Six-minute walk test in or out in evaluation of systemic sclerosis patients?

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ABSTRACT

Objective. *Interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) are the leading causes of death in systemic sclerosis (SSc) patients. Although the six-minute walk test (6MWT) is used for evaluating ILD and PAH in clinical practice, no data are available on six-minute walk distance (6MWD) and oxygen desaturation in SSc patients without ILD and PAH.*

Methods. *Prospectively collected data of the 6MWTs at baseline and 6-month follow-up of 300 consecutive SSc patients, included in the Ghent University Hospital Systemic Sclerosis Unit between May 2006 and April 2015 were analysed.*

Results. *The mean 6MWD of 165 SSc patients without ILD and PAH who performed a 6MWT at baseline or at the 6-month visit was 484±93m. Patients in the diffuse cutaneous (DcSSc) subgroup (435±94m) walked less than in the limited (LSSc) subgroup (499±91m, p=0.04) and tended to walk less than in the limited cutaneous (LcSSc) subgroup (483±92m, p=0.15). In 115 SSc patients without ILD and PAH who walked at both moments, there was no significant difference between the 6MWDs (mean difference -7.60m 95%CI [-19.93m; 4.73m], p=0.23) and the oxygen desaturation was not statistically different in 102 of them (mean difference 0.41% 95%CI [-0.49%; 1.31%], p=0.37).*

Conclusion. *In SSc without ILD and PAH, the 6MWD and oxygen desaturation is clinically stable over a 6 months period. The DcSSc subgroup walks less than the LSSc and the LcSSc subgroup.*

Introduction

Systemic sclerosis (SSc) is an orphan auto-immune connective tissue disease characterised by vasculopathy, auto-immunity and fibrosis of skin and visceral organs. Progressive fibrosis of skin and internal organs (gastrointestinal tract, heart, kidneys, and lungs) results in major organ damage and high morbidity and mortality (30-35% at 10 years after first diagnosis) (1, 2). Nowadays, interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) are the leading causes of disease-related mortality (counting for up to 60% of the disease related mortality) (1, 2).

The six-minute walk test (6MWT) is a submaximal, aerobic exercise test which correlates with the daily physical activity. It is a simple, safe, non-invasive, valid, reliable test. The six-minute walk distance (6MWD) of the 6MWT is generally used for evaluating functional exercise capacity, assessing prognosis, determining outcome of clinical trials and evaluating response to treatment in heart and lung diseases like PAH, ILD, chronic obstructive pulmonary disease (COPD) and congestive heart failure (3-5). However, data on 6MWD in SSc are conflicting. Although there are previous studies on 6MWT in unselected SSc cohorts and the 6MWD seems reproducible in SSc and SSc-ILD, there are no data available on normal values in SSc patients without PAH and ILD (6-9). A recently performed systematic review and meta-analysis shows that SSc-PAH patients walk less than SSc without PAH and that the pooled mean 6MWD in 3185 unselected SSc patients is 366m, 95% confidence interval (CI) (344-388m). The major limitations of this systematic review and meta-analysis were the different diagnostic tools and criteria used for diagnosing SSc-ILD and the variation in the methodology to perform a 6MWT in the included studies (10).

Oxygen desaturation during the 6MWT correlates with the diffusing capacity of the lung for carbon monoxide [DLCO] in SSc patients and in the sub-

group with diffuse cutaneous SSc and ILD (11, 12).
Since SSc patients are at risk for developing PAH and ILD and the 6MWT is generally used for evaluating PAH and ILD, this study wants to evaluate the 6MWT at baseline and 6-month follow-up in a cohort of unselected SSc patients and in the SSc subgroup without ILD and PAH.

Methods

Patient selection

Data of the prospective collection of the 6MWT test results at baseline and at month 6 of a SSc-specific evaluation visit of 300 consecutive SSc patients, fulfilling the preliminary classification criteria of the American College of Rheumatology (ACR), the LeRoy and Medsger criteria for early SSc and/or the ACR/European League Against Rheumatism (EULAR) classification criteria, included in the Ghent University hospital systemic sclerosis unit between May 2006 and April 2015 were analysed (13-15). Patients were classified as limited systemic sclerosis (LSSc), limited cutaneous systemic sclerosis (LcSSc) or diffuse cutaneous systemic sclerosis (DcSSc) according to the Leroy classification criteria (16). Approval was obtained by the Ethics Committee of the Ghent University Hospital and all patients signed informed consent.

The six-minute walk test

All 6MWTs were performed on a 50-m corridor at room air without additional oxygen, at the same location and time throughout the study. According to the American Thoracic Guidelines, blood pressure, heart rate and oxygen saturation were measured at the beginning and the end of the 6MWT (3). Oxygen saturation was determined using finger probe pulse oximeter or ear lobe probe when no good pulse signal was obtained by the finger probe. Oxygen desaturation was defined as a decrease in peripheral capillary oxygen saturation (SpO2) of ≥4% and a severe desaturation as SpO2 ≤88% at the end of the test (11). Patient self-reported postwalk dyspnea and fatigue were evaluated using the Borg scale, which is a well-validated scoring system on a 0-10 point scale to grade the patients perception of shortness of breath and level of fatigue (0= nothing at all, 10= maximum) (3).

