed during the 3-year followup period were identified as having incident PAH.

The duration of followup was defined as the time that elapsed from study entry until the last assessment of the patient. The cumulative incidence of PAH was calculated as the ratio of new diagnoses of PAH during the followup period and was expressed as the number of patient-years. The 95% confidence interval (95% CI) of the cumulative incidence was determined by dividing the Poisson confidence interval for the number of events by the duration of the followup period and was expressed in patient-years. Comparisons between patients with incident PAH and patients with neither incident PAH nor PH were conducted using the Mann-Whitney U test for continuous variables and either the chi-square test or Fisher's exact test for discrete variables.

SAS software, version 9.1 (SAS Institute, Cary, NC), was used to perform statistical analyses. Results are expressed

as the mean  $\pm$  SD for continuous variables and as numbers with percentages for categorical variables.

## RESULTS

**Composition of the study population.** A total of 599 patients were enrolled in the ItinérAIR-Sclérodermie Study in 2003, and we previously reported the prevalence of PAH in this population (3). Of this group, 45 patients were not included in the present study because either the study center or the investigator at another center where they had been recruited elected not to participate in the followup study. In addition, a total of 4 patients declined to participate, and a further 4 patients were lost to followup. Of the 546 remaining patients, 47 had a diagnosis of PAH either before or at entry into the study and were therefore not included. The remaining 499 patients without PAH comprised the intent-to-screen population for this study. Data describing vital status were available for each of these 499 patients at the end of the followup period.

For a further 115 patients, the study protocol was not strictly adhered to: 109 patients did not have at least 1 echocardiogram of sufficient quality with VTR measurement during followup, and 6 patients did not undergo RHC when the presence of PAH was suspected (4 declined consent and 2 were considered too frail). These patients were therefore not included in the present analysis. The remaining 384 patients who satisfied all of the screening protocol requirements were included in the present analysis. The baseline characteristics of this population are summarized in Table 1.

**Incidence of pulmonary hypertension.** The mean  $\pm$  SD duration of followup was  $41.03 \pm 5.67$  months (median 40.92 months), representing a total of 1,313 patient-years. Based on our modified algorithm, 26 patients underwent RHC. PAH was diagnosed in 8 of

**Table 1.** Characteristics of the 384 SSc patients at baseline\*

Age, mean $\pm$ SD years	$53.1 \pm 12.0$
No. (%) female	333 (86.7)
Age at first non-RP symptom, mean $\pm$ SD years	$44.4 \pm 12.9$
Age at SSc diagnosis, mean $\pm$ SD years	$46.1 \pm 12.9$
Time since onset of RP, mean $\pm$ SD years	$14.3 \pm 11.7$
Time since first non-RP symptom, mean $\pm$ SD years	$8.7 \pm 7.6$
No. (%) with lcSSc	292 (76.0)
Rodnan skin thickness score, mean $\pm$ SD	$12.4 \pm 9.7$
No. (%) with previous digital ulcer(s)	200 (52.1)
No. (%) with antitopoisomerase antibodies	104 (28.1)
No. (%) with anticentromere antibodies	172 (46.5)

\* SSc = systemic sclerosis; RP = Raynaud's phenomenon; lcSSc = limited cutaneous systemic sclerosis.

**Table 2.** Estimated incidence of pulmonary hypertension during the 3-year followup period\*

	Estimated incidence (no. of cases per 100 patient-years)	95% CI
All forms of pulmonary hypertension	1.37	0.74–2.00
Pulmonary arterial hypertension	0.61	0.26–1.20
Among patients with lcSSc	0.40	0.11–1.03
Among patients with dcSSc	1.25	0.34–3.20
Postcapillary pulmonary hypertension	0.61	0.26–1.20
Pulmonary hypertension secondary to pulmonary fibrosis	0.15	0.02–0.55

\* 95% CI = 95% confidence interval; lcSSc = limited cutaneous systemic sclerosis; dcSSc = diffuse cutaneous systemic sclerosis.

these patients, and postcapillary PH was diagnosed in another 8 patients. PH associated with severe pulmonary fibrosis was diagnosed in 2 patients who exhibited a reduction in FVC and/or TLC values from  $\geq 60\%$  to  $< 60\%$  during followup. These 2 patients exhibited a proportionate increase in mPAP (26 mm Hg at rest for the first patient; 20 mm Hg at rest and 31 mm Hg at exercise for the second patient). The incidence of PH is summarized in Table 2.

