Incidence of pulmonary hypertension and determining factors in patients with systemic sclerosis

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ABSTRACT The objective of this study was to evaluate the incidence of pulmonary hypertension (PH) and determining factors in patients with systemic sclerosis (SSc) and a diffusing capacity of the lung for carbon monoxide (D_{LCO}) <60% predicted.

In this bicentric, prospective cohort study, patients with SSc were clinically assessed at baseline and after 3 years, including right heart catheterisation (RHC). Analysis of determining factors for the development of PH was performed using univariate and multivariate analyses.

96 patients with a mean pulmonary arterial pressure (mPAP) <25 mmHg at baseline were followed for 2.95±0.7 years (median 3 years). Of these, 71 had a second RHC; 18 of these 71 patients (25.3%) developed PH, and five (7%) developed SSc-associated pulmonary arterial hypertension. For patients with an mPAP of 21–24 mmHg at baseline, the likelihood of presenting with PH as opposed to normal pressures on follow-up was significantly higher (p=0.026). Pulmonary vascular resistance, tricuspid regurgitation velocity, diffusion capacity and the size of the inferior vena cava at baseline were independent predictors for the development of PH during follow-up.

In a selected cohort of SSc patients with a D_{LCO} <60%, pulmonary pressures appeared to rise progressively during follow-up. In this population, it was possible to identify manifest PH in almost 25% of patients using prospective RHC during follow-up. Therefore, regular clinical assessment including RHC might be useful in patients with SSc.

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Introduction

Pulmonary hypertension (PH) is a common complication of systemic sclerosis (SSc) that can occur at any stage of the disease. It has been observed in 15–27% of symptomatic patients and in 8–12% of asymptomatic patients using right heart catheterisation (RHC) for screening [1, 2]. If there is no other underlying disease, *i.e.* heart or lung disease, causing the PH, the disease is classified as SSc-associated pulmonary arterial hypertension (SSc-APAH). Three-year survival for patients with untreated SSc-APAH is estimated to be 56%, compared with 91% in patients without pulmonary arterial hypertension (PAH) [3, 4]. At PAH diagnosis, >85% of patients with SSc are already in advanced stages of the disease (World Health Organization (WHO) functional classes III and IV) [3]. Today, 10 PAH-targeted drugs are available for these patients [5]; these have already been shown to improve symptoms, exercise capacity and outcome. Therefore, an early diagnosis of PH and APAH is essential in patients with SSc.

The diagnosis of PAH is defined by a mean pulmonary arterial pressure (mPAP) $\geqslant$25 mmHg at rest, a pulmonary arterial wedge pressure $\leqslant$15 mmHg and a pulmonary vascular resistance (PVR) >3 Wood units, measured by RHC [6]. A normal mPAP at rest is 14±3 mmHg with an upper limit of approximately 20 mmHg [6, 7]. According to current guidelines, the clinical significance of an mPAP of 21–24 mmHg is not known [5].

Patients at high risk of developing PH, *e.g.* patients with connective tissue disease, who present with mPAP values within this range should be carefully monitored [6]. Recent data in SSc patients have shown that pulmonary arterial pressures of 21–24 mmHg lead to decreased exercise capacity and higher hospitalisation and mortality [8–10]. In retrospective studies, SSc patients with an mPAP of 21–24 mmHg were more likely to develop PAH than patients with normal pulmonary arterial pressure [11, 12].

In 2014 the DETECT algorithm supplied the first evidence-based approach to early detection of SSc-APAH [13]. Visovatti *et al.* [14] characterised borderline pulmonary arterial pressures as an individual subgroup of SSc in a representative *post hoc* analysis of the DETECT study cohort and hypothesised that this is an intermediate stage between normal pulmonary arterial pressures and PAH.

Determinants of PAH in SSc have already been investigated in several studies [15–19]. In a prospective cohort study, Allanore *et al.* [17] found that N-terminal pro-brain natriuretic peptide (NT-proBNP) and the diffusing capacity of the lung for carbon monoxide (*D*LCO) divided by alveolar volume (*V*A), also referred to as the transfer coefficient of the lung for carbon monoxide (*K*CO), had prognostic relevance for the development of PAH in SSc. An association of SSc-APAH with low *D*LCO has been confirmed by several cohort studies [15, 16, 18, 19]. These studies were, however, mostly retrospective and did not include systematic assessment of haemodynamic parameters by RHC in all patients.

In the DETECT study, using only echocardiography at rest missed about 50% of PH diagnoses. Therefore, a study with a systematic assessment of haemodynamic parameters by RHC of all patients during follow-up is needed to assess the true incidence and determinants of PAH in SSc.

The aim of this study was to assess the incidence of PH in patients with SSc, to characterise the clinical course of the patients and to investigate determining factors for PH during follow-up. A specific focus was set on the clinical course of patients who presented with borderline pulmonary arterial pressures at baseline.

Material and methods

Study population and design

Patients who were included in the DETECT study in London and Heidelberg who did not have PH when they were initially screened using RHC were systematically followed and reassessed after 3 years. In addition, each centre recruited 10 additional DETECT-eligible patients without PH, who agreed to be followed up.