Systemic sclerosis specific visit

In line with (inter)national clinical practice guidelines, medical history and drug intake of each patient were recorded at each visit and a standard clinical examination was performed including measurement of skin involvement (modified Rodnan Skin Score [mRSS]), evaluating vascular involvement (digital pitting scars, ulcerations or gangrene) and musculoskeletal involvement (synovitis, tendon friction rubs, joint contractures, muscle weakness) (2, 17). A chest x-ray, a transthoracic echocardiography, a pulmonary function test (including total lung capacity [TLC], forced vital capacity [FVC], forced expiratory volume in 1 second [FEV1] and DLCO, expressed as % of the predicted value), a standard blood test (with erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], haemoglobin, serum creatinin, creatin kinase [CK] level, complement factors C3 and C4 and serum SSc-specific antibody screening) and an electrocardiography were done at each visit (17, 18). High resolution chest computed tomography (HRCT) was performed at baseline. Optional investigation (HRCT on visits beside the baseline visit, right heart catheterisation [RHC], ventilation-perfusion scintigraphy, arterial blood gas sampling) was at the discretion of the treating physicians and since 2009 according to the guidelines on diagnosis of pulmonary hypertension by the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) (19, 20).
Patients were asked to complete the Health Assessment Questionnaire and the SSc Disease Activity Score (DAS) and Disease Severity Score (DSS) were calculated (21, 22). The 10 items of the DAS were recorded by anamnesis (patient self-reported items), clinical examination (mRSS, scleredema, digital necrosis, arthritis), laboratory measures (ESR and complement factors C3 and C4) and pulmonary function test (DLCO) (21).
The DSS were calculated for 9 different organ systems: general, peripheral vascular, skin, joints and tendons, muscle, gastrointestinal, lung, heart, and kidney. Each DSS is graded from 0 (no involvement) to 4 (major involvement), based on strictly defined criteria (22).

Interstitial lung disease

For ILD, the patients were classified independently by 2 investigators (EV, KT) in three subgroups (no ILD, limited ILD or extensive ILD), according to the simplified flow diagram described by Goh *et al*. (23). Patients were classified in the no ILD subgroup when no disease specific abnormalities were detected on HRCT. Extensive ILD was defined as extent of disease >20% on HRCT or FVC <70% when the disease extent on HRCT was indeterminate. Limited ILD was defined as extent of the disease on HRCT <20% or FVC ≥70% when HRCT extent was indeterminate. If there were no HRCT and/or pulmonary functional testing data available, data on ILD were reported as missing. The interrater variability for scoring ILD was good ($\varkappa$=0.81, p<0.001, 95%CI 0.74-0.88).

Pulmonary arterial hypertension

Patients were screened for PAH by clinical examination and echocardiographic parameters according to the ESC/ERS guidelines (19). PAH was confirmed by RHC: mean pulmonary artery pressure ≥25mmHg during RHC with pulmonary capillary wedge pressure (PCWP) ≤15mmHg in the absence of extensive ILD as described above (19). Patients were excluded for subgroup classification SSc with or without PAH when the tricuspid valve regurgitation (TR) peak gradient was above 2.8 meter per second (m/s), in the absence of RHC or when RHC confirmed pulmonary hypertension (PH) not classified as PAH.

Statistical analysis

For descriptive purposes, absolute numbers with percentages were shown for nominal categorical variables, medians with interquartile ranges (IQR) for ordinal categorical variables and

means with standard deviation (SD) for continuous variables. Means of continuous outcome variables between subgroups were compared using the independent samples t-test or the ANOVA test with application of the Tukey correction procedure for multiple testing for pairwise comparisons. Means of continuous outcome variables within subgroups were analysed using the paired samples t-test. A significance level of 0.05 was assumed for the statistical tests. All *p*-values were the results of two-tailed tests. Statistical analysis was performed with SPSS statistical software, v. 23.0.

Results

Patient characteristics

From the 300 SSc patients included in the Ghent University hospital systemic sclerosis unit between May 2006 and April 2015, all patients fulfilled the LeRoy and Medsger criteria for early SSc and 161 (54%) the preliminary ACR classification criteria (13, 14). From the 43 SSc patients included in the cohort since December 2013, 38 (88%) fulfilled the ACR/EULAR classification criteria for SSc (15).

286 SSc patients performed a first 6MWT at baseline or at 6-month visit and 205 patients performed a 6MWT at both moments (Fig. 1). The baseline characteristics of those 286 SSc patients at the time of the first 6MWT are depicted in Table I. 76% were female with a mean age of 52±14 years. 25% were classified as LSSc, 58% as LcSSc and 17% as DcSSc. Five SSc patients were not evaluated by HRCT or pulmonary function testing and were excluded for subgroup classification SSc with or without ILD. At the time of the first 6MWT, 110 (39%) patients had ILD (34% limited ILD and 6% extensive ILD). Sixteen patients were excluded for subgroup classification SSc with or without PAH, since 15 had a TR peak velocity above 2.8 m/s, but were not evaluated by RHC and one had PH secondary to left heart disease. Seven patients had PAH.

