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Assessment of systemic and pulmonary arterial remodelling in women with systemic sclerosis

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Objectives: Systemic sclerosis (SSc) leads to pulmonary circulation dysfunctionand there are some indications of systemic circulation impairment. We evaluated the influence of SSc on the elastic properties of large systemic arterial walls and potential correlations between systemic and pulmonary circulation involvement.
Method: We examined 75 consecutive women (mean age 53.13 ± 10.1 years) with confirmed SSc [mean disease duration (DD) 7.1 ± 9.1 years] and 21 age-matched female volunteers (mean age 52.6 ± 8.3 years, ns). Pulse wave velocity (PWV) and transthoracic echocardiography were performed. SSc patients were divided into two groups according to the median of DD: ≤ 3 years (39 patients) and > 3 years (36 patients).
Results: Patients with DD > 3 years had higher PWV than those with DD ≤ 3 years and controls (log PWV: 2.23 ± 0.23 vs. 2.13 ± 0.16 and vs. 2.11 ± 0.16 m/s; p = 0.028 and 0.029, respectively). In addition, echocardiographic indices showed impaired right ventricular (RV) function in the patients with DD > 3 years. Also in these SSc patients, PWV correlated with clinical and echocardiographic parameters of pulmonary circulation: age (r = 0.64, p < 0.0001), acceleration time of pulmonary ejection (AcT; r = −0.38, p = 0.021), and tricuspid regurgitation peak gradient (TRPG; r = 0.34, p = 0.04). Multiple linear regression analysis showed that PWV was independently associated with DD (β = 0.22, p = = 0.02), AcT (β = −0.215, p = 0.03), and age (β = 0.44, p < 0.001).
Conclusions: In patients with SSc lasting more than 3 years, the disease is characterized by increased stiffness of the large systemic arteries. Longer duration of SSc leads simultaneously to the increased stiffness of the large systemic arteries and to the progressive impairment of RV function and its coupling to the pulmonary arterial bed.

Systemic sclerosis (SSc) is a connective tissue disease characterized by progressive fibrosis of the skin and internal organs. Cardiopulmonary complications adversely influence the prognosis in SSc patients. SSc can lead to pulmonary hypertension and right ventricular (RV) dysfunction (1, 2). Some data suggest that SSc is associated with the prevalence of large vessel disease, endothelial function impairment, and increased arterial wall stiffness, but the underlying mechanisms remain unclear (3, 4). The relationship between parameters of systemic and pulmonary arterial wall dysfunction has not yet been established. Echocardiography is a widely available diagnostic tool for the detection of RV dysfunction. Aortic pulse wave velocity (PWV) reflects the whole aorta function and is used to evaluate the stiffness of large vessels (5).

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The aim of this study was to evaluate the influence of SSc on large systemic arterial wall properties and examine the correlations between systemic and pulmonary circulation.

Method

We examined 75 consecutive women (mean age 53.1 ± 10.1 years) with confirmed SSc according to the American College of Rheumatology (ACR) criteria (6) and 21 age-matched female volunteers (mean age 52.6 ± 8.3 years) with no signs and symptoms of pulmonary disease, who presented no echocardiographic evidence of structural heart disease. The exclusion criteria were: coronary artery disease; atrial fibrillation; cardiac pacing; and significant valvular heart disease. Additionally, to minimize the influence of systemic hypertension, we excluded patients with arterial hypertension grade II-III, according to the European Society of Cardiology/European Respiratory Society (ESC/ESH) 2013 guidelines of management in

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hypertension (7), and left ventricular hypertrophy (LVH) on echocardiography with LV wall thickness > 11 mm. Restrictive LV filling at resting echocardiography was also an exclusion criterion. We also excluded patients with advanced interstitial lung disease, renal failure requiring replacement therapy, and age below 18 years.

All patients gave written consent. The study was accepted by the Local Bioethics Committee (no. KB/216/2012).

Clinical examination, including advancement of skin involvement with the use of the Rodnan score, was performed in every patient according to a standardized questionnaire.

