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

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Summary: This is the first prospective study indicating that borderline elevation of mPAP is associated with higher incidence of PH in high risk SSc-patients using systematic recatheterisation.

Abstract

Objective: The objective of this study was to evaluate the incidence of pulmonary hypertension (PH) and determining factors in patients with systemic sclerosis (SSc).

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

Results: Ninety-six patients with mean pulmonary artery pressure (mPAP) < 25 mmHg at baseline were followed 2.95±0.7 (median 3) years, 71 had a second RHC, 18 of the 71 patients (25,3%) developed PH, 5 (7%) a SSc-associated pulmonary arterial hypertension. Patients with mPAP between 21 and 24mmHg at baseline significantly more often presented PH or "borderline" pressures during follow-up ($p<0.001$). Pulmonary vascular resistance, tricuspid regurgitation velocity, diffusion capacity and size of inferior vena cava at baseline were independent predictive for development of PH during follow-up.

Conclusion: In SSc patients pulmonary pressures appear to rise progressively during follow up. Using RHC during follow-up it was possible to identify manifest PH in almost 25% of patients. Therefore, regular clinical assessment including RHC might be useful in SSc-patients.

Words: 205

Keywords: Systemic sclerosis, pulmonary hypertension, risk stratification

Introduction

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

The diagnosis of PAH is defined by a mean pulmonary arterial pressure ≥25 mmHg at rest, a pulmonary arterial wedge pressure ≤15 mmHg and a pulmonary vascular resistance >3 wood units, measured by right heart catheterization [6]. Normal mean pulmonary arterial pressures at rest are 14±3 mmHg with an upper limit of approximately 20 mmHg [6, 7]. According to the current guidelines, the clinical significance of a mean pulmonary arterial pressure between 21 and 24 is not known [5].

It is recommended, that patients who are at high risk to develop pulmonary hypertension, e.g. patients with connective tissue disease (CTD), who present with mean pulmonary arterial pressure 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, higher hospitalization and mortality [8-10]. In retrospective studies SSc-patients with mean PAP between 21- and 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. characterized borderline pulmonary arterial pressures as an individual subgroup of systemic sclerosis in a representative post-hoc analysis of the DETECT study cohort and hypothesized that this is an intermediate stage between normal pulmonary arterial pressures and PAH [14].

Determinants of PAH in SSc have already been investigated in several studies [15-19]. In a prospective cohort study Allanore et al. found DLCO/VA and NT-proBNP as being prognostically relevant for the development of PAH in SSc [17]. An association of SSc-APAH with low DLCO has been confirmed by several cohort studies [15, 16, 18, 19]. These studies were however mostly retrospective and did not include a systematic assessment of hemodynamics by right heart catheterization in all patients.

In the DETECT study, echocardiography at rest alone missed about 50% of PH diagnoses. Therefore, a study with a systematic assessment of hemodynamics by right heart catheterization 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 SSc-patients, characterisation of the clinical course of the patients and investigation of determining factors for PH during follow-up. Furthermore, 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 at initial screening using right heart catheterization were systematically followed and reassessed after 3 years. In addition, each centre recruited further 10 DETECT eligible patients without PH, who agreed to follow up.

For study inclusion patients ≥ 18 years of age were considered. SSc was diagnosed according to American College of Rheumatology criteria and a duration > 3 years of non-Raynaud symptoms or mixed connective tissue disease > 3 years was required [20]. SSc-patients receiving endothelin receptor antagonists or other targeted PAH-therapy were not included.

Clinical examinations at baseline and after 3 years comprised of medical history, vital signs, lung function, diffusion capacity, 6-minute walking distance, echocardiography, laboratory including NTproBNP and right heart catheterization. Right heart catheterization was performed according to the current guidelines [5].

After the final assessment including the second right heart catheterization, patients were followed by their hospital visits or contacted via phone for survival analysis.