Of these 286 SSc patients, 259 (91%) performed the first 6MWT at baseline and 27 (9%) at the 6-month visit, mainly due to logistic problems (Fig. 1). In the group of 259 patients that performed the first 6MWT at baseline, there was a higher percentage of LSSc and a lower percentage of DcSSc patients as compared to the group of 27 patients who performed the first 6MWT at 6-month visit (LSSc/LcSSc/DcSSc 68 [26%]/151 [58%]/40 [15%] and 3 [11%]/16 [59%]/8 [30%] respectively, p=0.02). In accordance with this finding, there was a significant difference in the mRSS between the 2 groups. (Supplementary File 1).

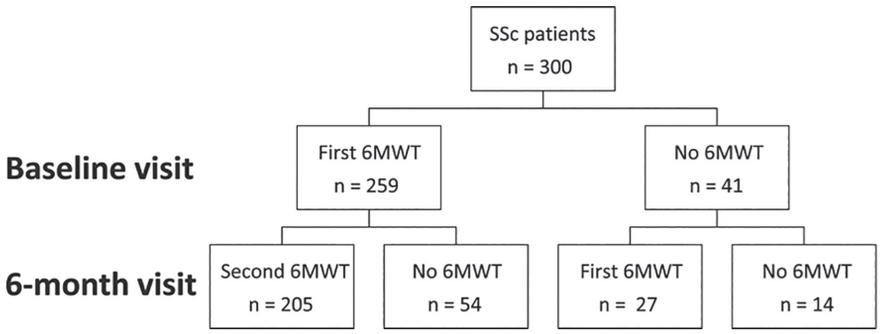

Fig. 1. Number of patients performing a 6MWT at baseline and at 6-month visit.
SSc: systemic sclerosis; n: number of patients; 6MWT: six-minute walk test.

Table I. Characteristics of 286 SSc patients at the moment of the first 6MWT (at baseline or at 6-month visit).

Characteristic	n	
Age (years) °	286	51.53 ± 13.76
♀/♂*	286	216/70 (75.5/24.5)
Raynaud*	286	281 (98.3)
Disease duration since first Raynaud (months)#	281	70 (20-158.5)
Disease duration since first non-Raynaud (months)#	253	32 (11-99)
LSSc/LcSSc/DcSSc*	286	71/167/48 (24.8/58.4/16.8)
mRSS #	286	5.0 (0.0-10.0)
DAS #	276	0.5 (0.5-2.0)
ACA*	286	132 (46.2)
AntiScl70 AB*	286	51 (17.8)
PAH*	270	7 (2.6)
Limited ILD*	281	94 (33.5)
Extensive ILD*	281	16 (5.7)

°: mean ± SD, *: n (%), #: median (IQR).
N: number of patients; SD: standard deviation; IQR: interquartile range; ♀: women; ♂: men; n: number; %: percent; Raynaud: presence of Raynaud's phenomenon; non-Raynaud: presence of first non-Raynaud's phenomenon; LSSc: limited systemic sclerosis; LcSSc: limited cutaneous systemic sclerosis; DcSSc: diffuse cutaneous systemic sclerosis; mRSS: modified Rodnan Skin Score; DAS: disease activity score; ACA: anti-centromere antibodies; AntiScl70 AB: anti-topoisomerase I antibodies; ILD: interstitial lung disease; PAH: pulmonary arterial hypertension.

Percentage performing a 6MWT

From the 300 SSc patients, 14 did not perform a 6MWT at baseline nor at the 6-month visit. After exclusion of 8 SSc patients due to logistic problems, 286 of the 292 (98%) SSc patients performed a 6MWT. Six patients were unable to perform a 6MWT (2 due to leg amputation and 4 due to immobility).

First 6MWD in different subgroups

The mean 6MWD for 286 unselected SSc patients was 457±111m. After exclusion of 121 patients, the mean 6MWD for 165 SSc patients without ILD or PAH was 484±93m (Table II). Subgroup analysis within the SSc group without ILD and PAH showed that DcSSc patients (435±94m) walked less than LSSc patients (499±91m, *p*=0.04) and tended to walk less than LcSSc patients (483±92m, *p*=0.15). There was no significant difference in the mean 6MWD between the LSSc and the LcSSc subgroup (*p*=0.53). Subgroup analysis within the unselected SSc group revealed similar findings on 6MWD for the LSSc, LcSSc

Table II. 6MWD during the first 6MWT in different subgroups of SSc.