Inclusion criteria were age $\geqslant$18 years, a diagnosis of SSc according to American College of Rheumatology criteria, and >3 years of non-Raynaud symptoms or mixed connective tissue disease [20]. Patients with SSc who were receiving endothelin receptor antagonists or other targeted PAH therapy were not included.

Clinical examinations at baseline and after 3 years comprised a medical history; assessment of vital signs, lung function, diffusion capacity and 6-min walking distance (6MWD); echocardiography; laboratory tests, including measurement of NT-proBNP; and RHC, which was performed according to the current guidelines [5].

After the final assessment, including the second RHC, patients were followed up during their hospital visits or contacted *via* telephone for survival analysis.

Significant lung disease was evaluated by lung function tests and high-resolution computed tomography (HRCT). Lung involvement of SSc was considered significant when the forced vital capacity (FVC) was

<60% or HRCT showed severe fibrosis, or when FVC was 60–70% and HRCT was "not available" or the fibrosis was moderate-severe, or, in cases of other lung diseases apart from fibrosis, through the clinical decision of the treating physician. In the case of suspected coronary artery disease and in patients with elevated wedge pressures, patients were referred for left heart catheterisation.

The study was conducted in accordance with the Declaration of Helsinki. All patients gave written informed consent for the study. The study was approved by the ethics committees of the University of Heidelberg and the Royal Free Hospital, London, which were based on ethics committee approvals for the DETECT study registered on clinicaltrials.gov (no. NCT00706082).

Statistical analysis

Data were analysed by two statisticians (CF and NB). Values are presented as mean±SD or n (%). Baseline and follow-up characteristics of patients with borderline (21–24 mmHg) *versus* normal (<21 mmHg) mPAP at baseline were compared using the 2*3 Chi-squared test with two degrees of freedom. Individual changes over time were analysed by the Wilcoxon signed rank test.

Determining factors of PH were analysed using a two-step approach: the first step was Pearson regression analysis, including univariate analysis, for variable selection; the second step was a multivariate stepwise forward procedure with the centre as the fixed factor. Parameters for univariate analysis were selected according to clinical significance. Only parameters with >80% valid values were considered for the uni- and multivariate analysis.

Analysis of survival was performed using the Kaplan–Meier method. The date of initial screening served as the baseline date. Patients were regarded as censored at their last date of contact with the study team. The end point for survival was either death by any cause or lung transplantation. p-values <0.05 were considered statistically significant.

Results

The baseline analysis included 96 patients (81 female, 75% limited cutaneous SSc, 66% WHO functional class ⩾II) with 48 patients from each centre. In 83 patients (86.5%), a clinical follow-up assessment was performed after 2.95±0.7 years (median 3 years). RHC was used to assess haemodynamic parameters in 71 patients (74%) during follow-up. A total of 12 patients refused an invasive assessment, one of whom was pregnant at the time of the 3-year follow-up and one of whom had newly diagnosed lung cancer. None of these patients showed clinical signs of PH. Thus, our final study group consisted of 71 patients who were assessed by a second RHC during follow-up. During the course of the study, 14 patients developed lung involvement of SSc: 11 patients had an FVC <60%, and three patients showed an FVC of 60–70% and "moderate-severe" lung disease on HRCT. A further nine patients were considered to have significant lung disease according to the treating physician. Patient characteristics at baseline are given in table 1. An extended description of all patients at baseline and in several subgroups is given in the supplementary tables.

Incidence of pulmonary hypertension

PH with an mPAP ⩾25 mmHg was detected in 18 patients (25.3%, 95% CI 15.7–37.1) during follow-up. Patients with an mPAP of 21–24 mmHg at baseline were significantly more likely (p=0.026) to present with PH during follow-up compared with patients with normal pressures (figure 1). The incidence for PH in the cohort of 71 patients who had a second RHC was 6.11 per 100 patient-years (95% CI 3.67–9.5). Of the 18 patients with PH at the second RHC, five had PH due to left heart disease and eight due to lung disease. Five patients (7%, 95% CI 2.3–15.7) were diagnosed with SSc-APAH during follow-up.

Progression of haemodynamic and clinical parameters during follow-up

The study cohort showed a significant worsening in 6MWD, NT-proBNP levels, lung function parameters (FVC, forced expiratory volume in 1 s (FEV_1)), diffusion capacity (D_{LCO}, K_{CO}, D_{LCO} %, K_{CO} %), echocardiography (tricuspid regurgitation velocity (TRV)/systolic pulmonary arterial pressure (sPAP)) and invasive haemodynamic parameters (mPAP, PVR) (table 2). During the course of the study, mean right atrial pressure (RAP) significantly increased by 1.3±3.5 mmHg (p=0.001). The change in RAP (baseline to follow-up) between patients with normal and borderline pressures did not significantly differ (p=0.076). The rate of progression to PAH was 3 of 21 (14%) with an mPAP of 21–24 mmHg at baseline *versus* 2 of 50 (4%) with normal mPAP at baseline. When looking at PH, the rate of progression was 7 of 21 (33%) for patients with an mPAP of 21–24 mmHg at baseline and 11 of 50 (22%) for patients with normal mPAP. In this population of SSc patients with a D_{LCO} <60%, the change in mPAP from baseline to 3 years did not significantly differ between patients presenting with normal mPAP (+4.26±6.01 mmHg) and those with borderline pressures (+2.81±3.98 mmHg) at baseline.