Fasting blood samples were taken from an antecubital vein. Serum N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration was measured using Elecsys and Cobas E analysers (Roche Diagnostics GmbH, Mannheim, Germany) and a value higher than 125 pg/mL was regarded as abnormal, as indicated by the manufacturer.

In all patients, high-resolution computed tomography (HRCT), chest radiography, pulmonary function testing, and measurement of single breath diffusing lung capacity for carbon monoxide (DLCO) were performed.

Echocardiographic studies were performed with a Phillips iE33 system (Andover, MD, USA). The dimensions of the right and left ventricles were measured in the parasternal long-axis view in the late diastole. Left ventricular ejection fraction (LVEF) was calculated according to Simpson's formula. Tricuspid annulus plane systolic excursion (TAPSE) was measured using one-dimensional M-mode echocardiography. Using continuous-wave Doppler, the tricuspid regurgitation peak gradient (TRPG) was calculated according to the simplified Bernoulli equation (8). Acceleration time of pulmonary ejection (AcT) was measured using pulse wave Doppler. The RV Tei index was calculated as described previously (9).

PWV was determined three times in every patient using the Complior SR system (Artech Medical, Paris, France) with two tonometric sensors TY-306, which recorded pressure changes in the range 0.1–100 Hz over the carotid and femoral arteries. A pulse wave curve was created after computer processing of these impulses. Automatically determined delay time of the wave appearance has been used for aortic PWV counting. According to the ESC guidelines, a value of > 10 m/s was considered abnormal (7).

Normality of distribution was verified using the Shapiro-Wilk test. Variables characterized by a normal distribution are expressed as mean and standard deviation. Parameters without a normal distribution are expressed as median (interquartile range). Positively skewed parameters were log transformed to normalize their distributions. Patients with SSc and controls were compared with the Mann-Whitney U-test or the Student's t-test depending on the parameter distribution. For categorical variables, groups were compared with the χ^2 test or Fisher's exact test. Correlations between PWV and other parameters were evaluated by Spearman's correlation coefficients or Pearson's product-moment correlation coefficient. Multiple linear regression evaluated predictors of log PWV; $p < 0.05$ was considered statistically significant.

Results

The study comprised 75 SSc women and 21 female volunteers. The mean disease duration (DD) was 7.1± 9.1 years. Basic data obtained from the studies performed in SSc and controls are shown in Table 1.

Table 1. Comparison of data for SSc patients and the control group.

Parameters	SSc patients (n = 75)	Control group (n = 21)	p-value
log PWV (m/s)	2.14 (1.81–2.65)	2.11 (1.72–2.47)	ns*
Biochemical parameters			
log NT-proBNP	4.58 ± 0.80	4.27 ± 0.38	0.031†
Echocardiographic parameters			
LVEF (%)	66 (53–80)	66 (60–70)	ns*
LVDD (mm)	44.8 ± 4.6	42.6 ± 3.1	0.007†
RV (mm)	25.63 ± 3.28	23.55 ± 2.35	0.009†
RV/LV	0.56 (0.41–0.90)	0.52 (0.43–0.65)	ns*
TRPG (mmHg)	26.19 ± 5.48	18.00 ± 3.94	< 0.0001†
AcT (ms)	120 (65–180)	130 (110–160)	0.026*
TAPSE (mm)	18 (11–30)	23 (22–30)	< 0.0001*
Tei RV	0.38 ± 0.06	0.29 ± 0.02	< 0.0001†

SSc, Systemic sclerosis; PWV, pulse wave velocity; NT-proBNP, N-terminal pro-brain natriuretic peptide; LVEF, left ventricular ejection fraction; LVDD, left ventricular diastolic dysfunction; TRPG, tricuspid regurgitation peak gradient; AcT, acceleration time; TAPSE, tricuspid annulus plane systolic excursion; Tei RV, right ventricular myocardial performance; ns, not significant.
* Mann–Whitney U-test.
†Student's t-test.
Values given as median (interquartile range) or mean ± standard deviation.