	n	First 6MWD mean ± SD (m)		n	First 6MWD mean ± SD (m)		n	First 6MWD mean ± SD (m)	*p*
SSc	286	456.55±110.85							
♀SSc	216	446.23±110.64	♂SSc	70	488.40±106.05				0.005
LSSc	71	475.35±108.84*#°	LcSSc	167	460.15±106.27*#”	DcSSc	48	416.21±121.40*°”	*0.013 #0.590 °0.012 “0.039
SSc-noILD	171	477.75±98.02*#°	SSc-limitedILD	94	432.31±119.83*#”	SSc-extensiveILD	16	399.81±121.24*°”	*<0.001 #0.003 °0.016 “0.501
SSc-noPAH	263	465.91±104.13	SSc-PAH	7	328.86±147.31				0.001
SSc-noILD-noPAH	165	484.2±92.65							
♀SSc-no-ILD-noPAH	124	478.91±92.80	♂SSc-noILD-noPAH	41	500.2±91.45				0.203
LSSc-noILD-noPAH	58	499.22±90.73*#°	LcSSc-noILD-noPAH	92	482.79±91.72*#”	DcSSc-noILD-noPAH	15	434.73±93.80*°”	*:0.054 #:0.534 °: 0.042 “: 0.146

6MWT: six-minute walk test; n: number of patients; 6MWD: six-minute walk distance; m: meter; SD: standard deviation; SSc: systemic sclerosis; noILD: without interstitial lung disease; ILD: interstitial lung disease; noPAH: without pulmonary arterial hypertension; PAH: pulmonary arterial hypertension; ♀: women; ♂: men; LSSc: limited systemic sclerosis; LcSSc: limited cutaneous systemic sclerosis; DcSSc: diffuse cutaneous systemic sclerosis.

Table III. Evolution of the 6MWD from the baseline to the 6-month visit.

	n	6MWD T0 (m) mean ± SD	6MWD T6 (m) mean ± SD	Pearson's correlation coefficient	Mean Difference (95%CI) (m)	*p*
SSc	205	461.96 ± 103.36	463.95 ± 98.31	0.804	1.99 (-6.73; 10.71)	0.653
LSSc	54	469.63 ± 113.95	463.13 ± 104.73	0.828	-6.50 (-24.18; 11.18)	0.464
LcSSc	118	466.94 ± 96.21	471.23 ± 88.65	0.767	4.29 (-7.29; 15.87)	0.465
DcSSc	33	431.61 ± 107.79	439.27 ± 117.83	0.859	7.67 (-13.85; 29.18)	0.473
SSc-extensiveILD	10	357.20 ± 123.58	397.20 ± 144.51	0.897	40.00 (-5.82; 85.82)	0.080
SSc-limitedILD	72	449.82 ± 107.42	457.35 ± 100.91	0.867	7.53 (-5.19; 20.25)	0.242
SSc-no ILD	120	478.72 ± 94.64	474.34 ± 91.14	0.736	-4.38 (-16.58; 7.83)	0.479
SSc-PAH	7	328.86 ± 147.31	374.14 ± 144.98	0.947	45.29 (1.22; 89.35)	0.046
SSc-no PAH	186	470.81 ± 97.93	470.70 ± 94.43	0.784	-0.11 (-9.27; 9.06)	0.982
SSc-noILD-no PAH	115	485.84 ± 88.99	478.24 ± 90.52	0.723	-7.60 (-19.93; 4.73)	0.225
LSSc-no-ILD-noPAH	42	499.81 ± 91.09	488.38 ± 89.33	0.735	-11.43 (-31.90; 9.04)	0.266
LcSSc-noILD-noPAH	64	487.70 ± 80.32	485.58 ± 77.31	0.611	-2.13 (-19.51; 15.26)	0.808
DcSSc-noILD-noPAH	9	407.33 ± 107.35	378.67 ± 129.07	0.929	-28.67 (-66.66; 9.32)	0.120

n: number of patients; 6MWD: six-minute walk distance; T0: baseline visit; T6: 6-month visit; m: meter; SD: standard deviation; CI: confidence interval; SSc: systemic sclerosis; LSSc: limited systemic sclerosis; LcSSc: limited cutaneous systemic sclerosis; DcSSc: diffuse cutaneous systemic sclerosis; ILD: interstitial lung disease; noILD: without interstitial lung disease; PAH: pulmonary arterial hypertension; noPAH: without pulmonary arterial hypertension.

and DcSSc subgroups, but the level of significance was reached for the difference between the DcSSc and LcSSc subgroup (p=0.04), and between the DcSSc and LSSc subgroup (p=0.01) (Table II).

SSc-PAH patients walked significantly less than SSc patients without PAH (p<0.01). There was a significant difference in the 6MWD between the SSc extensive ILD, SSc limited ILD and SSc no ILD subgroups (p<0.01). Patients without ILD (478±98m) walked significantly more than the patients with limited ILD (432±120m, p<0.01) and patients with extensive ILD (400±121m, p=0.02). The mean 6MWD for patients with limited ILD and extensive ILD was not statistically significant (p=0.50). Female SSc patients walked less as compared to males in the unselected SSc population (p<0.01) and tended to walk less in the subgroup without ILD and PAH (p=0.20) (Table II).

