# Clinical determinants of elevated systolic pulmonary artery pressure measured by transthoracic Doppler echocardiography in early systemic sclerosis

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## ABSTRACT

**Objective.** *To explore the prevalence and clinical associations of elevated systolic pulmonary artery pressure (sPAP), measured by Transthoracic Doppler-echocardiography (TTE) in patients with early systemic sclerosis (SSc).*

**Methods.** *A cross-sectional analysis of the prospective EULAR Scleroderma Trial and Research (EUSTAR) database was performed. SSc patients with <3 years from the first non-Raynaud's phenomenon (RP) symptom at baseline EUSTAR visit, were selected. Elevated sPAP was defined as sPAP>40 mmHg on baseline TTE. First visit SSc related variables, including disease subsets, antibodies and visceral involvement, were examined.*

**Results.** *From 1,188 patients, 81% were women. Mean (SD) age at first non-RP symptom was 50 (14) years, 55% had limited cutaneous SSc (lcSSc) and 42% active disease. Elevated sPAP was found in 17% of patients, both lcSSc and diffuse cutaneous SSc (dcSSc). In lcSSc, older age at first non-RP symptom, ACA positivity, joint contractures, restrictive defect and lower DLCO, were independently associated with elevated sPAP. In dcSSc, older age at first non-RP symptom, longer time between RP onset and first non-RP symptom, digital ulcers, cardiac blocks, and proteinuria were associated with elevated sPAP.*

**Conclusion.** *The prevalence of elevated sPAP on TTE in early SSc patients is considerable. Association with cardiac, lung and renal involvement suggests that, although some patients might have pulmonary arterial hypertension, others may present pulmonary hypertension secondary to lung or heart involvement. Our findings emphasise the need to consider right heart catheterisation in selected early SSc patients with PH suspicion, to clearly determine the cause of PH.*

## Introduction

Pulmonary hypertension (PH) is a relatively frequent complication (1) and a major cause of morbidity and mortality (2, 3) in systemic sclerosis (SSc). PH is not a specific disease, but a haemodynamic condition characterised by a mean pulmonary pressure ≥25 mmHg. In SSc, because of the great variability in clinical manifestation, it is possible to identify due to left heart disease, PH due to respiratory disease or pulmonary arterial hypertension. The knowledge of PH and the right diagnosis are crucial to assess the most appropriate therapeutic strategy (4).

The reported prevalence of PH in SSc varies widely between 5% and 50%, depending on the definitions and techniques used to measure pulmonary artery pressure. Different types of PH according to the Nice classification may develop in SSc patients (5). Precapillary PH in SSc patients can be either type 1 PH or pulmonary arterial hypertension (PAH), as a result of obstructive proliferative vasculopathy of small and medium-size pulmonary arterial circulation, and type 3 PH, secondary to pulmonary fibrosis (PF) (1, 6, 7). Many authors include patients with limited PF, based on the extension of disease in high resolution thoracic (HRCT) scan and/or the level of Forced Vital Capacity (FVC), in the type 1 PAH group. Although these definitions have not been validated, it has been recently observed that precapillary PH in SSc

patients is independent of the degree of PF extension in HRCT scan (8). PAH has been classically considered as a late complication of the disease, associated with female sex, limited cutaneous involvement (lcSSc), anticentromere antibodies (ACA) and low diffusion capacity of the lung for carbon monoxide (DLCO) (1, 9-16). However, early-onset PAH, diagnosed within 3 to 5 years of the first non-Raynaud phenomenon (RP) manifestation has also been described in SSc patients, both in the lcSSc and in the diffuse cutaneous (dcSSc) subsets (17).

Other forms of PH have been also reported in SSc patients. These include pulmonary veno-occlusive disease, which has been found in lung specimens of patients with SSc associated PAH (1, 18), and type 2 postcapillary PH, secondary to left-heart involvement. The latter is common in SSc (19), and it has been suggested that perhaps is the most frequent cause of PH in SSc patients (1, 20-22). Clinical associations of left heart involvement have not been clearly analysed in SSc patients, but include a wide range of conditions, from true cardiomyopathy due to myocardial inflammation and fibrosis, to hypertensive heart disease in scleroderma renal crisis, or left ventricular diastolic dysfunction, a very common finding in SSc patients, and also in older but otherwise healthy people.

Several studies have suggested that earlier diagnosis of PAH in SSc patients may lead to better survival (23). Differentiation of PAH from other forms of PH is important, but has proven to be a difficult task in SSc patients. Since PAH specific therapies might have deleterious effects in other forms of PH (24), it is necessary to accurately diagnose the true origin of PH in SSc. Transthoracic Doppler-echocardiography (TTE) is commonly used as a non-invasive and easily available screening method, to identify SSc patients at high risk of PAH. Estimated sPAP can be calculated adding the estimated right atrial pressure to the tricuspid regurgitant jet velocity (TRJ) obtained with this technique. However, TTE has many limitations, including the inability to distinguish PAH from other forms of PH. Right heart catheterisation (RHC) remains the gold standard for the diagnosis of PH, and should be performed to confirm suspected PH in SSc patients (25). The European Society of Cardiology/European Respiratory Society (ESC/ERS) recommends performing RHC to any SSc patient with TRJ higher than 3.4 m/s, and also to those with lower TRJ but who are symptomatic, although these symptoms have not been clearly defined (26). Important efforts are being made to accurately identify patients at high risk of PH/PAH, while optimising the use of an invasive technique as RHC (25). In this setting, the evidence based DETECT algorithm (27, 28), has shown high sensitivity for early PAH detection.