Significant lung disease was evaluated by lung function test and high resolution computed tomography. Lung involvement of SSc was considered significant when FVC<60% or HRCT showed severe fibrosis or when FVC was 60%-70% and HRCT was „not available“ or fibrosis „moderate-severe“ or in case of other lung diseases apart from fibrosis by 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 catheterization.

The study was conducted in accordance with the declaration of Helsinki. All patients gave written informed consent to the study. The study was approved by the ethics committee of the University of Heidelberg and London which were based on ethics committee approvals for the DETECT-study that has been registered on clinicaltrials.gov (no. NCT00706082).

Statistical analysis

Data were analysed by two statisticians (CF and NB). Values are presented as mean ± standard deviation or n and percent, respectively. Baseline and follow-up characteristics of patients with borderline (21-24 mmHg) vs. normal (<21 mmHg) mPAP at baseline were compared using the 2*3 Chisqare test with two degrees of freedom. Individual changes during time were analysed by Wilcoxon signed rank test.

Analysis of determining factors of PH was performed by a two-step approach of Pearson regression analysis including univariate analysis for variable selection as first and multivariate stepwise forward procedure with centre as fixed factor as second step. Parameters for univariate analysis were selected according to clinical significance. For uni- and multivariate analysis, only parameters with more than 80% valid values were considered for the analysis.

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

Results

Ninety-six patients (81 female, 75% limited cutaneous SSc, 66% WHO functional class ≥II) with 48 patients from each centre were included in the baseline analysis. In 83 (86.5%) patients clinical follow-up assessment after 2.95±0.7 (median 3) years was performed. Assessment of hemodynamics by right heart catheterization was conducted in 71 (74%) patients during follow-up. Twelve patients refused invasive assessment, of whom one was pregnant at the time of the 3-year follow-up and one 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 within follow-up. Lung involvement of SSc developed in 14 patients during the course of the study, 11 patients had a FVC<60%, three patients showed FVC 60%-70% and HRCT „moderate-severe“ lung disease. Further 9 patients were considered as significant lung disease according to the treating physician. Patient characteristics at baseline are given in Table 1. Extended description of all patients at baseline and in several subgroups is given in the supplementary tables.

Incidence of pulmonary hypertension

In 18 patients (25.3 %, 95% CI: 15.7%-37.1%) pulmonary hypertension with a mPAP ≥ 25 mmHg was detected during follow-up. Patients with mPAP between 21 and 24 mmHg at baseline exhibited a trend toward more PH during follow-up (Figure 1). The incidence for PH in the cohort of 71 patients who had a second right heart catheterization was 6.11/100 patient years (95% CI 3.67/100 – 9.5/100). Of the 18 patients with PH at the second RHC, 5 had PH

due to left heart disease, 8 due to lung disease. In 5 patients (7%, 95% CI 2.3%-15.7%) SSc-APAH was diagnosed during follow-up.

Progression of hemodynamics and clinical parameters during follow-up

The study cohort showed a significant worsening in 6-minute walking distance, NTproBNP-levels, lung function parameters (forced vital capacity, FEV1), diffusion capacity (DLCO, DLCO VA, DLCO %, DLCO VA%), echocardiography (Tricuspid regurgitation velocity/systolic pulmonary artery pressure) and invasive hemodynamics (mPAP, PVR, Table 2). During the course of the study, mean RAP significantly increased by 1.3±3.5mmHg (p=0.001). Change in RAP (baseline to follow-up) between normal and borderline patients did not significantly differ (p=0.076). The rate of progression to PAH was 3 of 21 (14%) with mPAP 21mmHg - 24mmHg 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 mPAP 21mmHg – 24mmHg at baseline and 11 of 50 (22%) for patients with normal mPAP. In this population of SSc patients with a DLCO < 60%, the change of 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).