Table 2. Comparison of SSc patients with disease duration (DD) > 3 years and the control group.

Parameter	SSc with DD > 3 years (n = 36)	Control group (n = 21)	p-value
log PWV	2.23 ± 0.23	2.11 ± 0.16	0.029†
PWV > 10 m/s	13 (36.1)	2 (9.5)	0.028
log NT-proBNP	4.62 ± 1.0	4.27 ± 0.38	ns†
LVEF (%)	65 (53–73)	66 (60–70)	ns*
LVDD (mm)	44.72 ± 4.94	42.6 ± 3.11	ns*
RV (mm)	25.69 ± 3.61	23.55 ± 2.35	0.01†
TRPG (mmHg)	26.83 ± 5.32	18.0 ± 3.94	< 0.0001†
AcT (ms)	120 (65–180)	130 (110–160)	0.028*
TAPSE (mm)	18 (11–30)	23 (22–30)	< 0.0001*
Tei RV	0.368 ± 0.06	0.29 ± 0.02	< 0.0001†

SSc, Systemic sclerosis; PWV, pulse wave velocity; NT-proBNP, N-terminal pro-brain natriuretic peptide; LVEF, left ventricular ejection fraction; LVDD, left ventricular diastolic dysfunction; TRPG, tricuspid regurgitation peak gradient; AcT, acceleration time; TAPSE, tricuspid annulus plane systolic excursion; Tei RV, right ventricular myocardial performance; ns, not significant.
* Mann–Whitney U-test.
†Student's t test.
Values given as n (%), median (interquartile range), or mean ± standard deviation.

The mean PWV values in SSc patients (9.0 ± 1.9 m/s) and in the control group (8.3 ± 1.3 m/s) were similar (p = 0.34). We separately analysed two groups of SSc patients identified by an arbitrary distinction according to the DD: ≤ 3 years (39 patients) and > 3 years (36 patients). These groups did not differ in basic clinical parameters [body surface area (BSA), Rodnan score] or renal and lung function. However, the former had significantly lower PWV than the latter (log PWV: 2.13 ± 0.16 vs. 2.23 ± 0.23 m/s, p = 0.028).

There was no difference in age between the controls and SSc patientswith DD > 3 years (52.6 ± 8.3 vs. 54.83 ± 10.3, p = 0.40) and between SSc patients with DD ≤ 3 years and SSc patients with DD > 3 years of DD (51.56 ± 9.6 vs. 54.83 ± 10.3, p = 0.16). We compared patients with SSc with DD > 3 years and the controls (Table 2).

Patients with DD > 3 years presented echocardiographic parameters indicating RV involvement and higher PWV than the controls (log PWV: 2.23 ± 0.23 vs. 2.11 ± 0.16 m/s, p = 0.029) (Figure 1).

We found that, in SSc patients, PWV correlated positively with age (r = 0.56, p < 0.0001) and DD (r = 0.34, p = 0.003), and negatively with AcT (r = −0.37, p = 0.001) and EF (r = −0.36, p = 0.002). In SSc patients with DD > 3 years, PWV correlated positively with age (r = 0.64, p < 0.0001) and TRPG (r = 0.34, p = 0.041), and negatively with AcT (r = −0.38, p = 0.021) and EF (r = −0.58, p < 0.0001).

Multiple regression analysis was performed using the whole SSc group. The model obtained showed that increased PWV was significantly related to the DD even after the adjustment for age and AcT. We found that PWV was independently associated with AcT (β = −0.215, p == 0.03), age (β = 0.438, p < 0.0001), and DD (β = 0.22, p == 0.02).

Discussion

Pulmonary circulation involvement, especially pulmonary arterial hypertension, is one of the most serious complications in SSc (1). Identification of non-invasive predictors of RV dysfunction by using transthoracic echocardiography (1) may allow early detection of cardiac involvement and may help to select patients for further invasive evaluation.