The aim of our study was to analyse the prevalence and clinical associations of elevated sPAP on TTE, in a large international cohort of patients with early SSc. In clinical practice, this might help to guide decisions on screening and PH accurate diagnosis, and to select the adequate therapeutic interventions in SSc patients.

## Methods

This is a cross-sectional analysis of the baseline visit from the EUSTAR database.

### *EUSTAR database*

The EUSTAR database has been previously described (29). Briefly, the database was initiated in June 2004 and documents a multinational (194 centres), prospective and open SSc cohort. Participating centres obtain ethics committee approval, followed by the entry of the Minimal Essential Data set (MEDS) for all consecutive consenting patients with SSc, including data on demographics, disease onset, clinical features and disease activity. Data are updated annually. For the purposes of the present study, all patients included in the EUSTAR database until June 2008 (time of data extraction for this analysis), fulfilling the preliminary 1980 ACR classification criteria for SSc (30), and with less than 3 years from the first non-RP symptom attributable to SSc at the baseline EUSTAR visit, were selected. A group of patients with less than 3 years from the first SSc symptom, including Raynaud`s phenomenon, was also studied (results are presented in the supplementary file).

### *Variables*

The dependent variable was elevated sPAP as a dichotomous variable, based on the estimated sPAP at each centre, using a cut-off of 40 mmHg.

For a detailed definition of variables, see previous EUSTAR report (28).Only objective variables, defined/measured by validated criteria, specific measurements or imaging techniques were considered. Subjective variables such as dyspnoea or palpitations were not examined. Digestive tract symptoms (oesophagus, stomach and gut symptoms), although subjective, were integrated into one variable (digestive tract involvement), and analysed. The presence of RP and ANA positivity, as dichotomised variables, were also excluded from the analyses because they were present in more than 90% of the study sample.

Along with elevated sPAP, we also analysed the following variables: a) sociodemographics including sex, age (at EUSTAR entry, at RP, at first non-RP symptom; b) disease related variables such as time between the onset of RP and the onset of the first non-RP symptom; disease duration calculated from the onset of the first non-RP symptom; SSc subsets, dcSSc and lcSSc as previously described (31); positivity for anti-Scl70 antibodies and ACA; modified Rodnan Skin Score (mRSS); active disease, calculated from the composite score proposed by the European Scleroderma Study Group (32) and considered positive if score >=3 (total range 0 to10); elevation of acute phase reactants (erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)); vascular involvement including digital ulcers; joint involvement including synovitis, joint contractures or tendon friction rubs; muscle involvement as creatine kinase (CK) elevation; digestive tract involvement as previously described; lung involvement including the presence of PF and restrictive defect on pulmonary function tests; DLCO (% of predicted); cardiac involvement,

including conduction blocks, left ventricular diastolic dysfunction and left ventricular ejection fraction <55%;scleroderma renal crisis and proteinuria.

*Statistical analysis*

The description of EUSTAR baseline data was performed using measures of central tendency (mean) and dispersion (standard deviation) for quantitative variables, and distribution of percentages for qualitative variables.

The association between elevated sPAP with demographic and clinical characteristics was assessed calculating crude association measures (OR) with its 95% confidence interval (CI).

Clinical associations of elevated sPAP were analysed following multivariate logistic regression models. In these models, independent factors associated with elevated sPAP in the bivariate analysis with a *p*-value <0.20 were included (complete model). Thereafter, backward stepwise regression was used for modelling variables selection (model 2). Comparison of models was performed by information measures, Akaike information criteria (AIC), and Bayesian information criteria (BIC). Results were expressed as OR with 95% CI. In order to identify possible differences in clinical determinants of diffuse and limited cutaneous subgroups of the disease, bivariate and multivariate association analysis were conducted independently for both subsets (stratified analysis).

After Bonferroni adjustment for multiple comparisons a *p*-value <0.0001 was considered statistically significant. Analyses were performed using Stata 12 statistical software (Stata Corporation, College Station, TX, USA).

## Results

The baseline characteristics of the study cohort are shown in Table I.

From the 1,188 patients with early SSc included in the analysis, 81% were women, with mean (SD) age at first non-RP symptom of 50 (14) years, and mean (SD) time between RP onset and first non-RP symptom of 3 (7) months. Fifty five percent presented with lcSSc and 42% with active disease.