One outlier was detected in the NTproBNP values, probably due to measurement errors. This patient with NTproBNP baseline value of 7000ng/mL developed lung cancer within the study period and showed normal right ventricular function at baseline, creatinine of 1.15 mg/dL and uric acid of 4.0mg/dL. As both right ventricular function and renal function do not explain this value, the NTproBNP was excluded from the analysis. Within the whole cohort, NTproBNP showed a significant increase (p=0.005 Wilcoxon rank test) throughout the study. The increase in NTproBNP did not significantly differ between patients with normal mPAP at baseline and those with pressures between 21 and 24mmHg (<21mmHg 195.9±1199.5 median 13 vs. 21-24mmHg 168.8±404.0mmHg median 42.5).

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

Patients presenting with mPAP between 21 and 24 mmHg at baseline showed significantly lower 6WMD, DLCO %, cardiac output and significantly higher tricuspid regurgitation velocity, systolic pulmonary arterial pressure, transpulmonary gradient and pulmonary vascular resistance both at baseline and during follow-up (all p<0.05; Table 3). Furthermore, lung function parameters at baseline were significantly worse in patients with mPAP 21-24 mmHg for forced vital capacity, forced expiratory volume in one second (FEV1), FEV1%, total lung capacity % and residual volume % (all p<0.05). For some parameters baseline values did not differ, however at follow-up right atrial area was significantly larger (p=0.037), and tricuspid

annular plane systolic excursion showed significantly lower values (p=0.004) in patients with mPAP 21-24 mmHg compared to mPAP <21 mmHg at baseline.

Determining factors of mPAP during follow-up

Results of univariate and multivariate analyses are given in Table 4. High pulmonary vascular resistance at baseline was independent predictor of the development of PH during follow-up (p=0.002, r=0.460). When only parameters of noninvasive assessments were included in the analysis elevated tricuspid regurgitation velocity 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 due to the following reasons: pulmonary fibrosis (n=2), PH (n=2; 1 PAH, 1 postcapillary PH), cancer (n=2), primary biliary cholangitis (n=1), left heart failure (n=1). While the earliest death occurred after 1.0 year, the latest death occurred after 5.6 years of follow-up (m = 3.2 years, M = 3.1). One further patient with lung cancer was lost to follow-up three years after baseline.

Survival was not significantly different between patients with mPAP of 21-24 mmHg at baseline compared to patients with mPAP <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 an 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 pulmonary hypertension (PH) in patients with systemic sclerosis (SSc) using a systematic screening assessment including right heart catheterisation at baseline and after 3 years. The high incidence of PH (25,3%) and PAH (7%) within this time suggests that it is useful to perform regular clinical assessment with a low threshold for RHC in at risk SSc-patients. In our study on average pulmonary pressure tended to rise over time in this population. High pulmonary vascular resistance at baseline, elevated tricuspid regurgitation velocity, high 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 pulmonary hypertension.

Incidence of PH/PAH

The incidence for PH in our cohort was 6.11/100 patient years, when only entering the 71 RHC-controlled patients into calculation. Among those the incidence of PAH was 7% similar to the findings of Valerio et al. where progression to PAH for all patients was 8,3% after 3 years. Of note, in the Valerio et al study patients with pulmonary fibrosis were excluded from follow up, while in the DETECT cohort, patients with mild to moderate pulmonary fibrosis were included.

Our results show a higher rate of development of PH when compared with two further previous studies that analyzed the incidence of PH [16, 21]. The estimated incidence of PH over a period of 3 years, which was observed in a French nationwide study, was 1.37cases/100 patient years; incidences did not differ between PAH and postcapillary PH [21]. In an Italian study, PH incidence was 1.85/100 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. reported an incidence of 0.75/100 patient years [22]. In all of these studies right heart catheterisation was only performed in those suspected clinically or on non-invasive investigation of having developed PAH.

In contrast to Hachulla et al., Ludici et al. and Kovacs et al. we used a systematic assessment via right heart catheterization in all patients, capturing all incident cases.