TABLE 1 Demographics of study cohort at baseline n=96

Characteristic	n (%) or mean±SD
Sex	
Female	81 (84.4)
Demography	
Age years	56.2±12.0
Body height cm	164.5±8.6
Body weight kg	68.1±14.5
BMI kg·m^{-2}	25.2±4.8
Vital signs	
Systolic blood pressure mmHg	117.8±17.4
Diastolic blood pressure mmHg	72.0±10.8
Heart rate beats per min	76.8±12.1
SSc characteristics	
Modified Rodnan Skin Score#	11.9±8.8
Duration months	11.5±9.6
Type of SSc¶	
Diffuse cutaneous	15 (15.6)
Limited cutaneous	71 (74.0)
Mixed connective tissue disease	10 (10.4)
WHO functional class#	
I	22 (22.9)
II	33 (34.4)
III	31 (32.3)

BMI: body mass index; SSc: systemic sclerosis; WHO: World Health Organization. #: Modified Rodnan Skin Score and WHO functional class as obtained in clinical examination; ¶: type of SSc as diagnosed by the treating rheumatologist.

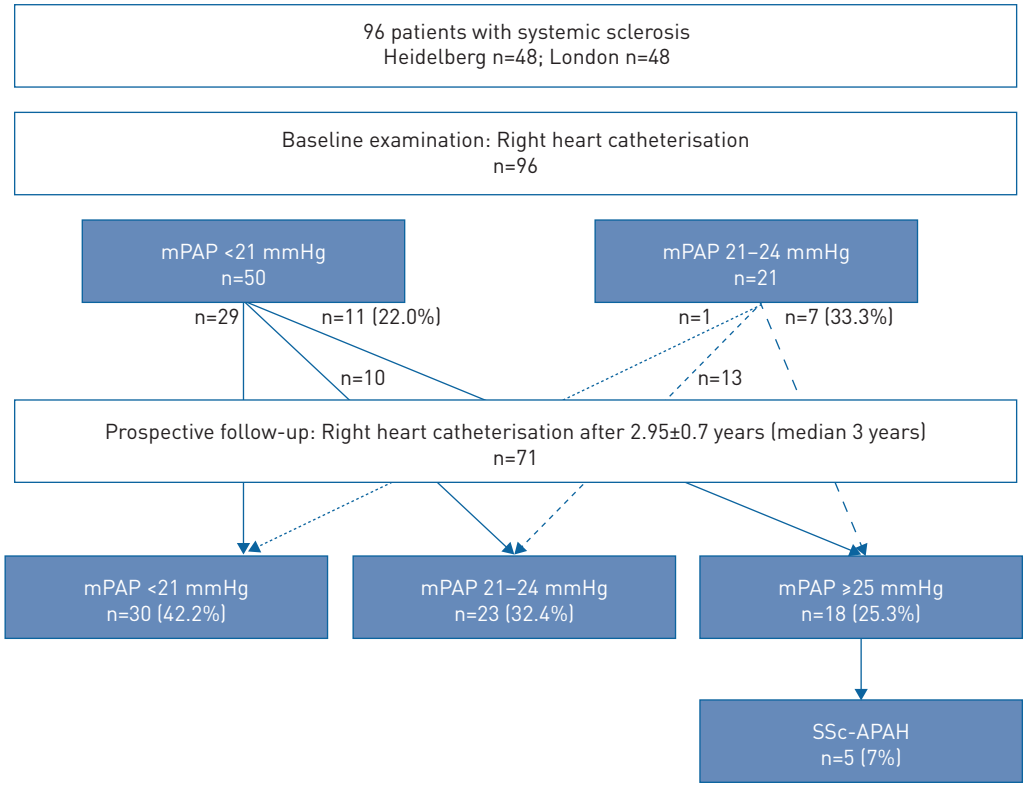

FIGURE 1 Clinical course and classification of patients throughout the study. The distribution of patients during follow-up significantly differed between patients with a baseline mean pulmonary arterial pressure (mPAP) of 21–24 mmHg (seven manifest, one normal) and patients with an mPAP <21 mmHg (11 manifest, 29 normal; Chi-squared p<0.026). SSc-APAH: systemic sclerosis-associated pulmonary arterial hypertension.