Evolution of the 6MWD from the baseline to the 6–month visit

205 unselected SSc patients performed a 6MWT at baseline and at 6-month visit. There was no significant difference in the distance walked at both moments in 205 unselected SSc patients (mean difference 1.99m, 95 confidence interval [CI] [-6.73m; 10.71m], p=0.65) and in 115 SSc patients without ILD and PAH (mean difference -7.60m 95%CI [-19.93m; 4.73m], p=0.23). Similar findings with small CI's were seen in the SSc subgroup without ILD and the SSc subgroup without PAH. For the subgroups of SSc and SSc without ILD and PAH according to Leroy and Medsger classification, the 95%CIs were broader (Table III).

Oxygen saturation during the first 6MWT in different subgroups

Oxygen saturation was measurable by finger probe in 250 (87%) of the 286 SSc patients performing a 6MWT. The

Table IV. Oxygen saturation during the first 6MWT in different subgroups of SSc.

	N	SpO2 Begin SpO2 End mean±SD (%)	ΔSat mean±SD (%)	Δsat≥4% Sat≤88% N(%)		N	SpO2 Begin SpO2 End mean±SD (%)	ΔSat mean±SD (%)	Δsat≥4% Sat≤88% N(%)		N	SpO2 Begin SpO2 End mean±SD (%)	ΔSat mean±SD (%)	Δsat≥4% Sat≤88% N(%)	p
SSc	250	98±3 98±4	0±4	17 (7) 9 (4)											
♀ SSc	189	98±2[a] 98±4[b]	0±3[c]	10 (5)[d] 5 (3)[e]	♂SSc	61	97±3[a] 97±5[b]	1±4[c]	7 (12)[d] 4 (7)[e]						[a] 0.03 [b] 0.02 [c] 0.31 [d]0.14 [e]0.23
LSSc	70	98±3[f *#°] 98±3[g*#°]	0±3[h*#°]	1 (1)[i*#°] 2 (3)[j*#°]	LcSSc	140	98±2[f*#”] 97±5[g*#”]	1±4[h*#”]	15 (11)[i*#”] 7 (5) [j*#”]	DcSSc	40	97±2[f*°”] 98±2[g*°”]	0±2[h*°”]	1(3)[i*°”] 0(0)[j*°”]	[f*]0.75/[#]0.98/[°]0.85/[”]0.73 [g*]0.24/[#]0.22/[°]0.85/[”]0.73 [h*]0.11/[#]0.13/[°]0.97/[”]0.38 [i*]0.02/[#]0.03/[°]0.97/[”]0.16 [j*]0.30/[#]0.71/[°]0.72/[”]0.30
SSc-noILD	153	98±2[k*#°] 98±4[l*#°]	0±4[m*#°]	10 (7) [n*#°] 5 (3) [o*#°]	SSc-limited ILD	80	97±3[k*#”] 97±4[l*#”]	0±4[m*#”]	5 (6)[n*#”] 3 (4)[o*#”]	SSc-extensive ILD	12	98±1[k*°”] 97±3[l*°”]	1±3[m*°”]	2 (17)[n*°”] 0 (0)[o*°”]	[k*]<0.01/[#]0.33/[°]0.72/[”]0.74 [l*]0.22/[#]0.28/[°]0.52/[”]0.92 [m*]0.40/[#]0.80/[°]0.52/[”]0.38 [n*]0.40/[#]1.00/[°]0.38/[”]0.39 [o*]0.79/[#]0.98/[°]0.82/[”]0.78
SSc-noPAH	232	98±2[p] 98±4[q]	0±3[r]	12 (5)[s] 7 (3)[t]	SSc-PAH	6	95±4[p] 89±8[q]	6±8[r]	4 (67)[s] 2 (33)[t]						[p]0.02 [q] <0.01 [r]<0.01 [s] <0.01 [t]0.02
SSc-noILD-noPAH	148	98±2 98±4	0±4	9 (6) 5 (3)											
♀ SSc-no-ILD-noPAH	112	99±2[u] 98±4[v]	0±4[w]	5 (4)[x] 3 (3)[y]	♂SSc-noILD-noPAH	36	97±2[u] 97±4[v]	0±4[w]	4 (11)[x] 2 (6)[y]						[u]<0.01 [v]0.10 [w]0.89 [x]0.22 [y]0.60
LSSc-noILD-noPAH	57	98±2[z*#°] 99±2[A*#°]	0±2[B*#°]	1 (2)[C*#°] 1 (2)[D*#°]	LcSSc-noILD-noPAH	79	98±2[z*#”] 98±5[A*#”]	1+/-5[B*#”]	7 (9)[C*#”] 4 (5)[D*#”]	DcSSc-no ILD-noPAH	12	98±1[z*°”] 98±2[A*°”]	0+/-2[B*°”]	1 (8)[C*°”] 0 (0)[D*°”]	[z*]0.93/[#]0.99/[°]0.93/[”]0.95 [A*]0.37/[#]0.34/[°]0.94/[”]0.90 [B*]0.32/[#]0.29/[°]0.86/[”]0.95 [C*]0.22/[#]0.20/[°]0.66/[”]1.00 [D*]0.46/[#]0.55/[°]0.95/[”]0.64