In addition, our cohort was preselected for possible PAH, as patients with impaired DLCO were selected. Mean DLCO % was 73.2±18 in Hachulla et al. and 71±21 in Ludici et al. and 82.2% (range 64.5-93.9) in Kovacs et al. [22], at baseline, while our cohort had a DLCO % of 48.9±10.8 [16, 21]. The low DLCO appears to be a major reason for the higher apparent incidence of pulmonary hypertension in our cohort. A low DLCO may indicate to perform a closer clinical and invasive follow-up in patients with SSc.

Comparison of mPAP groups – are “borderline” pulmonary pressure an interim stage?

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

In our study patients with borderline pulmonary arterial pressures at baseline showed significantly lower 6MWD, DLCO %, cardiac output, higher TRV, sPAP, TPG and PVR at baseline and follow-up examination. TAPSE was significantly lower and right atrial area significantly larger at follow-up. 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 mPAP between 21 and 24 mmHg showed significantly poorer lung function at baseline than patients with mPAP <21 mmHg. This suggests pulmonary comorbidity is prevalent among those with mildly elevated pressures as shown in the PHAROS registry, reporting a higher prevalence of pulmonary fibrosis and abnormal lung physiology in patients with mPAP ≥25 mmHg (difficult to highlight the Pharos study, where mPAP > 25 is the group of interest when we are presenting inof on borderline PH, Kovacs study should be first, followed by Pharos as mPAP 25 – 30 could also be considered mild) [23]. Kovacs et al. also described a higher prevalence of cardiac comorbidity and decreased lung function [9] 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 co-morbidity were excluded.

Determining factors of developing PH

A reduction of DLCO is a frequent finding in systemic sclerosis, and in PH [24]. Compared to other PAH subgroups CTD-APAH patients showed lower DLCO [25, 26]. In our study DLCO/VA% was a significant predictor of developing PH along with enlarged size of inferior vena cava and tricuspid regurgitation velocity, 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 who confirmed a strong association of DLCO and SSc-aPAH [15, 16, 18, 19]. However these studies were mostly retrospective and partially based diagnosis on echocardiography or did not use systematic right heart catheterization of all patients.

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

In analysis of non-invasive parameters only, tricuspid regurgitation velocity and size of inferior vena cava showed to be significant predictors. TRV has already been identified as independently associated factor in one study [14], Inferior vena cava has not previously been reported as predictor of mPAP or PH.

Progression of hemodynamics, regardless of the baseline stage (mPAP group)

Our study cohort showed a significant worsening in lung function parameters (forced vital capacity, FEV1), diffusion capacity (DLCO, DLCO VA, DLCO %, DLCO VA%), 6-minute walking distance, echocardiography (sPAP / TR-jet) and invasive hemodynamics (mPAP, PVR) during the course of the study. The change of 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 three year period, which was also observed in a recent study with 1.1 mmHg/year [12]. This supports previous observations [24] that patients with a reduced DLCO will tend to show worsening of pulmonary haemodynamics 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. The data from Kovacs et al. [22] suggests that in patients with a normal DLCO (mean 82%), progressive elevation of pulmonary pressures may not occur, since in that study among those selected for repeat catheterisation no trend toward increasing pressures was observed.

Limitations

Due to the DETECT inclusion criteria, this cohort is preselected for SSc-patients with DLCO<60%, which can limit its generalisability to an unselected SSc-population. In the analysis of determining factors the study centre was included as fixed factor to take centre effects into account. However, we cannot rule out difference between centres as a contributor to the findings. Right heart catheterization was performed in only 71 out of 96 patients (74%) after 3 years. We do not know, whether the other patients developed pulmonary hypertension within three years. However, 83 patients (87%) were assessed during follow-up by non-invasive assessments. In those patients who were not assessed by right heart catheterization, no clinical signs of pulmonary hypertension were detected. The size of the cohort does not allow independent assessment of the rate of progression to PAH (7 of 21 with mPAP 21 -24, vs. 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 progressive elevation of pulmonary pressure occurs in these patients over time. This would be expected to translate into an increased risk of PH and PAH in this population. We also provide further evidence that borderline pulmonary arterial pressure is a possible intermediate stage in the development of pulmonary hypertension. Using RHC during follow-up assessment it was possible to identify manifest PH in almost 25% of patients, PVR was an independent risk factor to develop manifest disease. Therefore, it seems to be useful to perform regular clinical assessment including RHC in SSc-patients with reduced gas transfer until more reliable non invasive tools are developed.