TABLE 2 Clinical data at baseline and during follow-up

	Baseline		Follow-up #		Change	p-value
	n	mean±SD	n	mean±SD	mean±SD	
6MWD	91	403.2±111.4	66	388±125	−21.8±79.3	0.039
NT-proBNP pg·mL^{-1}	95	216±266	77	396±1068	188±1030	0.005
Pulmonary function testing						
FVC L	94	2.9±1.0	75	2.7±1.0	−0.1±0.3	0.005
FVC %	96	91.2±23.7	76	89.2±24.6	−1.1±11.9	NS
FEV1 L	94	2.2±0.8	74	2.0±0.8	−0.1±0.3	<0.001
FEV1 %	95	85.7±22.9	75	82.6±21.7	−1.3±11.8	NS
*D*LCO mmol·min^{-1}·kPa^{-1}	93	7.5±4.0	68	3.9±1.5	−4.0±4.0	<0.001
*D*LCO %	95	48.9±10.8	70	46.3±11.8	−3.1±8.2	<0.001
*K*CO mmol·min^{-1}·kPa^{-1}·L^{-1}	93	2.5±1.5	69	1.5±1.1	−1.3±1.9	<0.001
*K*CO %	93	71.4±16.9	69	67.7±17.1	−5.1±23.0	0.011
TLC %	83	85.8±22.3	70	89.7±22.9	2.7±11.4	NS
RV %	84	85.8±33.1	63	94.4±34.2	5.5±23.1	NS
Echocardiography						
LA mm	93	29.1±6.4	72	30±7	0.5±6.4	NS
IVC mm	82	14.0±3.7	64	13±6	−2.0±6.8	NS
IVS mm	92	10.1±1.8	40	10±2	0.0±3.2	NS
RA cm^2	89	12.1±3.7	72	12.7±4.0	0.2±4.2	NS
RVD mm	85	29.1±5.6	42	31±7	3.8±7.6	0.01
RV cm^2	88	14.5±4.3	72	13.2±3.7	−1.2±4.1	0.043
LV-EDD mm	92	44.1±5.5	42	42±8	−1.5±8.5	NS
LV-ESD mm	91	27.0±5.1	42	27±7	0.0±7.0	NS
TRV m·s^{-1}	88	2.4±0.4	63	2.6±0.4	0.1±0.5	0.019
TAPSE mm	89	22.5±4.6	77	22±5	−0.4±6.1	NS
sPAP mmHg	87	29.1±7.1	63	32±9	3.1±9.1	0.017
Right heart catheterisation						
mPAP mmHg	96	17.1±4.0	71	22±6	3.8±5.5	<0.001
PAWP mmHg	96	8.5±3.3	71	11±3	1.9±4.3	<0.001
TPG mmHg	96	8.5±2.9	71	9±3	0.1±2.6	NS
CO L·min^{-1}	96	5.3±1.2	71	5.1±1.1	−0.1±0.9	NS
PVR dynes	96	135±55.4	71	182±118	43.5±96.1	0.001

6MWD: 6-min walking distance; NT-proBNP: N-terminal pro-brain natriuretic peptide; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 s; *D*LCO: diffusing capacity of the lung for carbon monoxide; *K*CO: transfer coefficient of the lung for carbon monoxide; TLC: total lung capacity; RV: residual volume; LA: left atrium; IVC: inferior vena cava; IVS: interventricular septum; RA: right atrium; RVD: right ventricular diameter; RV: right ventricle; LV: left ventricle; EDD: end-diastolic diameter; ESD: end-systolic diameter; TRV: tricuspid regurgitation velocity; TAPSE: tricuspid annular plane systolic excursion; sPAP: systolic pulmonary arterial pressure; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; TPG: transpulmonary gradient; CO: cardiac output; PVR: pulmonary vascular resistance; NS: nonsignificant. #: follow-up after 3 years.

One outlier was detected in the NT-proBNP values, probably due to measurement errors. At baseline, this patient had an NT-proBNP value of 7000 ng·mL^{-1}, normal right ventricular function, creatinine of 1.15 mg·dL^{-1} and uric acid of 4.0 mg·dL^{-1}, but developed lung cancer within the study period. Because neither right ventricular function nor renal function explains the NT-proBNP value, this NT-proBNP value was excluded from the analysis. Within the whole cohort, NT-proBNP showed a significant increase (Wilcoxon rank test p=0.005) throughout the study. The increase in NT-proBNP did not significantly differ between patients with normal mPAP at baseline and those with an mPAP of 21–24 mmHg (<21 mmHg 195.9±1199.5 ng·mL^{-1}, median 13; 21–24 mmHg 168.8±404.0 ng·mL^{-1}, median 42.5).

Comparison of mPAP <21 mmHg and 21–24 mmHg at baseline

Patients presenting with an mPAP of 21–24 mmHg at baseline showed significantly lower 6WMD, *D*LCO % and cardiac output, and significantly higher TRV, sPAP, transpulmonary gradient and PVR, both at baseline and during follow-up (all p<0.05; table 3). Lung function parameters at baseline were significantly worse in patients with an mPAP of 21–24 mmHg, including FVC, FEV1, FEV1 % predicted (% pred), percentage of total lung capacity and percentage of residual volume (all p<0.05). For some parameters baseline values did not differ; however, at follow-up the right atrial area was significantly larger (p=0.037)

TABLE 3 Comparison of patients presenting with a mean pulmonary arterial pressure (mPAP) of <21 mmHg *versus* 21–24 mmHg at baseline

