A prospective, longitudinal study evaluating the baseline six-minute walk test as an individual reference value in 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). Although the six-minute walk test (6MWT) is used for evaluating ILD and PAH, no data are available on the evolution of the six-minute walk distance (6MWD) in SSc patients without ILD and PAH and whether the baseline 6MWD could serve as individual reference value for the management of those who will develop PAH or ILD.*

Methods. *Prospectively collected data of the first 6MWT (at baseline or 6-month follow-up) and the 6MWTs at 18-, 30-, 42-, 54-, and 66-month visit of 165 consecutive SSc patients without ILD and PAH, included in the Ghent University SSc Cohort between May 2006 and December 2016 were analysed.*

Results. *96-100% of the included patients performed a 6MWT during the follow-up visits. The mean 6MWD during the baseline 6MWT of 165 SSc patients without ILD and PAH (35% limited, 56% limited cutaneous, 9% diffuse cutaneous SSc) was 484.20±92.65m with no significant difference in the 6MWD at different follow-up visits as compared to baseline. In 46 SSc patients without ILD and PAH who performed a 6MWT at baseline and at 66-month visit, the 6MWD walked at 66-month visit correlated with the baseline 6MWD (r=0.564, p<0.001).*

Conclusion. *In SSc without ILD and PAH, the 6MWT is feasible and the 6MWD is clinically stable over a 66 months period. Hence, the individual 6MWD might be used as individual reference value in management of those who will develop PAH or ILD.*

Introduction

Systemic sclerosis (SSc) is an orphan auto-immune connective tissue disease characterised by vasculopathy and fibrosis of the skin and visceral organs. Progressive fibrosis of the skin and internal organs (gastrointestinal tract, heart, kidneys and lungs) results in major organ damage and high morbidity and mortality (1). Today, interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) are the leading causes of disease related mortality in SSc (2-4).

The six-minute walk test (6MWT) is a submaximal, aerobic exercise test which correlates with the daily physical activity (5, 6). It is a simple, safe, non-invasive, reliable test and 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 such as PAH, ILD, chronic obstructive pulmonary disease (COPD), ischaemic heart disease, and congestive heart failure (5-8). From literature, the suggested minimal important difference (MID) in 6MWD in patients with heart or lung diseases (COPD, ILD and PAH) participating in a rehabilitation programme or receiving pharmacotherapy lies between 25 and 33m (6, 7). The European Society of Cardiology/ European Respiratory Society (ESC/ ERS) guidelines describe target values and treatment goals for 6MWD in PAH (>440m), but they emphasise that the treatment goals should be adjusted to the clinical context of the individual patient (9, 10). SSc is a heterogeneous disease and the 6MWD might be influenced by non-cardiopulmonary disease manifestations (11, 12). Yet, no

attempts have been made to describe a reference value for the individual SSc patient who eventually will develop PAH and the question whether the baseline 6MWD obtained at the time of SSc diagnosis can be used as an individual reference value for those SSc patients without ILD and PAH who develop ILD or PAH during follow-up still has not been attested yet. Even though the 6MWD seems reproducible in SSc and SSc-ILD and in SSc-PAH, the 6MWD at the moment of PAH diagnosis is no adequate surrogate marker for haemodynamic parameters at that moment and follow-up 6MWDs are no appropriate outcome measure to assess changes in haemodynamics during follow-up of treated SSc-PAH patients (13-15). Recently, one study evaluated the 5 year follow-up of the 6MWT in a subgroup of SSc patients (diffuse cutaneous SSc [DcSSc] with ILD) (16). Another study found that during a follow-up period of 20 months, worsening of the 6MWD was associated with echocardiographic proven cardiac dysfunction in SSc patients without ILD and pulmonary hypertension (non-invasive evaluated by echocardiography) (17).