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Support statement.

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Table 1. Demographics of study cohort at baseline n=96

Characteristics	n (%) or mean (SD)
gender	
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/m²	25.2 ± 4.8
Vital Signs	
Blood Pressure, systolic, mmHg	117.8 ± 17.4
Blood Pressure, diastolic, mmHg	72.0 ± 10.8
Heart rate, /min	76.8 ± 12.1
Systemic sclerosis characteristics	
Modified Rodnan Skin Score	11.9 ± 8.8
Duration of SSc, months	11.5 ± 9.6
Type of systemic sclerosis	
Diffuse cutaneous SSc	15 (15.6%)
Limited cutaneous SSc	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, Type of systemic sclerosis as diagnosed by treating rheumatologist, Modified Rodnan Skin Score and WHO-Functional class as obtained in clinical examination.

Table 2. Clinical data at baseline and during follow-up

	baseline			follow-up			changes		p-value
	n	mean	SD	n	mean	SD	mean	SD	
6-MWD	91	403.2	± 111.4	66	388	± 125	-21.8	± 79.3	0.039
NT-proBNP, pg/ml	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	n.s.
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	n.s.
DLCO, mmol/min/kPa	93	7.5	± 4.0	68	3.9	± 1.5	-4.0	± 4.0	<0.001
DLCO, %	95	48.9	± 10.8	70	46.3	± 11.8	-3.1	± 8.2	<0.001
DLCO/VA, mmol/min/kPa/l	93	2.5	± 1.5	69	1.5	± 1.1	-1.3	± 1.9	<0.001
DLCO/VA, %	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	n.s.
RV, %	84	85.8	± 33.1	63	94.4	± 34.2	5.5	± 23.1	n.s.
echocardiography									
LA, mm	93	29.1	± 6.4	72	30	± 7	0.5	± 6.4	n.s.
IVC, mm	82	14.0	± 3.7	64	13	± 6	-2.0	± 6.8	n.s.
IVS, mm	92	10.1	± 1.8	40	10	± 2	0.0	± 3.2	n.s.
RA, cm2	89	12.1	± 3.7	72	12.7	± 4.0	0.2	± 4.2	n.s.
RVD, mm	85	29.1	± 5.6	42	31	± 7	3.8	± 7.6	0.01
RV, cm2	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	n.s.
LV-ESD, mm	91	27.0	± 5.1	42	27	± 7	0.0	± 7.0	n.s.
TRV, m/s	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	n.s.
sPAP, mmHg	87	29.1	± 7.1	63	32	± 9	3.1	± 9.1	0.017
right heart catheterization									
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	n.s.
CO, l/min	96	5.3	± 1.2	71	5.1	± 1.1	-0.1	± 0.9	n.s.
PVR, dynes	96	135	± 55.4	71	182	± 118	43.5	± 96.1	0.001

SD = standard deviation, follow-up = follow-up after 3 years, 6-MWD = 6-minute walking distance, NTproBNP = N-terminal end of pro brain natriuretic peptide, FVC = forced vital capacity, FEV1 = forced expiratory volume in one second, DLCO = diffusion capacity of the lung for carbon monoxide, VA = alveolar volume, 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 hypertension, mPAP = mean pulmonary arterial pressure, PAWP = pulmonary arterial wedge pressure,
TPG = transpulmonary gradient, CO = cardiac output, PVR = pulmonary vascular resistance.