N: number of patients; SpO2 Begin: oxygen saturation at the beginning of the 6MWT; SpO2 End: oxygen saturation at the end of the 6MWT; Δsat: oxygen desaturation during the 6MWT; %: percent; SD: standard deviation; SSc: systemic sclerosis; noILD: without interstitial lung disease; ILD: interstitial lung disease; noPAH: without pulmonary arterial hypertension; PAH: pulmonary arterial hypertension; ♀: women; ♂: men; LSSc: limited systemic sclerosis; LcSSc: limited cutaneous systemic sclerosis; DcSSc: diffuse cutaneous systemic sclerosis.

Table V. Evolution of the oxygen desaturation from the baseline to the 6–month visit.

	n	Δsat T0 (%) mean ± SD	Δsat T6 (%) mean ± SD	Pearson's correlation coefficient	Mean Difference (95%CI) (%)	*p*
SSc	176	0±4	0±4	0.755	-0.15 (-0.91; 0.62)	0.703
LSSc	54	0±3	0±2	0.023	0.48 (-0.26; 1.23)	0.201
LcSSc	97	1±4	0±5	0.961	-0.68 (-1.97; 0.61)	0.296
DcSSc	25	0±2	1±2	0.779	0.56 (-0.74; 1.86)	0.383
SSc-extensiveILD	7	2±4	-2±6	0.712	-3.86 (-10.07; 2.36)	0.180
SSc-limitedILD	60	0±4	0±5	0.386	-0.48 (-2.00; 1.03)	0.525
SSc-no ILD	106	0±4	0±3	0.495	0.29 (-0.58; 1.17)	0.510
SSc-PAH	6	6±8	0±9	0.367	-5.8 (-14.99; 3.33)	0.163
SSc-noPAH	162	0±3	0±4	0.456	0.10 (-0.66; 0.87)	0.788
SSc-noILD-noPAH	102	0±4	0±3	0.571	0.41 (-0.49; 1.31)	0.366
LSSc-no-ILD-noPAH	42	0±3	0±1	0.631	0.67 (-0.21; 1.55)	0.134
LcSSc-noILD-noPAH	54	0±4	1±3	0.579	0.26 (-1.29; 1.81)	0.738
DcSSc-noILD-noPAH	6	1±3	1±4	0.700	0.00 (-4.20; 4.20)	1.00

n: number of patients; Δsat: oxygen desaturation during the 6MWT; T0: baseline visit; T6: 6-month visit; %: percent; SD: standard deviation; CI: confidence interval; SSc: systemic sclerosis; LSSc: limited systemic sclerosis; LcSSc: limited cutaneous systemic sclerosis; DcSSc: diffuse cutaneous systemic sclerosis; ILD: interstitial lung disease; noILD: without interstitial lung disease; PAH: pulmonary arterial hypertension; noPAH: without pulmonary arterial hypertension.

mean oxygen saturation was 98+/-3% at the beginning of the test and 98±4% at the end of the test. Oxygen desaturation was seen in 17 (7%) and severe desaturation in 9 (4%) SSc patients. For 148 SSc patients without ILD or PAH, similar findings were found (Table IV).

Evolution of the oxygen desaturation from the baseline to the 6-month visit

For 176 unselected SSc patients performing a 6MWT at baseline and at 6-month visit, oxygen saturation was measurable by finger probe. There was no significant difference in the mean desaturation at both moments (mean difference -0.15% 95%CI [-0.91%; 0.62%], *p*=0.70) in 176 SSc patients and in 102 SSc patients without ILD and PAH (mean difference 0.41% 95%CI [-0.49%; 1.31%], *p*=0.37) (Table V).

Evolution of disease-related parameters from the baseline to the 6-month visit in the subgroup without ILD and PAH

In the SSc subgroup without ILD and PAH, the mean differences for CRP, CK, Creatinin, HgB level, lung functional parameters (TLC, FVC, FEV1), echocardiographic parameters (tricuspid valve regurgitation peak gradient and left ventricular ejection fraction) were similar between the 2 visits. Only the mean difference for mRSS and for DLCO was significantly different at the 6-month visit as compared to baseline (respectively 5.39 vs 4.61, mean difference 0.77 95%CI [0.18; 1.36], *p*=0.01 for mRSS and 76.16% vs 77.99%, mean difference -1.83% 95%CI [-3.56%; -0.11%], *p*=0.04 for DLCO), but this was without clinical relevance (Table VI).