However, data on 6MWD in SSc patients without ILD and PAH are scarce (18). Such data might be handy on individual patient level. More specifically, if the 6MWD would be stable over time in such a cohort then it could serve as individual reference value for management of those who will develop PAH or ILD. 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 (19). Nevertheless, to our knowledge, there are no data available on the long-term evolution of the 6MWDs walked during follow-up 6MWTs in SSc patients without ILD and PAH.

Since SSc patients are at risk for developing PAH and ILD and the 6MWT is generally used for evaluating PAH and ILD, the aim of the study is to evaluate the evolution of the 6MWT from baseline to 66-month follow-up in a cohort of unselected SSc patients without ILD and PAH and to evaluate whether the baseline 6MWT could be used as individual reference value in those who futurely develop PAH or ILD.

Methods

Study population

Data of the prospective collection of the 6MWT results obtained at each SSc-specific evaluation visit from May 2006 until December 2016 of the first 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 Scleroderma Cohort of the Ghent University Hospital, were analysed (20-22). The visits were planned at baseline, at month 6, and yearly thereafter (month 18, 30, 42, 54 and 66). Patients were classified according to the LeRoy classification criteria as limited cutaneous systemic sclerosis (LcSSc) -with skin thickening restricted to the skin of the face and distal of elbows and knees-, diffuse cutaneous systemic sclerosis (DcSSc) -with more extensive skin thickening- or limited systemic sclerosis (LSSc) -without skin involvement. (23) Approval was obtained by the Ethics Committee of the Ghent University Hospital (2008/385) and all patients signed informed consent.

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 at the end of the 6MWT (5). Oxygen saturation was determined using a finger probe pulse oximeter or an ear lobe probe when no good pulse signal was obtained by the finger probe. 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) (5).

According to The Belgian Systemic Sclerosis Cohort, medical history and drug intake of each patient were recorded at each visit (baseline, month 6, 18, 30, 42, 54 and 66) and a standard clinical examination was performed including measurement of skin involvement (modified Rodnan Skin Score [mRSS]), evaluation of vascular involvement (digital scars, ulcerations or gangrene) and of musculoskeletal involvement (synovitis, tendon friction rubs, joint contractures, muscle weakness). 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 diffusing capacity of the lung for carbon monoxide [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 (19, 24-26). High resolution chest computed tomography (HRCT) was performed at baseline. Optional investigations (HRCT on visits beside the baseline visit, right heart catheterisation, ventilation-perfusion scintigraphy, arterial blood gas sampling) were at the discretion of the treating physicians and since 2009 according to the ESC/ERS guidelines on diagnosis of pulmonary hypertension (the 2009 and in 2015 revised guidelines) (9, 10, 27).

Patients were asked to complete the Health Assessment Questionnaire (HAQ). The SSc Disease Activity Score (DAS) and Disease Severity Score (DSS) were calculated at each visit (28, 29). 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) (28).

The DSS was 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 (29).

The baseline 6MWT was defined as the

first 6MWT performed in the first year after inclusion in the cohort (at baseline or at 6-month visit when not available at baseline). The accompanied baseline characteristics are those of the visit associated with the first 6MWT (19).

For ILD, the patients were classified in three subgroups (no ILD, limited ILD or extensive ILD), according to the simplified flow diagram described by Goh *et al*. (30) 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 available at baseline, data on baseline ILD were reported as missing. During the follow-up visits, patients kept their former classification, or were revaluated with HRCT when the yearly pulmonary function test or clinical examination changed.

Patients were screened for PAH by clinical examination and echocardiographic parameters according to the 2009 ESC/ERS guidelines. PAH was confirmed or dismissed by right heart catheterisation (RHC): mean pulmonary artery pressure ≥25mmHg with pulmonary capillary wedge pressure (PCWP) ≤15mmHg in the absence of ILD as described above (9). Patients were excluded for classification as SSc with/without PAH when the peak tricuspid valve regurgitation velocity (peak TVR) 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 and skewed continuous variables and means with standard deviation (SD) for symmetric continuous variables. Means of continuous outcome variables between subgroups were compared using the ANOVA test with application of the Tukey correction procedure for multiple testing for pairwise comparisons. Means of continuous outcome variables within subgroups between two time points were analysed using the paired samples T-test. The Pearson's correlation test (r) was used to determine any correlation between the 6MWD and clinical parameters with a normal distribution and the Spearman's correlation test (ϱ) for skewed distributed parameters. 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, version 23.0.