Table 3. Comparison of patients presenting with mean pulmonary arterial pressure <21 mmHg vs. 21-24 mmHg at baseline

	mPAP <21mmHg				mPAP 21-24mmHg				differences	
	baseline		follow-up		baseline		follow-up		p-value	
	n	mean SD	n	mean SD	n	mean SD	n	mean SD	baseline	follow-up
6-MWD	69	431 ± 93	49	419 ± 107	22	317 ± 122	17	298 ± 131	<0.001*	0.002 *
NT-proBNP, pg/ml	72	206 ± 263	54	401 ± 1243	23	245 ± 278	23	384 ± 452	0.255	0.181
pulmonary function testing										
FVC, l	71	2.99 ± 1.00	56	2.76 ± 1.06	23	2.43 ± 0.75	19	2.41 ± 0.68	0.023 *	0.172
FVC, %	72	92.90 ± 24.09	55	88.92 ± 25.69	24	86.02 ± 21.97	21	90.07 ± 21.92	0.233	0.963
FEV1, l	71	2.39 ± 0.88	55	2.14 ± 0.87	23	1.78 ± 0.51	19	1.75 ± 0.49	0.004 *	0.113
FEV1, %	72	88.43 ± 24.16	55	83.32 ± 23.25	23	77.02 ± 15.73	20	80.65 ± 16.90	0.050 *	0.545
DLCO, mmol/min/kPa	70	7.26 ± 4.18	50	3.97 ± 1.01	23	8.06 ± 3.58	18	3.57 ± 2.41	0.228	0.003 *
DLCO, %	71	50.78 ± 9.56	50	49.44 ± 10.13	24	43.18 ± 12.54	20	38.55 ± 12.15	0.013 *	<0.001 *
DLCO/VA, mmol/min/kPa/l	70	2.35 ± 1.59	51	1.44 ± 1.09	23	2.93 ± 1.10	18	1.53 ± 1.31	0.061	0.280
DLCO/VA, %	70	72.80 ± 16.55	51	69.14 ± 16.93	23	67.33 ± 17.64	18	63.65 ± 17.28	0.226	0.170
TLC, %	63	88.80 ± 21.83	52	92.52 ± 21.68	20	76.21 ± 21.57	18	81.58 ± 24.96	0.028 *	0.070
RV, %	63	91.56 ± 32.66	45	99.68 ± 33.38	21	68.55 ± 28.82	18	81.36 ± 33.68	0.002 *	0.084
Echocardiography										
LA, mm	71	28.14 ± 6.48	52	30.07 ± 6.22	22	32.10 ± 4.95	20	30.45 ± 7.38	0.007 *	0.262
IVC, mm	65	13.83 ± 3.61	47	12.50 ± 6.01	17	14.50 ± 3.96	17	12.59 ± 5.38	0.432	0.681
IVS, mm	70	10.12 ± 1.81	23	9.66 ± 2.51	22	9.96 ± 1.80	17	10.79 ± 2.19	0.832	0.196
RA, cm2	68	11.76 ± 3.37	52	12.15 ± 3.77	21	13.14 ± 4.64	20	14.11 ± 4.48	0.317	0.037 *
RVD, mm	65	29.89 ± 5.70	22	31.10 ± 7.41	20	26.36 ± 4.16	20	30.92 ± 5.68	0.003 *	0.830
RV, cm2	68	14.25 ± 4.05	52	13.19 ± 3.59	20	15.19 ± 5.18	20	13.38 ± 3.94	0.495	0.692
LV-EDD, mm	70	43.54 ± 5.58	23	41.51 ± 9.50	22	46.03 ± 4.98	19	42.86 ± 6.83	0.062	0.889
LV-ESD, mm	69	26.64 ± 5.13	23	25.90 ± 7.84	22	28.18 ± 5.05	19	27.45 ± 5.51	0.238	0.486
TRV, m/s	65	2.35 ± 0.36	23	2.48 ± 0.36	23	2.65 ± 0.30	16	2.88 ± 0.45	<0.001*	0.003 *
TAPSE, mm	68	22.82 ± 3.92	23	23.02 ± 4.98	21	21.64 ± 6.37	22	19.75 ± 3.78	0.157	0.004 *
sPAP, mmHg	64	27.54 ± 6.78	23	30.16 ± 7.31	23	33.43 ± 6.27	16	38.97 ± 10.56	<0.001*	0.003 *
right heart catheterization										
mPAP, mmHg	72	15.40 ± 3.03	50	20.12 ± 5.86	24	22.17 ± 0.96	21	24.95 ± 4.12	<0.001*	<0.001 *
PAWP, mmHg	72	7.65 ± 2.99	50	10.74 ± 3.83	24	11.08 ± 2.67	21	11.24 ± 2.53	<0.001*	0.407