In our study we confirmed impairment of RV and pulmonary circulation in SSc patients. Not only was the RV dimension larger in the SSc group but also the Tei index was higher in SSc patients when compared to controls (Table 2). Moreover, shorter AcT in these patients suggests disturbed coupling to the pulmonary arterial bed. The mean TAPSE was decreased in SSc patients. Of note,

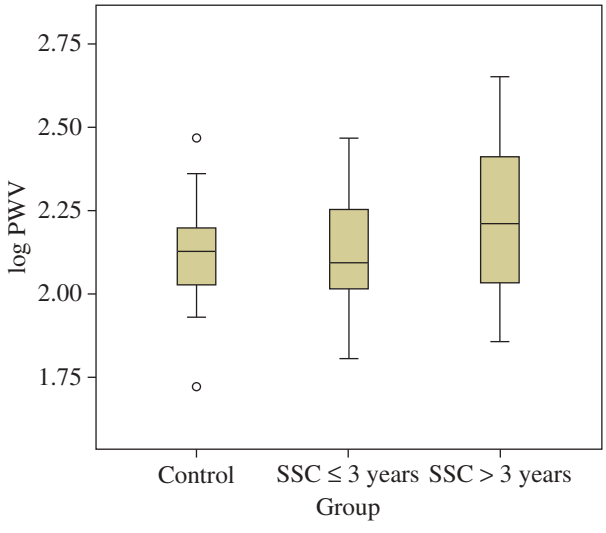

Figure 1. Pulse wave velocity (PWV) in SSc patients with disease duration (DD) ≤ 3 years, DD > 3 years, and controls.

these differences were evident not only in SSc patients with DD > 3 years but also in the whole SSc group compared to controls.

According to the recent expert consensus document on arterial stiffness, carotid-femoral pulse wave velocity (cfPWV) is the gold standard for the measurement of arterial stiffness (10). Recent data suggest increased arterial stiffness also in SSc patients (11, 12). Colaci et al (13) found higher PWV in SSc patients than in controls. They found that PWV was abnormal in almost all patients with DD $\geq$ 5 years but observed no correlation between arterial PWV and abnormal pulmonary artery pressure. By contrast, Roustit et al (14) found no differences in PWV between SSc patients and controls (8.6 vs. 8.7 m/s, p = ns), and similar data were reported by Zeng et al (15).

Our findings confirm an increased aortic stiffness in SSc patients with DD > 3 years compared with controls. Moreover, the abnormal value PWV (> 10 m/s) was more frequently observed in this group. In the patients studied, PWV strongly correlated with age ($r = 0.64$, $p < 0.0001$). Multiple linear regression analysis showed that PWV was independently associated with age.

Of interest, our study detected both pulmonary and systemic circulation impairment in SSc patients, PWV positively correlated with the TRPG and negatively with AcT. Multiple linear regression analysis also showed that PWV and was independently associated with AcT and time since diagnosis.

To our knowledge this is the first study showing a correlation between pulmonary and systemic circulation impairment in SSc patients. Despite the different physiology of pulmonary and systemic vessels, we have revealed that, in the course of SSc, simultaneous impairment of systemic and pulmonary circulation occurs.

Limitations of the study

In SSc patients systemic hypertension occurred more frequently than in the control group. However, we found no significant differences in systolic and diastolic blood pressure values between SSc patients and controls. In subgroups of patients (SSc with DD > 3 years, SSc $\leq$ 3 years and controls) there was no significant difference in the prevalence of systemic hypertension. In SSc patients, angiotensin-converting-enzyme (ACE) inhibitors, calcium channel blockers, diuretics, and statins were more frequently used than in controls but this group of agents is in fact protective for systemic circulation.

Conclusions

SSc in patients with the disease lasting more than 3 years was characterized by increased stiffness of the large systemic arteries. Longer duration of SSc leads simultaneously to an increased stiffness of the large systemic arteries and to the progressive impairment of RV function and its coupling to the pulmonary arterial bed.

Acknowledgements

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