Lack of Specificity of the 6-Minute Walk Test as an Outcome Measure for Patients with Systemic Sclerosis

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ABSTRACT. ***Objective.*** The 6-minute walk test (6MWT) is an important prognostic tool in various cardiovascular diseases and has been considered as a surrogate endpoint. However, conflicting results have been reported in systemic sclerosis (SSc). Our objective was to evaluate the relationships of the 6-min walking distance (6MWD) and organ damage in SSc.

Methods. Eighty-seven consecutive patients with SSc were included and prospectively investigated; they underwent 6MWT in addition to conventional assessment of possible lung, heart, kidney, skin, and muscle involvement, and disease activity scoring, severity, and quality of life determination.

Results. Twenty-six patients (30%) had an abnormal 6MWT and the mean 6MWD was 461.8 ± 103.0 m. When considering 6MWT as a binary variable — normal or abnormal — C-reactive protein (CRP) was the only independent variable associated with abnormal 6MWT. Considered as a continuous variable, the 6MWD was associated with measures of lung involvement and inflammation, with the activity and severity of disease, and also with quality of life; nevertheless, calcinosis was the only independent factor associated in multivariate analyses with a trend for an association for CRP.

Conclusion. The 6MWD relates to broad factors in SSc and these results raise doubts about the specificity of the 6MWD in this systemic disease, and its relevance to monitoring therapy. (J Rheumatol First Release June 1 2009; doi:10.3899/jrheum.081221)

Key Indexing Terms:
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Systemic sclerosis (SSc) is a heterogeneous connective tissue disorder characterized by widespread vascular lesions that culminates in fibrosis of the skin, vessels, and internal organs. Pulmonary and cardiac involvements have emerged as the leading causes of disease-related mortality[1]. In particular, pulmonary arterial hypertension (PAH) is a devastating condition recognized as a major complication of SSc that is responsible for excessive disability and mortality[2]. Therefore, early detection and management of PAH, and accurate methods of assessment of the efficacy of therapeutics are required. Despite the availability of several new drugs, outcome measures remain poorly defined and often poorly validated in the domain of SSc-related PAH (PAH-SSc)[3].

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The 6-minute walk test (6MWT) is a simple, safe, reproducible test used in the evaluation of several moderate to severe heart or lung diseases like primary PAH, idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease, and congestive heart failure[4-6]. This test is the most widely used as a primary outcome to assess therapeutic efficacy in PAH clinical trials[1,7-10] and the only measure of exercise capacity accepted by the U.S. Food and Drug Administration. The 6MWT was shown to be an independent predictor of mortality and a reliable tool for the assessment of exercise capacity in patients with idiopathic PAH. However, the 6MWT is not yet validated in the specific situation of PAH related to connective tissue diseases (CTD), particularly SSc. This is emphasized in the majority of studies, which included a majority of patients with idiopathic PAH and small nested subgroups of patients with PAH related to CTD. A recent metaanalysis of randomized controlled trials from our group has shown that new oral PAH treatments are less effective in improving exercise capacity in subsets of patients with CTD than in other patients, with nonsignificant effect sizes for exercise capacity. This point raised the question of the real efficacy of these drugs and/or the relevance of the 6MWT for the evaluation of treatment effect in PAH-SSc[11].

To date, no attempt has been made to investigate what is

actually being measured with the 6MWT in patients with SSc and which factors may account for the variability of 6MWT in SSc. To clarify this issue, we investigated the relationships between the 6MWT results and SSc-associated organ involvement in a cross-sectional study.

MATERIALS AND METHODS

This prospective study included all consecutive patients referred to our clinics during a 16-month period. All patients gave informed consent and the study was approved by the ethical committee.

A global evaluation of these patients was carried out. Age, sex, disease duration (first non-Raynaud's symptom), and cutaneous SSc subtype as defined by Leroy, *et al*[12] were collected. Patients underwent pulmonary function tests including forced vital capacity (FVC) and diffusion capacity for carbon monoxide (DLCO). Chest high-resolution computed tomography (HRCT) was used as recommended to identify SSc-associated interstitial lung disease (SSc-ILD). An echocardiography was performed: left ventricular (LV) dimension was recorded, systolic function was assessed by Simpson's method, diastolic dysfunction was assessed by pulsed tissue Doppler imaging (lateral annulus early diastolic velocity < 10 cm/s was considered abnormal), and systolic pulmonary artery pressure (sPAP) was approximated by continuous-wave Doppler measurement of the transtricuspid or transpulmonary pressure gradient, after the addition of an estimated 10-mm Hg right atrial pressure.