Discussion

By analysing the 6MWTs at baseline and 6-month visit in the Ghent University hospital systemic sclerosis unit, the major findings were: 1. execution of 6MWT is feasible, as 98% of the SSc patients have performed the test; 2. the baseline mean 6MWD of 286 unselected SSc patients is 457±111m and the baseline mean 6MWD of 165 SSc patients without ILD and PAH is 484±93m; 3. DcSSc patients without ILD and PAH walk less than LSSc and tended to walk less than LcSSc patients without ILD and PAH; 4. in 205 unselected SSc patients and 115 SSc patients without ILD and PAH, there is no significant difference in the distance walked during a 6MWT at baseline and after 6 months; and 5. oxygen desaturation was clinically stable over

Table VI. Evolution of disease-related parameters from the baseline to the 6–month visit in 115 SSc patients without ILD and PAH.

	n	T0 Mean ± SD	T6 Mean ± SD	Pearson's correlation coefficient	Mean Difference (95%CI)	*p*
mRSS	114	4.61 ± 5.53	5.39 ± 5.83	0.844	0.77 (0.18; 1.36)	0.011
CRP (mg/dL)	114	0.43 ± 0.85	0.40 ± 0.86	0.165	-0.03 (-0.24; 0.17)	0.764
CK (U/L)	108	97.64 ± 98.57	93.16 ± 61.02	0.433	-4.48 (-21.79; 12.83)	0.609
Creat (mg/dL)	114	0.94 ± 0.21	0.94 ± 0.22	0.868	0.00 (-0.02; 0.02)	0.993
HgB (g/dL)	114	13.33 ± 1.19	13.332 ± 1.15	0.796	0.00 (-0.14; 0.14)	0.980
TLC (%pred)	114	103.22 ± 14.82	102.31 ± 13.92	0.719	-0.91 (-2.92; 1.09)	0.369
FVC (%pred)	114	113.25 ± 18.17	112.92 ± 18.56	0.910	-0.33 (-1.78; 1.12)	0.649
FEV1 (%pred)	114	99.99 ± 14.77	100.63 ± 14.60	0.837	0.64 (-0.92; 2.20)	0.417
DLCO (%pred)	115	77.99 ± 14.92	76.16 ± 14.86	0.804	-1.83 (-3.56; -0.11)	0.037
TR peak gradient (mmHg)	91	21.32 ± 4.35	23.30 ± 17.50	0.094	1.98 (-1.69; 5.65)	0.287
LVEF (%)	112	66.34 ± 6.64	65.86 ± 7.83	0.190	-0.48 (-2.21; 1.25)	0.582

n: number of patients; ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; T0: baseline visit; T6: 6-month visit; SD: standard deviation; CI: confidence interval; mRSS: modified Rodnan Skin Score; CRP: C-reactive protein; mg/dL: milligram per deciliter; CK: creatine kinase level; U/L: units per liter; Creat: Creatinin level; HgB: haemoglobin; g/dL: gram per deciliter; TLC: total lung capacity; %pred: percent of the predicted value; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; DLCO: diffusing capacity of the lung for carbon monoxide; TR: tricuspid valve regurgitation; mmHg: millimeter of mercury; LVEF: left ventricular ejection fraction; %: percent.

a 6-month period in 176 SSc patients and in 102 SSc patients without ILD and PAH.

To our knowledge, this is the first manuscript reporting the 6MWD walked during a 6MWT in an unselected subgroup of SSc patients without ILD and PAH. Subgroup analysis within the SSc group without ILD and PAH shows that DcSSc patients walk significantly less than LSSc patients and tend to walk less than LcSSc patients. In the unselected SSc group similar findings were seen, with reaching the level of significance for the mean 6MWD between the DcSSc and LcSSc subgroup. Previous reports described no significant difference between the 6MWD for LcSSc and DcSSc, but smaller number of patients were included (48-95 SSc patients) and patients with ILD and/or with PAH were not excluded in these studies (7, 24).

In our cohort, the number of patients included in the DcSSc subgroup without ILD and without PAH is rather small, which might be an explanation for not reaching the level of significance comparing the DcSSc and LcSSc patients without ILD and without PAH. To our knowledge, no data have been reported for LSSc. We found a mean 6MWD of 499±91m for 58 LSSc patients without ILD and PAH.

All the mean distances walked during the 6MWT by our SSc patients are less than the reported mean 6MWD of 571±90m of 444 healthy persons between 40 and 80 years old (25). Possible explanations for the shorter walk distance could be gender differences, musculoskeletal involvement, skin fibrosis, microvascular damage or variations in methodology. It is known that SSc mostly affects women and that women walk less as compared to men. Casanova et al. reported a mean 6MWD of 555±81m in 206 healthy women and 585±96m in 238 healthy males (25). The percentage of women is higher in our SSc population as compared to the reported healthy population (76% *vs*. 46%) and SSc women walk less as compared to the males in the unselected SSc population, and tended to walk less in the SSc subgroup without ILD and PAH.