Table I. Baseline characteristics of 165 SSc without ILD and PAH.

Characteristic	n	
Age (years)°	165	48.02 ± 13.19
♀/♂*	165	124/41 (75.2/24.8)
Raynaud*	165	162 (98.2)
Disease duration since first Raynaud (months)§	162	60 (20-176)
Disease duration since first non-Raynaud (months)§	137	26 (10-74)
Smoker never/ex/current*	165	78/34/53 (47.3/20.6/32.1)
LSSc/LcSSc/DcSSc*	165	58/92/15 (35.2/55.8/9.1)
mRSS§	165	3 (0-7)
DAS§	162	0.5 (0-1.5)
HAQ§	141	0.25 (0.00-0.63)
AntiScl70 AB*	165	16 (9.7)
ACA*	165	100 (60.6)
FVC§	165	113 (99-126)
DLCO§	165	77 (69-88)
Peak TVR (m/s)§	131	2.3 (2.1-2.4)

°mean±SD; *n (%); §median (IQR).
SSc: systemic sclerosis; ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; n: number of patients; SD: standard deviation; IQR: interquartile range; ♀: women; ♂: men; %: 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; HAQ: health assessment questionnaire; AntiScl70 AB: anti-topoisomerase I antibodies; ACA: anticentromere antibodies; FVC: forced vital capacity, expressed as % of the predicted value; DLCO: diffusing capacity of the lung for carbon monoxide, expressed as % of the predicted value; Peak TVR: peak tricuspid valve regurgitation velocity; m/s: meter per second.

Results

Baseline characteristics

From the first 300 SSc patients included in the Systemic Sclerosis Cohort of the Ghent University, 165 SSc patients without ILD and PAH performed a 6MWT at baseline. 135 patients were excluded (110 having ILD at baseline [94 limited ILD, 16 extensive ILD], 8 having PH at baseline [7 PAH], 14 not performing a baseline 6MWT, and the others when no HRCT or RHC was performed at baseline, although recommended). All patients fulfilled the LeRoy and Medsger criteria for early SSc and 63 (38%) the preliminary ACR classification criteria. From the 25 SSc included in the cohort since December 2013, 22 (88%) fulfilled the ACR/EULAR classification criteria for SSc (20-22). Their baseline characteristics are depicted in Table I. 75% were female with a mean age of 48±13 years. 35% were classified as LSSc, 56% as LcSSc and 9% as DcSSc.

Evolution of the 6MWD from baseline to the different follow-up visits

The mean 6MWD of the 165 SSc patients without ILD and PAH at baseline was 484.20±92.65m and the median (IQR) follow-up was 42 (18–66) months. From the 165 SSc patients without ILD and PAH at baseline, 130/130 (100%) performed a 6MWT at the 18-month visit, 98/101 (97%) at the 30-month visit, 77/80 (96%) at the 42-month visit, 65/68 (96%) at the 54-month and 46/46 (100%) at the 66-month visit (Table II). In fact, at each visit, 96–100% of the patients performed a 6MWT. There was no significant difference in the distance walked at different follow-up visits as compared to baseline. The mean difference was 0.82m, 95%CI (-9.19m; 10.83m),

Table II. Evolution of the 6MWD from baseline to the different follow-up visits.