When sPAP at rest on Doppler echocardiography exceeded 40 mm Hg, right-heart catheterization was performed; PAH was confirmed for mean PAP > 25 mm Hg and was considered as SSc-associated precapillary PAH when associated with a pulmonary artery wedge pressure below 15 mm Hg[13]. The presence of active or healed digital ulcers, previous use of prostacyclin, and presence of acroosteolysis and calcinosis on hand and wrist radiographs were considered. The presence of knee pain with visual analog scale > 40 mm was taken into account. The following biological tests were carried out: routine blood tests including hemoglobin, creatinine, creatine phosphokinase, and C-reactive protein (CRP), and tests for antinuclear, anticentromere, and anti-topoisomerase I antibodies. The European activity score (European Scleroderma Study Group criteria) was used to assess disease activity[14], the Medsger severity scale to assess disease severity[15], and the SSc-Health Assessment Questionnaire (HAQ) as a measure of disability[16].

The 6MWT was performed as per American Thoracic Society guidelines[4]. All patients were tested in room air without additional oxygen under standardized conditions in the same pulmonary function laboratory by trained technicians not involved in the patients' daily care. Patients were instructed as follows: "The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able." Baseline blood pressure, heart rate, and saturation on pulse oximetry (SpO_2) were measured. Special attention was paid to the SpO_2 pulse signal. SpO_2 and heart rate were monitored throughout the walk. Total distance walked (6-min walking distance, 6MWD) was recorded.

For the purpose of data analysis, desaturation was defined as a 4% decrease from the baseline saturation (resting saturation: lowest saturation on 6MWT/resting saturation > 4%). The 6MWD was considered abnormal when below the lower limit of the normal range predicted by the first reference equation proposed by Enright and Sherrill[17], taking into account sex, age, height, and weight.

Statistical analysis. Statistical analysis was performed using the Stata statistical software, version 9.2 (StataCorp LP, College Station, TX, USA), with $p < 0.05$ considered significant. To assess the potential factors in relation with 6MWD variability, we first consider the 6MWT as a categorical datum — normal or abnormal — and evaluated the prevalence of abnormal testings among various characteristics using chi-squared and Mann-Whitney tests as indicated. The 6MWD was then expressed as a continuous measurement and the influence of patients' characteristics was examined using Mann-Whitney test for categorical variables, linear regression, and Spearman's correlation for continuous variables.

Logistic regression analysis was then performed and included all possibly pertinent variables ($p < 0.05$) according to univariate analysis. As age was accounted for in the determination of predicted normal 6MWD value, it was not included for further analysis.

RESULTS

Among the 94 patients with SSc evaluated during this period, 87 were included and the remaining 7 were excluded because they were not able to perform the 6MWD. Seventy patients (80.5%) were female and 36 (41%) were classified as having diffuse cutaneous SSc. Anticentromere antibody was positive in 17/87 (19.5%) and anti-topoisomerase I in 27/87 patients (31%). Table 1 summarizes the characteristics of the patients studied.

The mean 6MWD was 461 ± 103 m. Twenty-six patients

Table 1. Characteristics of patients with systemic sclerosis (SSc).