Elevated sPAP on TTE was found in almost 17% of patients, nearly equally distributed between SSc subsets. The rate was very similar in the subgroup of patients with less than 12 months of disease duration (data not shown). Regarding other organ involvement, digestive tract involvement was present in 68%; some form of pulmonary disease in about 30%, PF in 32% and restrictive defect in pulmonary function tests in 29%; left ventricular ejection fraction ≤55% in 5%; left ventricular diastolic dysfunction in 15.2%; DLCO <55% in 21.2%; scleroderma renal crisis in 3.4%; and digital ulcers in 29%.

In the bivariate analysis, patients with elevated sPAP on TTE were older at first non-RP symptom and presented with more active and severe disease, showing higher prevalence of visceral involvement, compared to patients without elevated sPAP (Table II). Cardiopulmonary involvement and proteinuria were clearly more prevalent in the elevated sPAP group, but there were not differences with regard to the prevalence of diffuse or limited cutaneous disease, or the presence of ACA or anti-Scl70 positivity.

The main associations of elevated sPAP in the whole study cohort (Table III), were older age at the onset of first non-RP symptom (OR 1.05; 95%CI 1.03-1.08), lower DLCO (OR 0.97; 95%CI 0.96-0.98), presence of digital ulcers (OR 2.08; 95%CI 1.20-3.16), cardiac conduction blocks (OR 2.38; 95%CI 1.14-4.97), and proteinuria (OR 3.00; 95%CI 1.32-6.83).

Bivariate associations between elevated sPAP and clinical characteristics according to SSc subset are shown in Table IV.

In both SSc subsets, elevated sPAP was associated with older age at onset of first non-RP symptom, lower DLCO, higher disease activity, PF, restrictive defect on pulmonary function tests, cardiac conduction blocks, diastolic dysfunction, and left ventricular ejection fraction ≤55%. Joint contractures were associated with elevated sPAP only in the lcSSc subset. The time between the onset of RP and the onset of first non-RP symptom, mRSS score, elevation of acute phase reactants, digital ulcers, scleroderma renal crisis and proteinuria, were associated with elevated sPAP exclusively in the dcSSc subset.

In the multivariate analyses of the lcSSc subset (Table V), older age at first non-RP symptom (OR 1.04; 95%CI 1.01-1.07), ACA positivity (OR 2.30; 95%CI 1.06-5.01), joint contractures (OR 3.68; 95%CI 1.65-8.20), restrictive defect on pulmonary function tests (OR 2.65; 95%CI 1.21-5.81) and lower level of DLCO (OR 0.97; 95%CI 0.95-

**Table I.** Study sample baseline characteristics.

| Quantitative variables, mean (SD) | | |
|---|---|---|
| Age (yr) | | |
| At first non-Raynaud's event | 50.3 | (14.6) |
| At first EUSTAR entry | 52.3 | (14.5) |
| Disease duration (m)* | 18.3 | (6.4) |
| Time between RO - non Raynaud's event (months) | 3.3 | (7.1) |
| mRSS (n=1,169) | 12.0 | (10.2) |
| DLCO (% of predicted) (n=754) | 71.0 | (20.7) |
| **Cualitative variables, n (percentage, %)** | | |
| Sex (women) | 953 | (80.6%) |
| Antibodies positives | | |
| Scl-70 | 407 | (35.15%) |
| ACA (n=1,128) | 324 | (28.7%) |
| Disease subset | | |
| dcSSc | 482 | (44.8%) |
| lcSSc | 594 | (55.2%) |
| Active disease | 486 | (42.3%) |
| Elevated acute phase reactants | 431 | (34.2%) |
| Digital ulcers | 346 | (29.2%) |
| Synovitis | 240 | (20.2%) |
| Joint contractures | 343 | (29.0%) |
| Tendon friction rubs | 175 | (14.9%) |
| CK elevation | 164 | (14.2%) |
| Digestive involvement† | 804 | (68.1%) |
| Pulmonary hypertension** | 193 | (16.7%) |
| Pulmonary fibrosis | 367 | (31.6%) |
| Lung restrictive defect | 334 | (28.9%) |
| Cardiac conduction blocks | 103 | (9.0%) |
| Diastolic dysfunction | 176 | (15.2%) |
| LVEF <55% | 54 | (4.7%) |
| DLCO<55% | 160 | (21.2%) |
| Renal crisis | 40 | (3.4%) |
| Proteinuria | 87 | (7.5%) |

yr: year; m: month; RO: onset of Raynaud's phenomenon; mRSS: modified Rodnan Skin Score; DLCO: diffusion capacity of the lung for carbon monoxide; ACA: anticentromere autoantibody; dcSSc: diffuse cutaneous systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; CK: creatin kinase; LVEF: left ventricular ejection fraction; SD: standard deviation* Disease duration was calculated on the basis of the onset of the first non-Raynaud's event.