TPG, mmHg	72	7.69 ± 2.63	50	7.84 ± 2.22	24	10.83 ± 2.60	21	10.90 ± 2.43	<0.001*	<0.001 *
CO, l/min	72	5.44 ± 1.17	50	5.24 ± 1.22	24	4.90 ± 1.13	21	4.86 ± 0.88	0.048 *	0.048 *
PVR, dynes	72	117.48 ± 39.04	50	151.48 ± 101.02	24	188.39 ± 63.37	21	253.70 ± 126.82	<0.001*	<0.001 *
RAP, mmHg	72	3.76 ± 2.33	48	5.65 ± 2.89	24	5.00 ± 2.50	21	5.43 ± 2.23	0.03 *	0.76

* denotes statistically significant differences

* SD = standard deviation, follow-up = follow-up after 3 years, 6-MWD = 6-minute walking distance, NTproBNP = N-terminal end of pro brain natriuretic peptide,

* FVC = forced vital capacity, FEV1 = forced expiratory volume in one second, DLCO = diffusion capacity of the lung for carbon monoxide, VA = alveolar volume,

* TLC = total lung capacity, 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 hypertension, mPAP = mean pulmonary arterial pressure, PAWP = pulmonary arterial wedge pressure, TPG = transpulmonary gradient, CO = cardiac output, PVR = pulmonary vascular resistance.

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
	FEV1	69	0.017	-0.286
	FEV1 %	70	0.057	-0.229
	DLCO %	71	0.025	-0.265
	DLCO/VA %	69	0.028	-0.265
NTproBNP		69	755	38
6-minute walking distance		66	0.097	0.206
Echocardiography				
	Inferior vena cava	58	0.04	0.271
	right atrial area	64	0.167	0.175
	right ventricular area	63	0.828	0.028
	Tricuspid regurgitation velocity	66	0.003	0.360
	systolic pulmonary arterial pressure	65	0.004	0.351
Right heart catheterization				
	mean pulmonary arterial pressure	71	0.001	0.402
	Transpulmonary gradient	71	<0.001	0.430
	pulmonary vascular resistance	71	<0.001	-0.456
Multivariate Analysis with centre as fixed factor				
Including invasive hemodynamics				
	pulmonary vascular resistance	56	0.002	0.460
Only noninvasive parameters				
	model 1Tricuspid regurgitation velocity	56	0.003	0.439
	model 2+ DLCO/VA %	56	0.046	0.512
	model 3+ Inferior vena cava	56	0.02	0.577

WHO = World Health Organization, FVC = forced vital capacity, FEV 1 = forced expiratory volume in one second, DLCO = diffusion capacity of the lung for carbon monoxide, VA = alveolar volume, NTproBNP = N-terminal end of pro brain natriuretic peptide,

Figure Legends

Figure 1

The figure displays the clinical course and classification of the patients throughout the study. Distribution of patients during follow-up significantly differed between patients with baseline mPAP 21-24 mmHg and patients with mPAP <21 mmHg ($p<0.001$).

Figure 2

The two figures (a and b) show survival analyses of a) patients with mPAP 21-24 mmHg vs. mPAP <21 mmHg and b) patients with significant lung disease vs. 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 ($p=0.029$).

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