	Baseline					Follow-up				
	mPAP <21 mmHg		mPAP 21–24 mmHg		p-value	mPAP <21 mmHg		mPAP 21–24 mmHg		p-value
	n	mean±SD	n	mean±SD		n	mean±SD	n	mean±SD	
6MWD	69	431±93	22	317±122	<0.001¶	49	419±107	17	298±131	0.002¶
NT-proBNP pg·mL^{-1}	72	206±263	23	245±278	0.255	54	401±1243	23	384±452	0.181
Pulmonary function testing										
FVC L	71	2.99±1.00	23	2.43±0.75	0.023¶	56	2.76±1.06	19	2.41±0.68	0.172
FVC %	72	92.90±24.09	24	86.02±21.97	0.233	55	88.92±25.69	21	90.07±21.92	0.963
FEV_1 L	71	2.39±0.88	23	1.78±0.51	0.004¶	55	2.14±0.87	19	1.75±0.49	0.113
FEV_1 %	72	88.43±24.16	23	77.02±15.73	0.050¶	55	83.32±23.25	20	80.65±16.90	0.545
D_{LCO} mmoL·min^{-1}·kPa^{-1}	70	7.26±4.18	23	8.06±3.58	0.228	50	3.97±1.01	18	3.57±2.41	0.003¶
D_{LCO} %	71	50.78±9.56	24	43.18±12.54	0.013¶	50	49.44±10.13	20	38.55±12.15	<0.001¶
K_{CO} mmoL^{-1}·min^{-1}·kPa·L^{-1}	70	2.35±1.59	23	2.93±1.10	0.061	51	1.44±1.09	18	1.53±1.31	0.280
K_{CO} %	70	72.80±16.55	23	67.33±17.64	0.226	51	69.14±16.93	18	63.65±17.28	0.170
TLC %	63	88.80±21.83	20	76.21±21.57	0.028¶	52	92.52±21.68	18	81.58±24.96	0.070
RV %	63	91.56±32.66	21	68.55±28.82	0.002¶	45	99.68±33.38	18	81.36±33.68	0.084
Echocardiography										
LA mm	71	28.14±6.48	22	32.10±4.95	0.007¶	52	30.07±6.22	20	30.45±7.38	0.262
IVC mm	65	13.83±3.61	17	14.50±3.96	0.432	47	12.50±6.01	17	12.59±5.38	0.681
IVS mm	70	10.12±1.81	22	9.96±1.80	0.832	23	9.66±2.51	17	10.79±2.19	0.196
RA cm^2	68	11.76±3.37	21	13.14±4.64	0.317	52	12.15±3.77	20	14.11±4.48	0.037¶
RVD mm	65	29.89±5.70	20	26.36±4.16	0.003¶	22	31.10±7.41	20	30.92±5.68	0.830
RV cm^2	68	14.25±4.05	20	15.19±5.18	0.495	52	13.19±3.59	20	13.38±3.94	0.692
LV-EDD mm	70	43.54±5.58	22	46.03±4.98	0.062	23	41.51±9.50	19	42.86±6.83	0.889
LV-ESD mm	69	26.64±5.13	22	28.18±5.05	0.238	23	25.90±7.84	19	27.45±5.51	0.486
TRV m·s^{-1}	65	2.35±0.36	23	2.65±0.30	<0.001¶	23	2.48±0.36	16	2.88±0.45	0.003¶
TAPSE mm	68	22.82±3.92	21	21.64±6.37	0.157	23	23.02±4.98	22	19.75±3.78	0.004¶
sPAP mmHg	64	27.54±6.78	23	33.43±6.27	<0.001¶	23	30.16±7.31	16	38.97±10.56	0.003¶
Right heart catheterisation										
mPAP mmHg	72	15.40±3.03	24	22.17±0.96	<0.001¶	50	20.12±5.86	21	24.95±4.12	<0.001¶
PAWP mmHg	72	7.65±2.99	24	11.08±2.67	<0.001¶	50	10.74±3.83	21	11.24±2.53	0.407
TPG mmHg	72	7.69±2.63	24	10.83±2.60	<0.001¶	50	7.84±2.22	21	10.90±2.43	<0.001¶
CO L·min^{-1}	72	5.44±1.17	24	4.90±1.13	0.048¶	50	5.24±1.22	21	4.86±0.88	0.048¶
PVR dynes	72	117.48±39.04	24	188.39±63.37	<0.001¶	50	151.48±101.02	21	253.70±126.82	<0.001¶
RAP mmHg	72	3.76±2.33	24	5.00±2.50	0.03¶	48	5.65±2.89	21	5.43±2.23	0.76

6-MWD: 6-min walking distance; NT-proBNP: N-terminal pro-brain natriuretic peptide; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; D_{LCO}: diffusing capacity of the lung for carbon monoxide; K_{CO}: transfer coefficient of the lung for carbon monoxide; TLC: total lung capacity; RV: right ventricle; LA: left atrium; IVC: inferior vena cava; IVS: interventricular septum; RA: right atrium; RVD: right ventricular diameter; LV: left ventricle; EDD: end-diastolic diameter; ESD: end-systolic diameter; TRV: tricuspid regurgitation velocity; TAPSE: tricuspid annular plane systolic excursion; sPAP: systolic pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; TPG: transpulmonary gradient; CO: cardiac output; PVR: pulmonary vascular resistance; RAP: right arterial pressure. #: follow-up after 3 years; ¶: denotes statistically significant differences.

and tricuspid annular plane systolic excursion showed significantly lower values (p=0.004) in patients with an mPAP of 21–24 mmHg compared to those with an mPAP of <21 mmHg at baseline.

Determining factors of mPAP during follow-up

Results of univariate and multivariate analyses are given in table 4. High PVR at baseline was an independent predictor of the development of PH during follow-up (r=0.460, p=0.002). When only parameters of noninvasive assessments were included in the analysis, elevated TRV measured by echocardiography, low diffusion capacity and enlarged size of inferior vena cava were further independent predictors of PH during follow-up (final model p<0.001).