	N 6MWT	N Tx visit	6MWD T0 (m) mean ± SD	6MWD Tx(m) mean ± SD	Pearson's correlation coefficient	Mean Difference (95%CI) (m)	*p*	N new ILD (lim/ext) Tx	N new PAH Tx
T0	165	165	484.20 ± 92.65						
T0 *vs*. T18	130	130	487.13 ± 94.41	487.95 ± 96.30	0.817	0.82 (-9.19; 10.83)	0.871	4 (4/0)	0
T0 *vs*. T30	98	101	490.62 ± 90.31	488.07 ± 85.98	0.745	-2.55 (-15.20; 10.10)	0.690	0 (0/0)	1
T0 *vs*. T42	77	80	481.56 ± 95.56	466.52 ± 105.49	0.694	-15.04 (-33.01; 2.93)	0.100	1 (1/0)	1
T0 *vs*. T54	65	68	480.79 ± 97.47	480.86 ± 102.53	0.765	0.08 (-16.96; 17.12)	0.993	2 (2/0)	0
T0 *vs*. T66	46	46	480.37 ± 90.25	483.74 ± 95.85	0.564	3.37 (-22.49; 29.23)	0.794	3 (3/0)	3

N 6MWT: number of patients performing a six-minute walk test; N Tx visit; number of patients having a follow-up visit at month x; 6MWD: six-minute walk distance; T0: baseline visit; Tx: x-month visit; T18: 18-month visit; T30: 30-month visit; T42: 42-month visit; T54: 54-month visit; T66: 66-month visit; m: meter; SD: standard deviation; CI: confidence interval; N newILD (lim/ext) Tx: number of new diagnoses of (limited/extended) interstitial lung disease at x-month visit; N newPAH Tx: number of new diagnoses of PAH at x-month visit.

Table IIIA. Correlation of the 6MWD at 66-month visit with the clinical parameters at baseline and at 66-month visit. Table IIIB. Correlation of the 6MWD at 66-month visit with the clinical parameters at baseline and at 66-month visit in those patients without ILD and without PAH at 66-month visit (After exclusion of the 8 patients who developed ILD and/or PAH).

Table IIIA	N	n°	correlation coefficient r or ϱ* (*p*)		N	n°	correlation coefficient r or ϱ* (*p*)
Length V0	46	169 (163-174)	0.084 (*p*=0.577)	Weight V0	46	67 (58-79)	-0.133 (*p*=0.380)
Dis dur Rayn V0	45	58 (19-183)	0.041 (*p*=0.790)	Dis dur nonRayn V0	38	45 (17-96)	-0.026 (*p*=0.875)
6MWD V0	46	481 (425-544)	0.564 (*p*<0.001)	Age V0	46	47 (41-54)	-0.246 (*p*=0.100)
mRSS V0	46	3 (0-6)	0.073 (*p*=0.629)	mRSS V66	43	6 (3-9)	-0.025 (*p*=0.876)
ESR V0	46	8 (3-15)	-0.023 (*p*=0.880)	ERS V66	44	10 (4-18)	-0.296 (*p*=0.051)
CRP V0	46	0.1 (0.1-0.3)	-0.100 (*p*=0.510)	CRP V66	45	0.3 (0.1-0.5)	-0.526 (*p*<0.001)
HgB V0	46	13.3 (12.9-14.2)	0.364 (*p*=0.013)	HgB V66	45	13.4 (12.3-14.2)	0.484 (*p*=0.001)
Creat V0	46	0.99 (0.90-1.07)	0.009 (*p*=0.953)*	Creat V66	45	0.85 (0.73-0.93)	-0.074 (*p*=0.628)*
CK V0	45	75 (51-107)	0.022 (*p*=0.886)	CK V66	44	83 (57-110)	0.048 (*p*=0.759)
TLC V0	45	103 (96-118)	-0.125 (*p*=0.414)	TLC V66	46	105 (96-118)	0.059 (*p*=0.698)
FVC V0	46	115 (103-130)	-0.079 (*p*=0.602)	FVC V66	46	105 (97-123)	0.053 (*p*=0.725)
FEV1 V0	46	104 (90-112)	0.104 (*p*=0.492)	FEV1 V66	46	93 (86-107)	0.169 (*p*=0.262)
DLCO V0	46	81 (69-89)	0.088 (*p*=0.560)	DLCO V66	46	72 (60-83)	0.230 (*p*=0.124)
Peak TRV V0	41	2.3 (2.2-2.5)	-0.138 (*p*=0.388)	Peak TRV V66	34	2.3 (2.1-2.5)	-0.533 (*p*=0.001)