**Clinical characteristics of incident PAH.** For each of the 8 patients diagnosed as having PAH during the followup period, the clinical, echocardiographic, and hemodynamic data at baseline and at the time of PAH diagnosis are summarized in Table 3.

At baseline, 6 of the 8 patients with incident PAH were in NYHA functional class II or III, and 5 patients had DLco levels that were  $< 50\%$  of the predicted value. Four of the 8 patients had dcSSc (duration  $< 10$  years in all cases), and the remaining 4 patients had lcSSc (duration  $\geq 10$  years in all cases).

At the time of PAH diagnosis, DLco was recorded in 5 of the 8 patients with incident PAH. Among these patients, 3 had DLco levels that were  $< 50\%$  of predicted values. The 3 patients who did not undergo repeat measurement of DLco at the time of PAH diagnosis were among those with baseline DLco levels  $< 50\%$  of predicted values. The VTR was  $> 3.0$  meters/second in 5 patients. The mean PVRi among all 8 patients diagnosed as having PAH was  $702 \pm 508$  dynes  $\cdot$  seconds/cm $^5$ /m $^2$  (mean  $\pm$  SD). PAH was diagnosed during exercise in 2 patients who also exhibited the lowest PVRi at rest (247 and 320 dynes  $\cdot$  seconds/cm $^5$ /m $^2$ , respectively). In 1 of these patients, RHC performed 41 months after PAH diagnosis showed an elevated

**Table 3.** Clinical, echocardiographic, and hemodynamic data in the 8 patients with incident PAH identified during the followup period\*

	Patient							
	1	2	3	4	5	6	7	8
At baseline								
Age, years	67.8	68.6	62.6	54.6	41.5	64.9	42.8	74.6
Sex	F	F	F	F	F	F	F	F
SSc duration from first non-RP symptom, years	7	21	35	5	7	23	3	10
SSc subtype	dcSSc	lcSSc	lcSSc	dcSSc	dcSSc	lcSSc	dcSSc	lcSSc
NYHA functional class	III	III	II	III	II	I	-	III
DLCO, % predicted	48	77	37	30	47	93	67	36
VTR, meters/second	No TR	1.6	2.9	No TR	2.6	2.8	No TR	2.9
At diagnosis of PAH								
NYHA functional class	III	III	III	III	III	II	II	III
DLCO, % predicted	-	48	-	24	41	93	54	-
VTR, meters/second	4.3	3.2	3.9	3.3	2.9	2.8	4.1	2.8
mPAP at rest (during exercise), mm Hg	46	30	28	32	51	20 (72)	60	21 (41)†
mPAWP, mm Hg	9	13	11	4	9	10	10	9
PVRI, dynes · seconds/cm <sup>5</sup> /m <sup>2</sup>	1,644	406	498	673	963	247	1,127	320
Cardiac index, liters/minute/m <sup>2</sup>	1.80	3.35	2.73	3.33	3.49	3.24	3.55	3.00
Time from baseline, months	9	39	8	19	49	2	17	9

\* PAH = pulmonary arterial hypertension; SSc = systemic sclerosis; RP = Raynaud's phenomenon; dcSSc = diffuse cutaneous SSc; lcSSc = limited cutaneous SSc; NYHA = New York Heart Association; DLCO = diffusing capacity for carbon monoxide (expressed as a percentage of the theoretical value for persons of the same age, sex, height, and race); VTR = peak velocity of tricuspid regurgitation; mPAP = mean pulmonary artery pressure; mPAWP = mean pulmonary artery wedge pressure; PVRI = indexed pulmonary vascular resistance.

† Abnormalities noted on right-sided heart catheterization were controlled at 41 months following diagnosis in this patient, who exhibited elevated mPAP at rest (32 mm Hg), with an increased PVRI (427 dynes × seconds/cm<sup>5</sup>/m<sup>2</sup>) and stable NYHA functional class III.

mPAP at rest (32 mm Hg), with an increase in the PVRI (427 dynes · seconds/cm<sup>5</sup>/m<sup>2</sup>) and a stable NYHA functional class (class III).