Prognostic factors of survival

Eight patients died during follow-up owing to pulmonary fibrosis (n=2), PH (n=2; one PAH, one post-capillary PH), cancer (n=2), primary biliary cholangitis (n=1) and left heart failure (n=1). The earliest

TABLE 4 Baseline parameters predictive of mean pulmonary arterial pressure during follow-up

Variable	n	p-value	Pearson's R
Univariate analysis			
Age	71	0.016	0.286
Duration of systemic sclerosis	70	0.954	0.007
WHO functional class	70	0.485	0.084
Lung function			
FVC	69	0.051	−0.236
FEV_1	69	0.017	−0.286
FEV_1 %	70	0.057	−0.229
D_{LCO} %	71	0.025	−0.265
K_{CO} %	69	0.028	−0.265
NT-proBNP	69	755	38
6MWD	66	0.097	0.206
Echocardiography			
IVC	58	0.04	0.271
Right atrial area	64	0.167	0.175
Right ventricular area	63	0.828	0.028
TRV	66	0.003	0.360
sPAP	65	0.004	0.351
Right heart catheterisation			
mPAP	71	0.001	0.402
TPG	71	<0.001	0.430
PVR	71	<0.001	−0.456
Multivariate analysis with centre as fixed factor			
Including invasive haemodynamic PVR	56	0.002	0.460
Only noninvasive parameters			
Model 1 TRV	56	0.003	0.439
Model 2 + K_{CO} %	56	0.046	0.512
Model 3 + IVC	56	0.02	0.577

WHO: World Health Organization; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; D_{LCO}: diffusing capacity of the lung for carbon monoxide; K_{CO}: transfer coefficient of the lung for carbon monoxide; NT-proBNP: N-terminal pro–brain natriuretic peptide; 6MWD: 6-min walking distance; IVC: inferior vena cava; TRV: tricuspid regurgitation velocity; sPAP: systolic pulmonary arterial pressure; mPAP: mean pulmonary arterial pressure; TPG: transpulmonary gradient; PVR: pulmonary vascular resistance.

death occurred after 1.0 year and the latest after 5.6 years of follow-up (mean=3.2 years, median=3.1 years). One further patient with lung cancer was lost to follow-up 3 years after baseline.

Survival was not significantly different between patients with an mPAP of 21–24 mmHg at baseline and those with an mPAP of <21 mmHg (p=0.217, figure 2a). While survival curves show congruency in patients with and without significant lung disease in the beginning, patients presenting with significant lung disease at baseline showed impaired survival compared to patients without significant lung disease after >40 months (p=0.029, figure 2b).

Discussion

This is the first prospective study to evaluate incidence and determining factors of PH in patients with SSc using a systematic screening assessment that included RHC at baseline and after 3 years. The high incidence of PH (25.3%) and PAH (7%) within this time suggests that performing regular clinical assessment with a low threshold for RHC is useful in at-risk SSc patients. Likewise, the development of cardiac and pulmonary diseases should be monitored with particular attention, because significant left heart disease developed in five patients and significant lung disease in eight patients simultaneously to the progression to PH within the 3-year study period. In our study, pulmonary pressure tended to rise on average over time. High PVR at baseline, elevated TRV, low diffusion capacity and enlarged size of inferior vena cava were independent predictors for the development of PH during follow-up. This provides further evidence that borderline pulmonary arterial pressure is a possible intermediate stage in the development of PH.

Incidence of PH/PAH

The incidence for PH in our cohort was 6.11 per 100 patient-years when only entering the 71 RHC-controlled patients into the calculation. Among those, the incidence of PAH was 7%, similar to the