†Digestive involvement includes oesophagus, stomach and gut symptoms

**Pulmonary hypertension defined by estimated systolic pulmonary pressure > 40 mm Hg in Doppler-echocardiography.

**Table II.** Differences in clinical characteristics according to the presence of pulmonary hypertension, defined as an estimated systolic pulmonary pressure > 40 mm Hg on Doppler-echocardiography.

| | Pulmonary hypertension | | *p*-value |
|---|---|---|---|
| | No (n=961) | Yes (n=193) | |
| Age at 1st non Raynaud's event | 48.7 (14.4) | 58.5 (13.4) | <0.001 |
| Disease duration (mo)* | 18.3 (6.4) | 18.1 (6.6) | 0.587 |
| Time RO - Raynaud's event (mo) | 3.0 (6.4) | 4.2 (9.8) | 0.127 |
| mRSS | 11.4 (9.8) | 14.6 (11.6) | <0.001 |
| DLCO (% of predicted) | 73.0 (19.6) | 59.6 (23.7) | <0.001 |
| DLCO <55% | 109 (17.4%) | 49 (44.1%) | <0.0001 |
| Sex (men) | 180 (18.3%) | 45 (23.3%) | 0.152 |
| Scl-70 positive | 322 (34.0%) | 75 (40.1%) | 0.112 |
| ACA positive | 259 (28.1%) | 58 (31.2%) | 0.307 |
| Active disease | 364 (39.1%) | 110 (58.8%) | <0.0001 |
| Diffuse disease | 375 (39.4%) | 95 (49.5%) | 0.010 |
| Limited disease | 492 (51.7%) | 89 (46.3%) | 0.178 |
| Elevated acute phase reactants | 326 (34.5%) | 92 (49.5%) | <0.0001 |
| Digital ulcers | 260 (27.1%) | 80 (41.7%) | <0.0001 |
| Synovitis | 197 (20.5%) | 40 (20.7%) | 0.949 |
| Joint contractures | 257 (26.8%) | 78 (40.6%) | <0.0001 |
| Tendon friction rubs | 140 (14.6%) | 31 (16.4%) | 0.528 |
| CK elevation | 126 (13.4%) | 31 (16.5%) | 0.262 |
| Digestive involvement | 640 (66.9%) | 143 (74.5%) | 0.041 |
| Pulmonary fibrosis | 269 (28.2%) | 92 (49.2%) | <0.0001 |
| Lung restrictive defect | 236 (24.9%) | 93 (49.7%) | <0.0001 |
| Cardiac conduction blocks | 67 (7.0%) | 36 (19.5%) | <0.0001 |
| Diastolic dysfunction | 112 (11.7%) | 62 (32.6%) | <0.0001 |
| LVEF <55% | 29 (3.0%) | 25 (12.9%) | <0.0001 |
| Renal crisis | 27 (2.8%) | 13 (6.7%) | 0.007 |
| Proteinuria | 57 (6.1%) | 29 (15.4%) | <0.0001 |

yr: year; m: month; RO: onset of Raynaud's phenomenon; mRSS: modified Rodnan Skin Score; DLCO: diffusion capacity of the lung for carbon monoxide; ACA: anticentromere autoantibody; CK: creatin kinase; LVEF: left ventricular ejection fraction.
*Disease duration was calculated on the basis of the onset of the first non-Raynaud's event.
†Digestive involvement includes oesophagus, stomach and gut symptoms.

0.99),were independent factors associated with elevated sPAP.

Multiple variable regression analyses of the dcSSc subset (Table VI), showed that older age at the onset of first non-RP symptom (OR 1.08; 95%CI 1.04-1.12), longer time between onset of RP and onset of first non-RP symptom (OR 1.12; 95%CI 1.00–1.26), digital ulcers (OR 4.90; 95% CI 2.05–11.7), cardiac conduction blocks (OR 3.89; 95%CI 1.29–11.7), and proteinuria (OR 10.1; 95%CI 2.79–37.2), were significantly more frequent in patients with elevated sPAP on TTE.

From the total sample, 656 patients had disease duration of less than 3 years from the first SSc symptom, including Raynaud's phenomenon (504 women, with mean disease duration of 1.5±0.8 years). The results of the analysis of this subgroup were very similar to the results found in the whole sample (supplementary files).

## Discussion

PH is a devastating condition able to cause considerable morbidity and premature mortality in SSc (2, 3).While previous studies have already shown an elevated prevalence of PAH in long-standing SSc (1, 9, 29), our study underscores the importance of cardiac assessment in early disease to identify PAH, as well as other causes of PH.

Because it is non-invasive and easily available in many clinics, TTE is commonly used as screening method to identify SSc patients at high risk of PAH. In some previous studies, elevated sPAP on TTE has been considered as a surrogate for PAH or PH (29). However, elevated sPAP estimated in TTE cannot be considered diagnostic for PH, and also it is unable to differentiate between the various forms of PH that may occur in SSc patients. In our cohort, elevated sPAP on TTE was present in almost 17% of patients with early SSc, with a similar prevalence in the subgroup of patients with less than 12 months of disease duration (data not shown). A protocol for an accurate diagnosis of every PH cause, including the gold standard, RHC, was not available in the EUSTAR registry at the moment of data extraction for the present study. Although most EUSTAR centres have SSc specialised clinics, with easy access to expert PH units and RHC performance, this could not be the case for some other, also contributing, but smaller centres. Therefore, without RHC data, the relatively high prevalence of elevated sPAP in this cohort of early SSc patients cannot be attributed solely to the presence of true PAH.