Table IIIB	N	n °	correlation coefficient r or ϱ* (*p*)		N	n °	correlation coefficient r or ϱ* (*p*)
Length V0	38	169 (164-174)	0.213 (*p*=0.199)	Weight V0	38	65 (56-74)	-0.032 (*p*=0.850)
Dis dur Rayn V0	37	60 (20-194)	0.118 (*p*=0.487)	Dis dur nonRayn V0	31	36 (18-83)	0.095 (*p*=0.610)
6MWD V0	38	496.5 (435-556)	0.501 (*p*=0.001)	Age V0	38	47 (40-53)	-0.216 (*p*=0.192)
mRSS V0	38	3 (0-6)	0.323 (*p*=0.048)	mRSS V66	35	6 (2-9)	0.274 (*p*=0.112)
ESR V0	38	7.5 (3-12.5)	-0.295 (*p*=0.072)	ERS V66	36	10 (3-18)	-0.317 (*p*=0.060)
CRP V0	38	0.1 (0.1-0.2)	0.019 (*p*=0.911)	CRP V66	37	0.1 (0.1-0.4)	-0.208 (*p*=0.217)
HgB V0	38	13.3 (12.9-14.3)	0.424 (*p*=0.008)	HgB V66	37	13.4 (12.5-14.2)	0.337 (*p*=0.041)
Creat V0	38	0.99 (0.91-1.06)	0.042 (*p*=0.803)*	Creat V66	37	0.85 (0.73-0.93)	0.155 (*p*=0.359)*
CK V0	37	72 (53-119)	-0.245 (*p*=0.144)	CK V66	36	88 (61-130)	-0.027 (*p*=0.877)
TLC V0	37	103 (99-118)	-0.273 (*p*=0.102)	TLC V66	38	109 (98-119)	-0.203 (*p*=0.222)
FVC V0	38	115 (103-130)	-0.129 (*p*=0.440)	FVC V66	38	106 (97-127)	-0.067 (*p*=0.688)
FEV1 V0	38	102 (90-112)	0.017 (*p*=0.921)	FEV1 V66	38	94 (86-108)	0.001 (*p*=0.998)
DLCO V0	38	82 (69-90)	-0.088 (*p*=0.599)	DLCO V66	38	72 (60-82)	0.079 (*p*=0.639)
Peak TRV V0	34	2.3 (2.1-2.5)	-0.063 (*p*=0.724)	Peak TRV V66	27	2.2 (2.0-2.4)	-0.174 (*p*=0.386)

6MWD: six-minute walk distance (expressed in meter); V0: baseline visit; V66: 66-month visit; N: number of patients; n: value; °: median (interquartile range); length (expressed in centimeter); weight (expressed in kilogram); Dis dur Rayn: disease duration since first Raynaud (expressed in month); Dis dur nonRayn: disease duration since first non-Raynaud's phenomenon (expressed in month); age (expressed in year); mRSS: modified Rodnan skin score; ERS: erythrocyte sedimentation rate (expressed in millimeter per hour); CRP: C-reactive protein (expressed in milligram per deciliter): HgB: haemoglobin (expressed in gram per deciliter); Creat: serum creatinine (expressed in milligram per deciliter); CK: creatin kinase (expressed in units per liter); TLC: total lung capacity (expressed as % of the predicted value); FVC: forced vital capacity (expressed as % of the predicted value); FEV1: forced expiratory volume in 1 second (expressed as % of the predicted value); DLCO: diffusing capacity of the lung for carbon monoxide (expressed as % of the predicted value); peak TVR: peak tricuspid valve regurgitation velocity (expressed as meter/second); r: Pearson's correlation coefficient; ϱ: Spearman's correlation coefficient.
The Pearson's correlation coefficient (r) was used for all variables, except for *, where the Spearman's correlation coefficient (ϱ) was used (one patients received renal replacement therapy from baseline, explaining the skewed distribution of the serum creatinine at baseline and at 66-month visit).