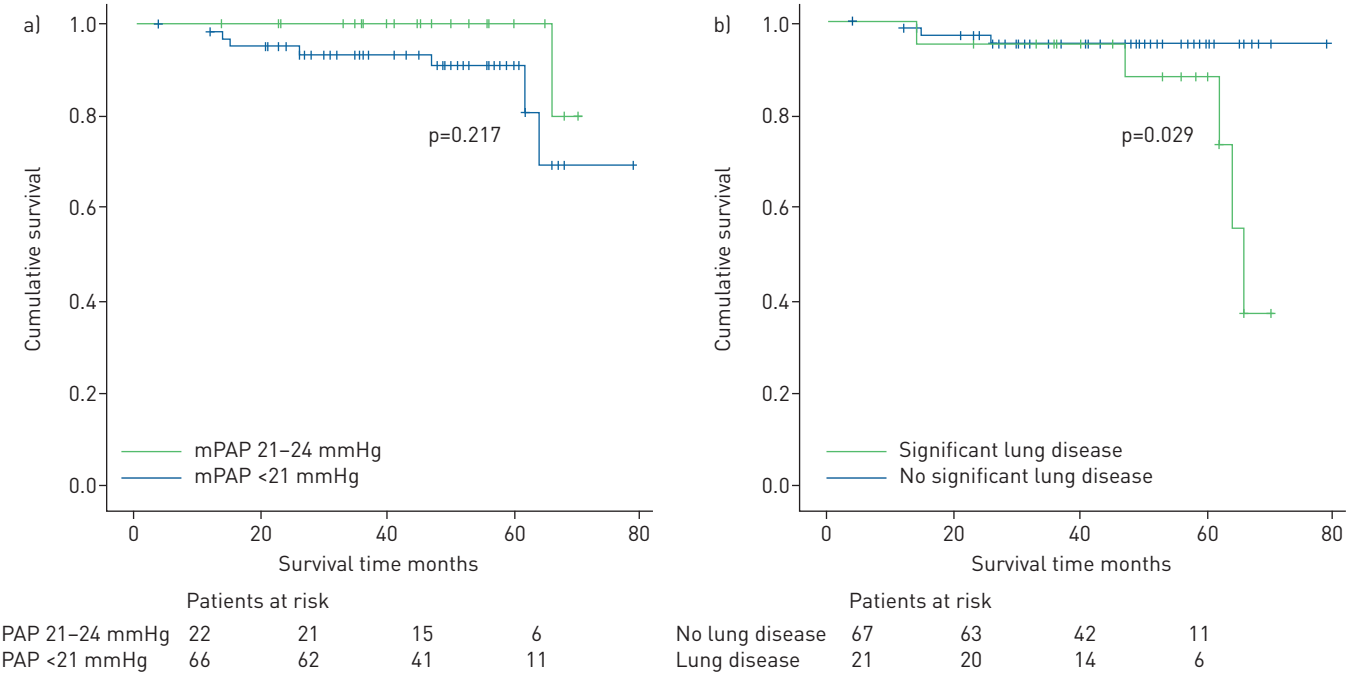

FIGURE 2 Survival analyses of a) patients with a baseline mean pulmonary arterial pressure (mPAP) of 21–24 mmHg *versus* <21 mmHg and b) patients with significant lung disease *versus* no significant lung disease. While mPAP at baseline did not affect survival, patients with significant lung disease presented with worse survival than patients without lung disease (p=0.029).

findings of Valerio *et al.* [12], where progression to PAH for all patients was 8.3% after 3 years. Of note, patients with pulmonary fibrosis were excluded from follow-up in the Valerio *et al.* [12] study, whereas patients with mild to moderate pulmonary fibrosis were included in the DETECT cohort.

Our results show a higher rate of development of PH than did two previous studies which analysed the incidence of PH [16, 21]. The estimated incidence of PH over a period of 3 years observed in a French nationwide study was 1.37 per 100 patient-years; incidences did not differ between PAH and post-capillary PH [21]. In an Italian study, PH incidence was 1.85 per 100 patient-years [16]. In both studies, only patients who presented with suspected PH by clinical presentation or TRV were selected for RHC. In a more recent study, Kovacs *et al.* [22] reported an incidence of 0.75 per 100 patient-years. In all of these studies, RHC was only performed in those suspected clinically or on noninvasive investigation of having developed PAH.

In contrast to Hachulla *et al.* [21], Iudici *et al.* [16] and Kovacs *et al.* [22], we used a systematic assessment *via* RHC in all patients, capturing all incident cases. In addition, our cohort was preselected for possible PAH, because patients with impaired *D*LCO were selected. Mean *D*LCO % at baseline was 73.2±18 in Hachulla *et al.* [21], 71±21 in Iudici *et al.* [16] and 82.2% (range 64.5–93.9) in Kovacs *et al.* [22], whereas our cohort had a *D*LCO % of 48.9±10.8. The low *D*LCO appears to be a major reason for the higher apparent incidence of PH in our cohort. A low *D*LCO may indicate the need to perform closer clinical and invasive follow-up in patients with SSc.

Comparison of mPAP groups: is "borderline" pulmonary pressure an interim stage?

A retrospective analysis of the DETECT cohort patients with borderline pulmonary arterial pressures showed significantly higher NT-proBNP, larger left atrium diameter and a greater TRV than in patients with normal pulmonary haemodynamic parameters [14]. 6MWD was not significantly different in this cohort [14].

In our study, patients with borderline pulmonary arterial pressures at baseline showed a significantly lower 6MWD, *D*LCO % and cardiac output, and higher TRV, sPAP, transpulmonary gradient and PVR at baseline and in follow-up examinations. Tricuspid annular plane systolic excursion was significantly lower and the right atrial area significantly larger at follow-up in patients with borderline elevation of pulmonary arterial pressures. These findings are consistent with two studies that reported lower exercise capacity among patients with borderline pulmonary arterial pressure and suggested borderline PH as being indicative of early cardiopulmonary impairment [9, 11].

In our cohort, patients with an mPAP of 21–24 mmHg showed significantly poorer lung function at baseline than patients with an mPAP <21 mmHg. This suggests that pulmonary comorbidity is prevalent among those with mildly elevated pressures, as shown in the PHAROS registry, which reported a higher prevalence of pulmonary fibrosis and abnormal lung physiology in patients with an mPAP of 21–24 mmHg [23]. Kovacs *et al.* [9] also described a higher prevalence of cardiac comorbidity and decreased lung function in patients with borderline pulmonary arterial pressures. Thus, the nature of the PH identified among populations during follow-up may also depend on the rigor with which cardiac and pulmonary comorbidity were excluded.