First, it is probable that some of our patients would not really have PH if assessed by RHC. Concordance between sPAP estimated on TTE and mean pulmonary pressure, measured with RHC, is low in most studies, even in very specialised centres (33).

Second, it is likely that at least some of the patients with elevated sPAP may have type 3PH, secondary to PF. In this regard, our study shows, in the bivariate analysis, in both SSc subsets, a clear association of elevated sPAP with PF and restrictive defect on pulmonary function tests. These results are also partially confirmed in the backward stepwise regression multivariate model in the lcSSc subset, but not in the dcSSc subset. Probably, in our cohort, both SSc subsets are clinically heterogeneous, and the dcSSc subset might include a higher number of patients with more severe visceral involvement outside the lung, such as renal or cardiac involvement, than could also contribute to sPAP elevation. Besides, we did not perform a specific study of elevated sPAP associations only in patients with pulmonary involvement, due to the low statistical power of a much smaller sample.

Third, type 2 PH, secondary to left heart disease, might explain some of the elevated sPAP observed in our cohort. Myocardial disease can develop in SSc patients for several reasons: cardiomyopathy, usually occurring in early patients with very active disease and frequently associated with myopathy (34);

**Table III.** Bivariate and multivariate analysis for pulmonary hypertension, defined as an estimated pulmonary systolic pressure > 40 mm Hg on Doppler echocardiography, in the whole study sample*.

| | Bivariate | | Multivariate | |
|---|---|---|---|---|
| | OR (CI 95%) | *p*-value | OR (CI 95%) | *p*-value |
| Age at 1st non Raynaud's event | 1.05 (1.04-1.07) | <0.001 | 1.05 (1.03-1.08) | <0.001 |
| Disease duration (m) | 0.99 (0.97-1.02) | 0.660 | - | - |
| Time RO - non RO (m) | 1.02 (1.00-1.04) | 0.047 | - | - |
| mRSS | 1.03 (1.01-1.04) | <0.001 | - | - |
| DLCO (% of predicted) | 0.97 (0.96-0.98) | <0.001 | 0.97 (0.96-0.98) | <0.001 |
| Sex (men) | 1.31 (0.90-1.90) | 0.153 | - | - |
| Scl70 positive | 1.30 (0.94-1.79) | 0.113 | - | - |
| ACA positive | 1.19 (0.85-1.68) | 0.308 | - | - |
| Active disease | 2.23 (1.62-3.07) | <0.001 | - | - |
| SSc subset (lcSSc) | 1.40 (1.02-1.93) | 0.038 | - | - |
| Elevated acute phase reactants | 1.86 (1.35-2.55) | <0.001 | - | - |
| Digital ulcers | 1.92 (1.40-2.65) | <0.0001 | 2.08 (1.20-3.16) | 0.009 |
| Synovitis | 1.01 (0.69-1.48) | 0.949 | - | - |
| Joint contractures | 1.87 (1.35-2.58) | <0.001 | - | - |
| Tendon friction rubs | 1.15 (0.75-1.75) | 0.528 | - | - |
| CK elevation | 1.28 (0.83-1.96) | 0.263 | - | - |
| Digestive involvement | 1.44 (1.01-2.05 | 0.042 | - | - |
| Pulmonary fibrosis | 2.47 (1.79-3.40) | <0.0001 | - | - |
| Lung restrictive defect | 2.98 (2.16-4.11) | <0.001 | - | - |
| Cardiac conduction blocks | 3.19 (2.05-4.95) | <0.001 | 2.38 (1.14-4.97) | 0.021 |
| Diastolic dysfunction | 3.65 (2.54-5.24) | <0.001 | - | - |
| LVEF <55% | 4.72 (2.70-8.27) | <0.0001 | - | - |
| Renal crisis | 2.49 (1.26-4.29) | 0.009 | - | - |
| Proteinuria | 2.82 (1.75-4.56) | <0.001 | 3.00 (1.32-6.83) | 0.009 |

yr: year; m: month; RO: onset of Raynaud's phenomenon; mRSS: modified Rodnan Skin Score; SSc: systemic sclerosis; DLCO: diffusion capacity of the lung for carbon monoxide; ACA: anticentromere autoantibody; lcSSc: limited cutaneous systemic sclerosis; CK: creatin kinase; LVEF: left ventricular ejection fraction; OR: odds ratio; CI: confidence interval.
*Disease duration was calculated on the basis of the onset of the first non-Raynaud's event.