Five patients had an mPAP value between 20 mm Hg and 25 mm Hg at baseline. PAH was diagnosed in 2 of these patients during the longitudinal phase of this

study. In 1 patient, the mPAP increased from 23 mm Hg to 28 mm Hg upon RHC. Another patient exhibited a dramatic increase in the mPAP, from 20 mm Hg at rest to 72 mm Hg upon exercise testing, thereby confirming the diagnosis of PAH. No RHC was performed in the remaining 3 patients because the VTR and the NYHA

**Table 4.** Comparison of baseline characteristics of patients with incident PAH and patients without PH or PAH\*

Parameter	Incident PAH (n = 8)	No PH or PAH (n = 366)	P
Age, mean ± SD years	59.7 ± 12.2	52.8 ± 12.0	0.11
No. (%) female	8 (100)	316 (86)	0.26
Age at first non-RP symptom, mean ± SD years	45.8 ± 12.6	44.3 ± 13.0	0.86
Time since onset of RP, mean ± SD years	15.4 ± 10.4	14.2 ± 11.5	0.54
Time since first non-RP symptom, mean ± SD years	13.9 ± 11.3	8.5 ± 7.4	0.14
No. (%) with dcSSc	4 (50)	82 (22)	0.09
No. (%) with previous digital ulcer(s)	4 (50)	192 (52)	1.00
No. (%) with NYHA functional class II/III	2/4 (75)	85/24 (30)	0.01
VTR, mean ± SD meters/second	2.56 ± 0.55	2.34 ± 0.31	0.07
DLCO, mean ± SD % predicted	54.4 ± 22.4	73.2 ± 18.0	0.02
Pao <sub>2</sub> , mean ± SD mm Hg	89.7 ± 15.7	89.2 ± 16.5	0.70
Paco <sub>2</sub> , mean ± SD mm Hg	36.8 ± 4.0	37.5 ± 4.2	0.70
No. (%) with antitopoisomerase antibodies	3 (38)	97 (27)	0.69
No. (%) with anticentromere antibodies	3 (38)	167 (47)	0.73

\* PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; RP = Raynaud's phenomenon; dcSSc = diffuse cutaneous systemic sclerosis; NYHA = New York Heart Association; VTR = peak velocity of tricuspid regurgitation; DLCO = diffusing capacity for carbon monoxide; Pao<sub>2</sub> = partial pressure of arterial oxygen; Paco<sub>2</sub> = partial pressure of arterial carbon dioxide.

functional class remained the same between study entry and followup evaluations.

**Disease characteristics associated with PAH.** Among the patients who were diagnosed as having PAH during the followup period, the mean  $\pm$  SD time since the baseline evaluation was  $576 \pm 499$  days (median 408 days). The baseline clinical characteristics of the patients with PAH diagnosed during the followup period were compared with those of the patients without either PAH or PH (Table 4). Due to the small number of patients with incident PAH, differences were rarely significant. Nevertheless, patients with incident PAH were typically older, had a longer history of SSc, and were more likely to have dcSSc ( $P = 0.09$ ). The baseline DLco in patients who developed PAH during the followup period was typically impaired ( $P = 0.02$ ), with 5 of the 8 patients having a DLco value  $<50\%$  predicted. No association between previous digital ulcers and incident PAH was noted.

**Postcapillary pulmonary hypertension.** During the followup period, postcapillary PH was diagnosed by findings on RHC in 8 patients. In 5 of these patients, the VTR was  $>3.0$  meters/second. The mean  $\pm$  SD mPAP at rest in these 8 patients was  $24.5 \pm 6.6$  mm Hg, and the mean  $\pm$  SD mPAWP was  $12.9 \pm 4.3$  mm Hg. In 5 of these patients, individual measurements of mPAP were  $<25$  mm Hg at rest but  $>30$  mm Hg during exercise, with an mPAWP  $>15$  mm Hg. The mPAP at rest was  $>35$  mm Hg in 1 of the patients. Echocardiographic findings were normal in all but 2 patients with postcapillary PH: one of them exhibited isolated moderate left atrial dilatation, and the other exhibited mild aortic sclerosis (peak velocity of aortic flow 2 meters/second). Four of these patients had a baseline DLco level  $<60\%$  of predicted.