Determining factors of developing PH

A reduction in *D*LCO is a frequent finding in SSc and PH [24]. Compared to other PAH subgroups, patients with both connective tissue disease and APAH show lower *D*LCO [25, 26]. In our study, *K*CO % was a significant predictor of developing PH, along with enlarged size of the inferior vena cava and TRV, when only noninvasive parameters were taken into account (final model p<0.001). Nevertheless, the effect size was small. Our findings are consistent with several previous studies that confirmed a strong association of *D*LCO with SSc-APAH [15, 16, 18, 19]. However, these studies were mostly retrospective and partially based on a diagnosis by echocardiography or did not use systematic RHC in all patients.

Mukerjee *et al.* [27] found the relationship between mPAP and *D*LCO to be weak and suggested that *D*LCO is an indicator of advanced rather than early PH, as had been suggested by Steen *et al.* [19].

In an analysis of echocardiographic parameters only, TRV and size of the inferior vena cava were significant predictors. TRV has already been identified as an independently associated factor in one study [14]; the inferior vena cava has not previously been reported as a predictor of mPAP or PH.

Progression of haemodynamic parameters, regardless of the baseline stage (mPAP group)

Our study cohort showed a significant worsening in lung function parameters (FVC, FEV1), diffusion capacity (*D*LCO, *K*CO, *D*LCO %, *K*CO %), 6MWD, echocardiography (sPAP/TRV) and invasive haemodynamic parameters (mPAP, PVR) during the course of the study. The change in mPAP from baseline to 3 years did not significantly differ between patients presenting with normal mPAP (+4.26 ±6.01 mmHg) and those with borderline pressures at baseline (+2.81±3.98 mmHg).

Our patients showed an increase in mPAP of 3.8±5.5 mmHg during a 3-year period; a recent study likewise showed an increase of 1.1 mmHg per year [12]. This supports previous observations [24] that patients with a reduced *D*LCO tend to show worsening of pulmonary haemodynamic parameters over time; however, without a catheter-based study of patients with normal gas transfers, we cannot be certain that this is not a general phenomenon among patients with SSc.

In the study by Kovacs *et al.* [22], no trend towards increasing pressures was observed in patients selected for repeat catheterisation, suggesting that progressive elevation of pulmonary pressures is not likely to occur in patients with a normal *D*LCO (mean 82%).

Limitations

Due to the DETECT inclusion criteria, this cohort comprised preselected SSc patients with a *D*LCO <60%, which can limit the study's generalisability to an unselected SSc population. In the analysis of determining factors, the study centre was included as a fixed factor to take centre effects into account. However, we cannot rule out difference between centres as a contributor to the findings. RHC was performed in only 71 out of 96 patients (74%) after 3 years. We do not know whether the other patients developed PH within 3 years. However, 83 patients (87%) were assessed during follow-up by noninvasive assessments. In patients who were not assessed by RHC, no clinical signs of PH were detected. The size of the cohort does not allow an independent assessment of the rate of progression to PH (7 of 21 with an mPAP of 21–24 mmHg, *versus* 11 of 50 with normal mPAP at baseline).

Conclusion

The results of this prospective study performing RHC at baseline and during follow-up in patients with SSc and reduced gas transfer indicate that there is a progressive elevation of pulmonary pressure in these patients. This would be expected to translate into an increased risk of PH and PAH in this population. Of the 18 patients with PH at the second RHC, five had PH due to left heart disease (27.8%) and eight due to lung disease (44.4%); concomitant diseases have to be taken into account during clinical follow-up. We also provide further evidence that borderline pulmonary arterial pressure is a possible intermediate stage in the development of PH. Using RHC during follow-up assessment, it was possible to identify manifest PH in almost 25% of patients, and PVR was an independent risk factor for developing manifest disease.

Therefore, it may be useful to perform regular clinical assessment including RHC in patients with SSc with reduced gas transfer until more reliable, noninvasive tools are developed.

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Conflict of interest: G. Coghlan received an unrestricted grant to support investigator-led study from Actelion Ltd, during the conduct of the study; and has received lecture fees and travel support from Bayer, lecture and consultancy fees from Actelion, and lecture fees from GSK, outside the submitted work. M. Distler has received grants and personal fees from Actelion, Bayer, Boehringer Ingelheim, Pfizer, Sanofi and Novartis, and personal fees from BiogenIdec, ChemomAb, espeRare foundation, Genentech/Roche, GSK, Inventiva, Lilly, medac, MedImmune, Pharmacyclics, Mitsubishi Tanabe Pharma, Sinoxa and UCB, outside the submitted work, to investigate potential treatments of scleroderma and its complications. In addition, M. Distler has a patent mir-29 for the treatment of systemic sclerosis licensed. C.P. Denton has received personal fees from Actelion, Bayer, Sanofi-Aventis, Boehringer Ingelheim, Roche, Bristol Myers Squibb and Merck-Serono, and grants and personal fees from GlaxoSmithKline and Inventiva, outside the submitted work. M. Doelberg is an employee of Actelion Pharmaceuticals Ltd. S. Harutyunova has received personal fees from Bayer, MSD, Actelion and GSK, outside the submitted work. A.M. Marra has received personal fees from Bayer, outside the submitted work. N. Benjamin has received lecture fees and travel support from Bayer, and lecture fees from Actelion, outside the submitted work. E. Grünig has received fees for lectures and/or consultations from Actelion, Bayer/MSD, GSK, United Therapeutics and Pfizer.

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