hypertensive heart disease, as a consequence of either scleroderma renal crisis (35) or essential hypertension; and left ventricular diastolic dysfunction, which is a very frequent finding in SSc patients (36), but also very common in otherwise healthy older people (37). In the bivariate analysis, cardiac involvement, non-specifically defined as low left ventricular ejection fraction or cardiac conduction blocks, is associated with elevated sPAP in both the lcSSc and dcSSc subsets. In the multivariate model, the presence of cardiac conduction blocks remains associated with elevated sPAP only in the dcSSc subset. Left ventricular diastolic dysfunction is also associated with elevated sPAP in the bivariate analysis, but this is not confirmed in any of the subsets in the multivariate model. In this regard, it is noteworthy that older age, the most common cause of diastolic dysfunction in the general population (37), is associated with elevated sPAP in all SSc subsets, both in the bivariate and multivariate analysis. A recent study has shown that left ventricular diastolic dysfunction might be the occult origin of PH (22), in patients with the presumptive diagnosis of SSc-associated PAH, and it has been suggested that this could be the most frequent cause of PH in these patients (21). These studies recommend performing RHC with left ventricular end-diastolic pressure (LVEDP) measurement pre and post-fluid challenge, in every SSc patient with PH suspicion, in order to definitively rule out left ventricular dysfunction as the cause of PH. Regarding to scleroderma renal crisis, it is also associated with elevated sPAP in both SSc subsets in the bivariate analysis, but only proteinuria remains strongly associated with dcSSc in the multivariate model. This might be due to the low prevalence of scleroderma renal crisis in the whole group, and especially in the lcSSc subset. Scleroderma renal crisis develops mainly in early dcSSc patients, and is clinically characterised by a severe systemic hypertension, frequently associated with left heart disease (38), which could be the cause of PH in this group of patients. On the other hand, endothelial cell dysfunction has been suggested to play a pathogenic role both in SSc-associated PAH and in scleroderma renal crisis (39). The association of elevated sPAP with the presence of digital ulcers in the dcSSc subset, both in the bivariate and the multivariate regression analysis would support this hypothesis.

Finally, probably some of our patients present true PAH, even at this early stage of the disease. Although PAH has been classically considered a late complication of lcSSc (12), many studies have shown that PAH may be similarly prevalent in the two subsets of the disease (9, 11, 17, 40). Moreover, recent studies (9, 14) have clearly shown that isolated PAH, not associated with interstitial lung disease or left cardiac involvement, could developing SSc patients as early as within the first 3 years of disease course.

Our results suggest that the presence of elevated sPAP, measured by TTE, in early SSc patients, may indicate the presence of a true isolated PAH, but also might be suggesting the presence of other severe visceral complications, as lung, cardiac or renal involvement. A recent study performed in selected SSc prevalent patients from the EUSTAR cohort, an estimated sPAP higher than 36 mmHg was significantly and independently associated with reduced survival, regardless of the presence of PH on RHC (41). Causes of death were not analysed in that study, but the results are in concordance with ours, and also might suggest that higher sPAP could be associated with a more severe disease, with higher visceral involvement and higher mortality.

Our study supports the use of screening tools, such as the algorithm proposed by the DETECT study (27, 28), or the evaluation of the risk factors found in the PHAROS study (42), for early detection of PH/PAH even in early SSc. This kind of approach could help identifying those selected patients in need of a RHC to confirm diagnosis and clarify the cause of PH.

The main strength of the present study

**Table IV.** Bivariate associations for pulmonary hypertension, defined as an estimated pulmonary systolic pressure >40 mm Hg on Doppler echocardiography, according to SSc subset.

| | lcSSC (n=594) | | dcSSc (n=482) | |
|---|---|---|---|---|
| | OR (95% CI) | *p*-value | OR (95% CI) | *p*-value |
| Age at 1st non Raynaud's event | 1.05 (1.03-1.07) | <0.001 | 1.06 (1.04-1.08) | <0.001 |
| Disease duration (m) | 0.99 (0.96-1.03) | 0.782 | 0.99 (0.96-1.03) | 0.625 |
| Time RO – non Raynaud's event (m) | 1.01 (0.98-1.04) | 0.467 | 1.07 (1.02-1.12) | 0.008 |
| mRSS | 1.02 (0.97-1.06) | 0.432 | 1.03 (1.01-1.06) | 0.008 |
| DLCO (% of predicted) | 0.96 (0.95-0.98) | <0.001 | 0.97 (0.95-0.98) | <0.001 |
| Sex (men) | 1.03 (0.53-2.01) | 0.919 | 1.30 (0.80-2.11) | 0.284 |
| Scl-70 positive | 1.04 (0.60-1.79) | 0.890 | 1.09 (0.68-1.73) | 0.724 |
| ACA positive | 1.45 (0.92-2.30) | 0.109 | 2.47 (1.00-6.10) | 0.050 |
| Active disease | 2.29 (1.41-3.73) | 0.001 | 2.06 (1.19-3.56) | 0.010 |
| Elevated acute phase reactants | 1.40 (0.86-2.28) | 0.179 | 2.19 (1.36-3.55) | 0.001 |
| Digital ulcers | 1.24 (0.76-2.03) | 0.384 | 2.49 (1.57-3.95) | <0.001 |
| Synovitis | 1.05 (0.58-1.89) | 0.879 | 1.04 (0.61-1.76) | 0.879 |
| Joint contractures | 2.43 (1.46-4.04) | 0.001 | 1.26 (0.80-1.98) | 0.319 |
| Tendon friction rubs | 1.42 (0.60-3.37) | 0.419 | 0.95 (0.57-1.60) | 0.856 |
| CK elevation | 1.63 (0.78-3-43) | 0.196 | 1.10 (0.62-1.95) | 0.732 |
| Digestive involvement | 1.31 (0.79-2.16) | 0.288 | 1.69 (0.97-2.92) | 0.062 |
| Pulmonary fibrosis | 2.40 (1.48-3.90) | <0.001 | 2.44 (1.52-3.91) | <0.001 |
| Lung restrictive defect | 4.08 (2.50-6.65) | <0.0001 | 2.26 (1.42-3.60) | 0.001 |
| Cardiac conduction blocks | 2.73 (1.36-5.48) | 0.005 | 3.53 (1.93-6.46) | <0.001 |
| Diastolic dysfunction | 4.46 (2.60-7.67) | <0.001 | 2.98 (1.78-4.99) | <0.001 |
| LVEF <55% | 3.55 (1.50-8.40) | 0.004 | 6.71 (2.91-15.5) | <0.001 |
| Renal crisis | 0.79 (0.09-6.48) | 0.824 | 3.04 (1.40-6.60) | 0.005 |
| Proteinuria | 1.93 (0.87-4.25) | 0.104 | 4.13 (2.15-7.20) | <0.001 |