## DISCUSSION

This 3-year followup study of a large multicenter cohort of patients with SSc in France was designed to investigate the incidence of PAH in patients with SSc. Using a revised screening algorithm for the diagnosis of PAH that was based on the presence of dyspnea and findings of a Doppler echocardiographic evaluation of VTR to refer patients for RHC, we followed up 384 SSc patients without severe respiratory disease or severe disease of the left side of the heart at baseline for a mean  $\pm$  SD of  $41.03 \pm 5.67$  months (median 40.92 months), and observed an overall incidence of PH of 1.37 cases per 100 patient-years (95% CI 0.74–2.00).

This study is, to our knowledge, the first large

prospective multicenter study to estimate the incidence of PH in a population of patients with SSc. In all instances, echocardiography was performed by experienced senior echocardiographers. The VTR threshold of 2.8 meters/second (transtricuspid gradient 31 mm Hg) selected for this study was associated with a decrease in the previously reported rate of false-positive results (from 36% to 30.7%) when a VTR threshold of 2.5 meters/second was used. Another interesting point is that the absence of detectable tricuspid regurgitation at baseline did not exclude the risk of PH occurrence within the following 3 years. This confirms the importance of regular screening in the diagnosis of either early mild PAH or aggressive severe PAH.

Among the 18 patients diagnosed as having PH, 8 had PAH (incidence 0.61 cases per 100 patient-years), 8 had postcapillary PH (incidence 0.61 cases per 100 patient-years), and 2 had PH due to pulmonary fibrosis (incidence 0.15 cases per 100 patient-years). In all cases, RHC was necessary for making the diagnosis of PAH and for excluding a diagnosis of postcapillary PH.

In the 8 patients who were diagnosed as having PAH during the followup period, specific features at baseline, such as dyspnea and impaired DLco, were observed. Six patients had dyspnea with a NYHA functional class II or class III. Five patients had DLco levels that were  $<50\%$  of predicted values. Furthermore, based on our observations, we consider that the patients with an mPAP of 20–25 mm Hg at baseline may have been at greater risk of developing PAH during the 3-year followup period.

There are limited data documenting the prevalence and incidence of PAH in patients with SSc. Mukerjee et al (13) observed a combined prevalence and incidence of PAH associated with SSc of 12% in a study that included serial assessments over a 4-year period. More recently, Vonk et al (14) estimated the combined prevalence of PAH and PH associated with pulmonary fibrosis in patients with SSc in The Netherlands to be 9.9%.

Using the previously described screening algorithm for the diagnosis of PAH in patients with SSc and excluding patients with severe pulmonary fibrosis, our group estimated the prevalence of PAH in a French population of SSc patients to be 7.85% (3). A trend toward a higher risk of developing PAH in patients with dcSSc was also observed (14% and 5.5% in dcSSc and lcSSc, respectively;  $P = 0.10$ ) (3). In the present study, a comparable trend was observed. The incidence of PAH was 0.40 cases per 100 patient-years (95% CI 0.11–1.03) in patients with lcSSc and 1.25 cases per 100 patient-

years (95% CI 0.34–3.20) in patients with dcSSc. Previous studies, however, have reported that patients with lcSSc are at greater risk of developing PAH than are patients with dcSSc (15–17). Yet, in each of these studies, the diagnosis of PAH was not always confirmed using RHC, and therefore, one cannot exclude the possibilities of false-positive results or postcapillary PH in a proportion of cases. In addition, lcSSc is estimated to be 3–5 times more frequent than dcSSc in Western Europe (3,18,19), and as a result, lcSSc may appear more frequently in association with PAH. In the Mukerjee study (13), 25% of 148 patients with PAH associated with SSc exhibited dcSSc, corresponding to the natural distribution of SSc in Europe.