Table IV. The 6MWD at 66-month visit for different subgroups.

	n	6MWD V66		n	6MWD V66		n		*p*
♀	36	479.56 ± 75.38	♂	10	498.80 ± 153.36				0.709
LSSc	15	490.27 ± 67.83*§°	LcSSc	28	481.25 ± 90.50*§”	DcSSc	3	474.33 ± 251.83*°”	*0.945 §0.955 °0.964 “0, 993
No ILD	41	490.76 ± 86.45	Limited ILD	5	426.20 ± 154.90				0.157
No PAH	42	496.00 ± 86.79	PAH	3	334.00 ± 115.58				0.004
Never Immunomodulatory	17	481.65 ± 89.17	Ever Immunomodulatory	29	484.97 ± 101.09				0.911
Never Vasodilatory	32	481.81 ± 102.66	Ever Vasodilatory	14	488.14 ± 81.51				0.839
No Pericardial effusion	43	490.12 ± 88.86	Pericardial effusion	2	322.50 ± 160.51				0.015

6MWD: six-minute walk distance; n: number of patients; V66: 66-month visit; ♀: female; ♂: male; LSSc: limited systemic sclerosis; LcSSc: limited cutaneous systemic sclerosis; DcSSc: diffuse cutaneous systemic sclerosis; ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; immunomodulatory: immunomodulatory drugs; vasodilatory: vasodilatory therapy.

p=0.87 for 130 patients between the 18-month visit and baseline and 3.37m, 95%CI (-22.49; 29.23m), *p*=0.79 for 46 patients between the 66-month visit and baseline. Over the 66-month period, 5 patients developed PAH, 10 patients limited ILD and none extensive ILD (Table II).

From the 46 patients without ILD and PAH at baseline who performed a 6MWT at baseline and at 66-month visit, 2 developed PAH, 4 developed limited ILD, 1 PAH and limited ILD and 1 PH secondary to left heart disease. With exclusion of these 8 patients, the mean difference was 10.53m, 95%CI (-14.83; 35.88m), *p*=0.41 between the 66-month visit (501.50±74.79m) and baseline (490.97±79.41m) (data not shown).

Correlations for the 6MWD at 66-month visit

For the 46 patients without ILD and PAH at baseline who performed a 6MWT at baseline and at 66-month visit, the 6MWD walked at 66 months, correlated with the baseline 6MWD (r=0.564, *p*<0.001), and with the peak TVR (r=-0.533, *p*=0.001), the haemoglobin level (r=0.484, *p*=0.001) and CRP level (r=-0.526, *p*<0.001) at 66 months. There was no significant correlation between the 6MWD at 66 month and the different pulmonary function parameters (Table IIIA).

After exclusion of the 8 patients who developed ILD or PAH, the 6MWD walked at 66 months, correlated with the baseline 6MWD (r=0.501, *p*=0.001) and with the haemoglobin level (r=0.337, *p*=0.041) at 66 months, but not with the CRP level (r=-0.208, *p*=0.217) at 66 months (Table IIIB).