yr: year; m: month; RO: onset of Raynaud's phenomenon; mRSS: modified Rodnan Skin Score; DLCO: diffusion capacity of the lung for carbon monoxide; ACA: anticentromere autoantibody; dcSSc: diffuse cutaneous systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; CK: creatin kinase; LVEF: left ventricular ejection fraction; OR: odds ratio; CI: confidence interval.
*Disease duration was calculated on the basis of the onset of the first non-Raynaud's event.
†Digestive involvement includes oesophagus, stomach and gut symptoms.

**Table V.** Multivariate logistic regression models for the clinical associations with pulmonary hypertension, defined as estimated systolic pressure > 40 mm Hg on Doppler echocardiography in lcSSc subset.

| | Model 1 Complete (n=349) | | Model 2 Backward stepwise (n=349) | |
|---|---|---|---|---|
| Variable | OR (95% CI) | *p*-value | OR (95% CI) | *p*-value |
| Age at 1st non Raynaud's event (yr) | 1.04 (1.01-1.07) | 0.017 | 1.04 (1.01-1.07) | 0.006 |
| DLCO (% of predicted) | 0.97 (0.95-0.99) | 0.004 | 0.97 (0.95-0.99) | 0.003 |
| Active disease | 1.69 (0.65-4.43) | 0.284 | - | - |
| ACA positive | 2.88 (1.16-7.14) | 0.023 | 2.30 (1.06-5.01) | 0.015 |
| Elevated acute phase reactants | 0.38 (0.14-0.99) | 0.048 | | |
| Joint contractures | 3.72 (1.59-8.67) | 0.002 | 3.68 (1.65-8.20) | 0.001 |
| CK elevation | 1.25 (0.36-4.36) | 0.725 | - | - |
| Pulmonary fibrosis | 1.09 (0.43-2.81) | 0.850 | - | - |
| Lung restrictive defect | 2.74 (1.18-6.37) | 0.019 | 2.65 (1.21-5.81) | 0.015 |
| Cardiac conduction blocks | 2.50 (0.80-7-75) | 0.113 | - | - |
| Diastolic dysfunction | 1.55 (0.58-4.13) | 0.382 | - | - |
| LVEF <55% | 0.74 (0.10-5.21) | 0.761 | - | - |
| Proteinuria | 1.41 (0.37-5.35) | 0.616 | - | - |
| Constant | 0.05 (0.01-0.54) | 0.014 | 0.05 (0.01-0.42) | 0.006 |
| AIC | 0.665 | | 0.644 | |
| BIC | -1757.53 | | -1795.48 | |
| BIC' | 19.492 | | -18.463 | |

OR: odds ratio; CI: confidence interval; yr: year; DLCO: diffusion capacity of the lung for carbon monoxide; ACA: anticentromere autoantibody; lcSSc: limited cutaneous systemic sclerosis; CK: creatin kinase; LVEF: left ventricular ejection fraction; AIC: Akaike information criteria; BIC: Bayesian information criteria.

is the large sample size of early SSc patients included. Besides, missing data are relatively low in the EUSTAR database (less than five percent in our cohort) (29, 43). This allowed us to assess the associations of elevated sPAP, measured by TTE, even across population subgroups as those with very early disease or the SSc subsets.It is also important to emphasise that our study analysed the associations of elevated sPAP with baseline clinical characteristics from the first EUSTAR visit of patients with less than 3 years from the first non-RP symptom, really at an early stage of the disease. In this regard, all the results are confirmed in the subgroup of 656 patients with less than three years from the first SSc symptom, including RP (data shown in supplementary material). Another important strength is the real life conditions of all patients included in the EUSTAR cohort. Therefore, we are confident that the study sample is representative and our results robust and reliable.