The observed incidence of postcapillary PH in the present study represents another important finding. Several patients with postcapillary PH had already been identified among, and excluded from, the original cohort of SSc patients in our previous study (3). Despite the exclusion of patients with disease of the left side of the heart at baseline, 10% of patients suspected of having PAH based on echocardiographic findings were ultimately diagnosed as having postcapillary PH (3). Postcapillary PH was diagnosed according to the findings of RHC in a further 8 patients during followup, but more than half of the patients had mild postcapillary PH diagnosed during exercise, emphasizing the importance of left ventricular diastolic disease in this patient population (20,21). This finding further emphasizes the necessity of confirming the diagnosis of PAH using RHC.

Another noteworthy observation from this study is the description of the natural history of patients with an mPAP above the normal physiologic range at study entry. Two of the 5 patients with an mPAP between 20 mm Hg and 25 mm Hg at study entry developed PAH within the 3-year followup period. Until now, little was known of the natural history of the disease in such patients. Our results support the hypothesis that these patients may be at greater risk of developing PAH over time, and we believe they should be carefully monitored. It is interesting to note that in 1 of these patients, it was necessary to measure hemodynamics by RHC during exercise to confirm the diagnosis of PAH.

The small number of patients with incident PAH did not allow for multivariate analysis to investigate the characteristics that may be predictive of incident PAH. It is well known that an isolated reduction in the DLco value can precede PAH for several years (22,23). Of the 8 patients who were diagnosed as having PAH during the followup period, 5 had a DLco level that was <50% of the predicted value at baseline. However, 3 of the 8

patients had a DLco level that was >60% at baseline, yet they still developed PAH. A DLco level <60% with normal lung volumes is reported to be strongly associated with echocardiographically diagnosed PH (24). Nevertheless, 4 of our 8 patients with postcapillary PH exhibited a DLco level <60%, confirming that the DLco, like the VTR or the echocardiographically estimated systolic PAP, should not be considered a surrogate marker for PAH (10). Although patients with a history of digital ulcers may exhibit more severe vasculopathy than do patients without such a history, we did not observe any association between a history of digital ulceration and incident PAH.

While this study provides important observations, there are a number of theoretical limitations that must be acknowledged. The exclusion at entry of patients with severe lung fibrosis or with significant disease of the left side of the heart may have led to an underestimation of the incidence of PAH, PH associated with severe pulmonary fibrosis, or postcapillary PH in these 2 populations. In addition, analyses were conducted only in the population of patients who completed all procedures listed in the screening algorithm for the diagnosis of PAH in SSc. We are therefore unable to quantify the incidence of PAH among patients who did not undergo all protocol procedures. A total of 109 patients did not undergo echocardiography during the 3-year followup, and 6 patients did not undergo RHC despite the suspected presence of PAH. These patients were therefore excluded from the analyses. Exhaustive data on mortality were obtained from the records of deaths and were investigated in these patients, and none had died of PAH during the followup period. Nevertheless, we cannot exclude the possibility that some of these patients may have developed PH or PAH that was not fatal.

Another potential limitation is that 1 of the centers and 1 investigator at another center involved in the original ItinérAIR-Sclérodermie Study did not participate in this 3-year followup study. Together, they contributed 45 patients (7.5%) to the 599 that were enrolled in the original study population. Furthermore, an unknown pool of SSc patients followed up at non-specialist centers may also exist. In addition, there may be differences in the referral patterns between the participating centers. We believe, however, that our results can be generalized, since our study population was comparable with other large series (13,25).

The results of this study, similar to the recent study reported by Hsu et al (10), suggest that the evaluation of pulmonary artery pressures during exercise may be beneficial in the detection of hemodynamic

abnormalities. Most patients who underwent RHC in the present study, however, were tested only at rest. This may have allowed the true incidence of PAH to be underestimated.

In conclusion, we have demonstrated by using a revised screening algorithm for diagnosis of PAH, which was based on the presence of dyspnea and the findings of Doppler echocardiographic evaluation of VTR to refer patients for RHC, that the incidence of PH in a selected population of SSc patients is 1.37 cases per 100 patient-years. The incidence of PAH was observed to be 0.61 cases per 100 patient-years. Our findings also serve as verification of the reason why RHC should be mandatory for the confirmation of a diagnosis of PAH, since postcapillary PH is frequent among patients with SSc and may mimic PAH. The implementation of echocardiographic screening programs for PAH associated with SSc should be performed in designated expert centers by multidisciplinary teams.