The correlations with the 6MWD at the different visits (baseline, 18-month, 30-month, 42-month and 54-month visit), for all the patients seen at that visit and for the patients seen at that visit without ILD and PAH are described in the Supplementary Tables I, II, III, IV and V. All the 6MWDs at the different follow-up visits, irrespective whether the patients with ILD or PAH were included or not at that follow-up visit, correlated with the baseline 6MWD and with the HgB level at baseline and at that follow-up visit. The 6MWDs at some follow-up visits correlated with the CRP level at that visit, but never with the CRP level at baseline (Table III and the Supplementary Tables).

The 6MWD at 66-month visit for different subgroups

For the 46 patients without ILD and PAH at baseline who performed a 6MWT at baseline and at 66-month visit, there were no significant differences in the 6MWD walked at 66 months between men and women, between the different subgroups according to LeRoy (LSSc, LcSSc, DcSSc), between the subgroup that developed limited ILD and the subgroup that did not develop ILD, between the subgroups ever/never receiving immunomodulatory medication and between the subgroups ever/never receiving vasodilatory drugs. There was a significant difference between the subgroups who developed PAH and those who did not develop PAH (Table IV). The 3 patients developing PAH during 66 months follow-up walked less at baseline compared to the 42 patients who did not develop PAH, but this was not statistically different (439.67±71.81m *vs*. 485.07±91.68m, *p*=0.41). The 2 patients who had pericardial effusion on their echo at 66 months follow-up walked less than the subgroup without pericardial effusion (Table IV).

Discussion

By analysing the evolution of the 6MWTs from baseline up to the 5-year follow-up in the Systemic Sclerosis Cohort of the Ghent University, the major findings were: 1. The execution of a 6MWT is feasible, as 96-100% of the SSc patients performed a 6MWT at the follow-up visits; 2. The mean 6MWD during the baseline 6MWT of 165 SSc patients without ILD and PAH is 484.20±92.65m with no significant difference in the distance walked at different follow-up visits as compared to baseline; 3. in 46 SSc patients without ILD and PAH who performed a 6MWT at baseline and at 66-month visit, the 6MWD walked at 66-month visit correlates with the distance walked during the first 6MWT and with the peak TRV at 66-month visit.

To our knowledge, this is the first report on the 5-year evolution of the 6MWD walked during a 6MWT in an unselected cohort of SSc patients without ILD and PAH.

From literature, data on the 6MWD were missing in up to 30% of SSc patients in different studies without any explanation why the data were not reported (18, 31-33). However, in our cohort 96–100% of the SSc patients performed a 6MWT at baseline and at the different follow-up visits (19).

In SSc patients without ILD and PAH, the 6MWD is clinically stable over a

66 months period. There is no significant difference in the distance walked at different follow-up visits as compared to baseline. The mean differences compared with the baseline 6MWD are between -15.04m and 3.37m with rather small CIs for the different visits and with only a small overlap of the in literature mentioned minimal important difference in 6MWD. A recently published systematic review on exercise testing identified a meaningful change of 30m (between 25 and 33m) in 6MWD in patients with moderate to severe pulmonary disease (ILD, COPD or PAH) who received rehabilitation, pharmacotherapy, surgery or no treatment (6, 7).

For 46 SSc patients without ILD and PAH who performed a 6MWT at baseline and at 66-month visit, the 6MWD walked at 66-month visit correlates with the 6MWD at baseline.

Since the 6MWT is feasible and the 6MWD is clinically stable over a 66 months period in SSc without ILD and PAH, to our opinion, each SSc patient without ILD and PAH should at least once perform a 6MWT at the time of the diagnosis of SSc. The 6MWD at the time of the SSc diagnosis can be an individual reference value to be used as a realistic treatment goal in each individual SSc patient who develops PAH or ILD in the future.

A recently published study describes the 6MWT as a sensitive tool for the prediction of pulmonary hypertension in SSc (34). From the PHAROS registry, the 6MWD was a risk factor for developing PH in SSc patients at risk for PAH (35). In the DETECT study, the 6MWD was not associated with the presence of PAH (36). However, in the DETECT study, only 75% (309/408) of the included SSc patients with PAH or without PH performed a 6MWT (36).