Our study has also several limitations. First, TTE is observer dependent, and there is significant variability in technique and interpretation of results. Both sPAP estimation and left ventricular diastolic dysfunction are frequently inaccurate. Although most EUSTAR centres have special interest in SSc, it is possible that the echocardiographic results could not be comparable between different centres. Second, since they were not available in the EUSTAR database at the time of data extraction, RHC measurements were not analysed in the study. Therefore, explanations about the associations of elevated sPAP, although plausible and clinically relevant, remain speculative. Third, while nowadays there is external monitoring done for a selection of patients, at the time of the data export, external monitoring was not part of the EUSTAR registry, then, although it is assumed that in each participating centre, all patients with SSc are included in the EUSTAR database, there could be a bias towards the inclusion of more severe cases only. Fourth, since the new 2013 ACR/EULAR classification criteria for SSc (44) were not available in this early database, only patients fulfilling the preliminary

**Table VI.** Multivariate logistic regression for the clinical associations of pulmonary hypertension, defined as estimated systolic pressure >40 mm on Doppler echocardiography in patients with dcSSc subset.

| | Model 1 Complete (n=231) | | | Model 2 Backward stepwise (n=231) | | |
|---|---|---|---|---|---|---|
| | OR (95% CI) | | *p*-value | OR (95% CI) | | *p*-value |
| Age at 1st non Raynaud's event (yr) | 1.07 | (1.03-1.12) | <0.0001 | 1.08 | (1.04-1.12) | <0.0001 |
| Time RO - non RO (yr) | 1.12 | (0.96-1.29) | 0.136 | 1.12 | (1.00-1.26) | 0.046 |
| mRSS | 1.02 | (0.97-1.07) | 0.458 | - | | - |
| DLCO (% of predicted) | 0.99 | (0.96-1.01) | 0.351 | - | | - |
| Active disease | 0.67 | (0.22-2.01) | 0.474 | - | | - |
| ACA positive | 3.23 | (0.54-19.1) | 0.196 | - | | - |
| Elevated acute phase reactants | 1.16 | (0.44-3.04) | 0.767 | | | |
| Digital ulcers | 4.17 | (1.61-10.8) | 0.003 | 4.90 | (2.05-11.7) | <0.0001 |
| Digestive involvement | 1.60 | (0.49-5.23) | 0.438 | - | | - |
| Pulmonary fibrosis | 1.18 | (0.45-3.10) | 0.736 | - | | - |
| Lung restrictive defect | 0.96 | (0.38-2.45) | 0.938 | - | | - |
| Cardiac conduction blocks | 3.04 | (0.88-10.4) | 0.078 | 3.89 | (1.29-11.7) | 0.016 |
| Diastolic dysfunction | 1.32 | (0.47-3.71) | 0.595 | - | | - |
| LVEF <55% | 2.43 | (0.44-13.4) | 0.307 | - | | - |
| Renal crisis | 1.47 | (0.25-8.68) | 0.670 | - | | - |
| Proteinuria | 7.27 | (1.60-33.0) | 0.010 | 10.1 | (2.79-37.2) | <0.0001 |
| Constant | 0.001 | (0.00-0.04) | <0.0001 | 0.001 | (0.00-0.01) | <0.0001 |
| AIC | 0.774 | | | 0.707 | | |
| BIC | -1019.9 | | | -1073.3 | | |
| BIC' | 9.800 | | | -43.611 | | |

OR: odds ratio; CI: confidence interval; yr: year; RO: onset of Raynaud's phenomenon; mRSS: modified Rodnan Skin Score; DLCO: diffusion capacity of the lung for carbon monoxide; ACA: anticentromere autoantibody; dcSSc: diffuse cutaneous systemic sclerosis; LVEF: left ventricular ejection fraction; AIC: Akaike information criteria; BIC: Bayesian information criteria.

1980 ACR criteria for the classification of SSc (30) were selected. It is known that there could be patients not fulfilling SSc ACR 1980 classification criteria with severe visceral involvement, especially PAH (45, 46). Nevertheless, these cases are rare (47). Also in relation to the criteria, data on telangectasias or capillaroscopy were not available at the time of data extraction, and both have been associated with increased risk of PAH (48). Finally, most EUSTAR patients come from European countries and the vast majority is therefore Caucasian. As a result, our findings should be carefully extrapolated to other ethnic groups (49).

In conclusion, we found that the prevalence of elevated sPAP on TTE is considerable (17%), and associated with severe visceral involvement in early SSc patients. This points out to the convenience of performing a complete cardiac assessment including careful sPAP measurement in all SSc patients, even at early stages of the disease. The association of elevated sPAP with other vascular findings, such as renal crisis or digital ulcers, would suggest the presence of a vascular phenotype in which endothelial cell dysfunction could play a major role. Addressing the true existence of such phenotype would need much more work and specific studies, not included in the scope of the present analysis. Our results suggest that, although some patients with elevated sPAP on TTE may present a true isolated PAH, others might have PH in the setting of severe pulmonary or left cardiac involvement. A screening strategy for the detection of PAH/PH could help to identify which of these early patients are in need of a RHC to diagnose and clearly determine the cause of PH.

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