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### AUTHOR CONTRIBUTIONS

Dr. Hachulla had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study design.** Hachulla, de Groote, Gressin, Carpentier, Kahan, Cabane, Clerson, Guillevin, Humbert.

**Acquisition of data.** Hachulla, de Groote, Sibilia, Diot, Carpentier, Mouthon, Hatron, Jego, Allanore, Tieb, Agard, Cosnes, Cirstea, Constans, Farge, Viallard, Harle, Patat, Imbert, Kahan, Cabane, Humbert.

**Analysis and interpretation of data.** Hachulla, de Groote, Allanore, Kahan, Cabane, Clerson, Guillevin, Humbert.

**Manuscript preparation.** Hachulla, de Groote, Gressin, Sibilia, Diot, Carpentier, Mouthon, Hatron, Allanore, Tieb, Agard, Farge, Harle, Cabane, Clerson, Guillevin, Humbert.

**Statistical analysis.** Hachulla, Clerson, Humbert.

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#### **APPENDIX A: ITINÉRAIR-SCLÉRODERMIE STUDY GROUP INVESTIGATORS AND STUDY CENTERS**

The ItinérAIR-Sclérodermie Study Group investigators who participated in the 3-year followup study were as follows (grouped by

location in France): Jean-François Viallard, Marie-Sylvie Doutre, Thierry Schaeverbeke, Marc-Alain Billès, Patricia Réant, and Claire Dromer (Bordeaux 1); Joël Constans, Philippe Gosse, and Philippe Lemetayer (Bordeaux 2); Antoine-Béclère: Marc Humbert, Olivier Sitbon, Xavier Jaïs, Abdul Monem Hamid, Vincent Ios, and Gérald Simonneau (Clamart); Anne Cosnes and Cécile Roiron (Henri-Mondor, Crétteil); Patrick Carpentier, Jean-Luc Cracowski, Carole Saurier, Muriel Salvant, Carole Schwobel, and Christophe Pison (Grenoble); Eric Hachulla, Pierre-Yves Hatron, David Launay, Viviane Queyrel, Marc Lambert, Sandrine Morell-Dubois, Hilaire Charlanne, Pascal de Groote, and Nicolas Lamblin (Lille); Jacques Ninet, Fadi Jamal, Geneviève Dérumeaux, and Jean-Yves Bayle (Lyon); Jean-Robert Harlé, Frédérique Retornaz, Gilbert Habib, Sébastien Renard, and Martine Reynaud-Gaubert (Marseilles); Daniela Cirstea, Jean-Dominique de Korwin, Christine Suty-Selton, and François Chabot (Nancy); Christian Agard, Mohamed Hamidou, Jean-Pierre Gueffet, Patrice Guérin, Erwan Bressolette, and Alain Haloun (Nantes); Thomas Papo, Olivier Lidove, Catherine Picard-Dahan, and David Messika-Zeitoun (Bichat, Paris); André Kahan, Yannick Allanore, Laure Cabanes, and Christian Spaulding (Cochin 1, Paris); Loïc Guillemin, Luc Mouthon, and Alice Berezné (Cochin 2, Paris); Camille Francès, Sellim Trad, Emmanuel Molinari, Anne-Claude Koeger, and Dominique de Zuttere (La Pitié-Salpêtrière, Paris); Jean Cabane, Kiet Phong Tieb, Stéphanie Ederhy, Nadjib Hammoudi, and Mohamed Ziani (St. Antoine, Paris); Isabelle Lazareth, Ulrike Michon-Pasturel, Yara Antakly-Hanon, and Jacques Serfaty (St. Joseph, Paris); Dominique Farge and Suzanne Ménasché (St. Louis, Paris); Patrick Jego, Jacqueline Chevrant-Breton, and Marcel Laurent (Rennes); Jean Sibilia, Hélène Petit, and Ari Chaouat (Strasbourg); Daniel Adoue, Nathalie Blot-Souletie, and Bruno Degano (Toulouse); and Elisabeth Diot, Laurent Machet, Frédéric Patat, Christian Marchal, and Cédric Giraudeau (Tours).