No significant difference is found in the distance walked during a 6MWT at baseline and 6- month visit in an unselected SSc population, in the SSc subgroup without ILD, the SSc subgroup without PAH and the SSc subgroup without ILD and PAH. This might indicate that the 6MWT is clinically stable over a short time-period in SSc and more specifically in the subgroups at risk for developing ILD and/or PAH. A systematic review on field walking tests in chronic respiratory disease found a pooled mean improvement of 26m on the second 6MWT for 13 studies on COPD and a pooled mean difference of 20m for 4 studies on ILD (4, 5). A study with 444 healthy subjects showed an improvement of 12m on the second 6MWT (25). In our study, the 95%CIs on the mean difference 6MWD did not show broad overlap with the above mentioned mean differences of 12-26m for the unselected SSc population, the SSc subgroup without ILD, the SSc subgroup without PAH and the SSc subgroup without ILD and PAH. Moreover, 6 months between the 2 tests seems a long period for a learning curve, none of these patients included in the subgroup without ILD and PAH was started with medication for ILD or PAH in this period and there were no arguments for disease progression in the SSc subgroup without ILD and PAH (Table VI). No conclusion can be made for the subgroups of SSc and SSc without ILD and PAH according to the Leroy and Medsger classification since the 95%CIs on the mean difference 6MWD are broader (up to 67m), possibly due to small number of patients included in the different subgroups.

Since 6MWT is generally used in heart and lung disease as PAH and ILD, to our opinion, each SSc patient without ILD and PAH should at least once perform a 6MWT at the time of diagnosis of SSc and if possible afterwards on a regular basis. The 6MWD and oxygen desaturation obtained at the time of SSc diagnosis can be an individual reference value that can be used as a realistic treatment goal in each SSc patient who develops PAH or ILD (4, 5). The 6MWD and oxygen desaturation are clinically stable over a short time-period in SSc patients without ILD and PAH, almost all SSc patients are able to perform a 6MWT and oxygen saturation by finger probe was measured in the majority of SSc patients. Reference values for SSc patients may give some orientation, but should not be used for this purpose, since DcSSc patients walk less than LcSSc and LSSc patients and in SSc, other confounding factors besides pulmonary and cardiac manifestations are known. Musculoskeletal involvement and the use of non-steroidal anti-inflammatory drugs (NSAID) at the moment of the 6MWT may interfere with the results of the 6MWT (6, 7). In our cohort, 58 patients (20%) took NSAID at the moment of the first 6MWT. From the 205 patients who performed serial 6MWTs, the majority took no NSAID at both moments (156 patients) or NSAID at both moments (31 patients). Only 10 patients took NSAID at baseline only and 8 patients at 6-month follow-up only. Only for the latter group, the 6MWD was less at 6-month visit, without reaching the level of significance (probably due to small number of patients) (for 156 with no treatment with NSAIDs at both moments: 462±108m *vs*. 466±101m, mean difference 3.79m 95%CI [-5.90m; 13.48m], p=0.44); for 31 patients with NSAID treatment on both moments 453±84m *vs*. 454±90m, mean difference 1.13m 95%CI [-23.29m; 25.54m], p=0.93; for 10 patients with only NSAID treatment at baseline 484±78m *vs*. 481±100m, mean difference -3.00m 95%CI [-52.18m; 46.18m], p=0.89; and for 8 patients with only NSAID treatment at 6-month follow-up 464±120m *vs*. 441±83m, mean difference -23.50m 95%CI [-97.42m; 50.42m], p=0.48).

The major limitations of our study are the small number of SSc patients with ILD and with PAH at baseline and the fact that repeated 6MWTs were not performed at baseline. Indeed, only 39% of the patients were diagnosed with ILD. That fact that almost a fourth of the patients included in our cohort had limited SSc, without skin involvement, has definitely contributed to the lower percentages ILD compared to data of other registries. In the literature, up to 90% of the SSc patients might have some inter-

stitial abnormalities on HRCT, sometimes without restriction in the pulmonary functional testing (23, 26). In our cohort, only 2.6% had PAH at the moment of the first 6MWT. Again, the fact that a fourth of the patients included in our cohort had limited SSc has contributed to the low percentage of PAH. Further, 15 patients with a TR peak velocity ≥2.8 m/s, but without performed RHC, were excluded for classification PAH or no PAH. Two of these patients were diagnosed with PAH by RHC at the next follow-up visit. Since the purpose of this study was to evaluate the 6MWT at baseline and 6 month follow-up in a cohort of unselected SSc patients and in the SSc subgroup without ILD and PAH, we focussed on the data in the unselected SSc population and the subgroup without ILD and PAH. Although the ERS/ATS standard measurement warns for a learning effect and advises 2 repeated tests at baseline, we did not perform 2 tests at baseline and a learning effect at 6-month visit cannot completely be excluded (4).

Conclusion

98% of the SSc patients are able to perform a 6MWT and in 87% of them, oxygen saturation was measurable before and after the 6MWT. The mean 6MWD in SSc patients without ILD and PAH is lower than the mean 6MWD of a historical reported healthy control population and is clinically stable over a 6 months period. Within the SSc patients without ILD and PAH, the DcSSc subgroup walks less than the LSSc and tends to walk less than the LcSSc subgroup. Oxygen desaturation remains clinically stable over a 6-month period. A baseline 6MWT does seem to be of use in SSc specific evaluation at least as reference for those who futurely develop SSc-PAH/ILD.

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