Although the aim of our study was not the evaluation of the 6MWT as screening tool, outcome parameter or predictor for development of PAH or ILD, we do want to mention the findings of a significant correlation between the 6MWDs and the peak TRVs at different follow-up visit and a significant difference in 6MWD between the subgroups who did/did not develop PAH at 66 months. The latter is in line with the previously published findings of the baseline 6MWDs of 300 unselected SSc patients in our cohort (the SSc patients with PAH walked less than those without PAH and the SSc with ILD walked less than those without ILD at baseline) (19). We found no significant correlation between the 6MWD walked at 66-month visit and the different pulmonary function parameters. These results should be interpreted with caution, taking into account the small number of SSc patients (46) that walked at 66 months, with only 3 of the 5 patients who developed PAH and 5 of the 10 patients who developed limited ILD walked at 66 months, and none of the patients were diagnosed with extensive ILD during follow-up.

In contrast to the diseases for which the 6MWT was originally designed for, SSc is a heterogeneous disease. Unfortunately, SSc patients often do not suffer from a solitary heart or lung disease but from combinations of heart, lung and/or multiple other manifestations (skin fibrosis, musculoskeletal involvement, renal involvement). This may confound the 6MWT in SSc. We found that the haemoglobin level at the moment of the 6MWT correlated with the 6MWD. The 6MWDs at some follow-up visits correlated with the CRP level at that visit. Schoindre *et al*. found in their cohort of 78 SSc patients (54% with ILD on HRCT), that the CRP level correlated with the 6MWD in univariate analysis (rho= 0.34, p=0.0008) and there was a tendency for an association in multivariate analysis (p=0.054) (12). Question is whether CRP is a solitary marker of disease or whether it should be seen as a marker for the inflammatory process in the lung or pulmonary arteries in those SSc patients who developed ILD or PAH. The results of the 6MWT should always be interpreted in the global clinical context of the patient. In our centre, all the patients are yearly followed by a multidisciplinary team with experience in SSc.

Whether one should be suspicious of the development of PAH or ILD in an individual SSc patients with a decline in walked 6MWD from the individual baseline reference value during serial follow-up 6MWTs remains debatable.

The main limitation of the study is a possible selection bias at two levels. First, none of the included patients developed extensive ILD. As already mentioned, evaluating correlations was not within the remit of the current study, due to underpowering. However, evaluation of correlation between different baseline parameters (including capillaroscopic patterns at baseline) and the future development of ILD and PAH would be interesting, as had been stipulated earlier in a unicentre and a dual centre study by our group (37, 38). In future large scale multicentre standardised clinical care follow-up studies, correlations between baseline capillaroscopy and future development of ILD and PAH should be evaluated. Secondly, a cohort is a dynamic phenomenon with loss of included patients (due to mortality or loss of follow-up), temporary not showing up at a yearly SSc-specific visit, and not reaching yet one specific visit. Of the 165 patients without ILD and PAH at baseline, there were 46 who performed a 6MWT at 66 months. Besides patients who did not yet reach their 66-month follow-up visit (79 patients) and those who died (4 patients, 2 due to malignancy and 2 due to PAH), there might be a selection bias for those who were lost of follow-up (36 patients). Nevertheless, the baseline characteristics were not statistically different between the 46 patients having their 66-month follow-up and the 36 patients who were lost of follow-up (data not shown), but this does not exclude a selection bias.

Conclusion

To our knowledge, this is the first report on the 5-years evolution of the 6MWD walked during a 6MWT in an unselected cohort of SSc patients without ILD and PAH. There is no significant difference in the distance walked at different follow-up visits as compared to baseline. Hence, each SSc patient without ILD and PAH should at least once perform a 6MWT at the time of SSc diagnosis to have a reference 6MWD for management of those who develop PAH or ILD during follow-up.

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