Characteristic	Patients, n = 87
Age, mean ± SD, yrs	55.2 ± 13.2
Disease duration, yrs, mean ± SD	7.2 ± 7.5
Disease duration < 5 yrs, n (%)	31 (35.6)
Weight, kg, mean ± SD	66.7 ± 11.6
Height, m, mean ± SD	162.2 ± 8.8
FVC % predicted, mean ± SD	97.3 ± 25
FVC < 75% predicted, n (%)	26 (29.9)
DLCO/AV % predicted, mean ± SD	77.5 ± 17.2
DLCO/AV < 75% predicted, n (%)	36 (41.4)
Interstitial lung disease on HRCT, n (%)	47 (54)
sPAP by echocardiography, mmHg, mean ± SD	32.4 ± 10
sPAP > 40 mmHg, n (%)	12 (13.8)
PAH by right-heart catheterization, n (%)	7 (8)
Left ventricular ejection fraction %, mean ± SD	67.9 ± 5.3
Diastolic left ventricular dysfunction, n (%)	27 (33.3)
Left ventricular mass, g, mean ± SD	160 ± 47
Active or healed digital ulcers, n (%)	24 (27.6)
Acroosteolysis, n (%)	18 (21.2)
Calcinosis, n (%)	20 (23.5)
Knee pain, n (%)	34 (39)
Hemoglobin, g/l, mean ± SD	12.9 ± 1.3
Creatinine, μmol/l, mean ± SD	72 ± 16.5
CRP, mg/l, mean ± SD	7.4 ± 12.2
Creatine phosphokinase, IU/l, mean ± SD	129 ± 290
Antinuclear antibodies > 1/160, n (%)	65 (74.7)
Medsger severity scale, n = 1–2; n = 3–4	53; 34
European activity score (EAS), mean ± SD	1.77 ± 1.64
EAS > 3, n (%)	15 (17.2)
sHAQ, mean ± SD	0.81 ± 0.62
sHAQ > 1, n (%)	26 (37.7)

DLCO: diffusion capacity for carbon monoxide; HRCT: high-resolution computed tomography; FVC: forced vital capacity; sPAP: systolic pulmonary artery pressure; PAH: pulmonary arterial hypertension; CRP: C-reactive protein; sHAQ: systemic sclerosis Health Assessment Questionnaire. AV: alveolar volume.

(29.9%) completed an abnormal 6MWT as defined by the reference equation[17]. Twenty-four patients (27.6%) experienced exercise desaturation, with 17/87 (20%) reaching a minimal saturation below 90%. Mean heart rate was 85 ± 15 beats per minute (bpm) before exercise and increased to 122 ± 21 bpm during exercise.

In univariate analyses, many variables were significantly associated with abnormal 6MWT (Table 2): lower percentages of predicted FVC (p = 0.0002) and predicted DLCO (p = 0.0015) were significantly associated with abnormal walking distance, as well as higher heart rate at baseline (p = 0.0054), exercise desaturation (p = 0.0232), having a decrease in desaturation with a minimal value below 90% (p < 0.001), high CRP level (p = 0.0010), positive anti-topoisomerase I antibody (p = 0.0247), Medsger's severity scale > 2 (p = 0.0103), and higher European activity score (p = 0.0322).

When considering the 6MWD as a continuous variable that was found to follow a normal distribution, there were significant correlations in univariate analyses between this walking distance and percentage of predicted FVC (rho = 0.37; p = 0.0005), percentage of predicted DLCO (rho = 0.49; p < 0.0001), sPAP (rho = 0.44; p < 0.0001), and CRP (rho = 0.34; p = 0.0008). In univariate analyses, exercise desaturation was significantly associated with a shorter walking distance (410.5 ± 106.9 m vs 481.3 ± 95.2 m; p = 0.0071), as well as PAH documented by right-heart catheterization (372.1 ± 77.2 m vs 469.6 ± 101.6 m; p = 0.0122), acroosteolysis (409.1 ± 123.4 m vs 478.3 ± 92.7 m; p = 0.0179), calcinosis (413.1 ± 125.4 m vs 479.2 ± 90.8 m; p = 0.0256), European activity score > 3 (404.6 ± 109.8 m vs 473.7 ± 98.2 m; p = 0.0305), Medsger's severity scale > 2 (414.4 ± 93.2 m vs 492.2 ± 98.1 m; p = 0.0009), and sHAQ > 1 (429.3 ± 97.1 m vs 483.2 ± 99.3 m; p = 0.025).

Multivariate logistic regression models that included the above factors are represented in Tables 3 and 4. For the 6MWD expressed as a categorical variable (Table 3), CRP was the only independent variable associated with abnormal 6MWD (p = 0.044). For the 6MWD expressed as a continuous variable (Table 4), only the presence of calcinosis was identified as a significant independent variable (p = 0.044), with a trend toward significance for CRP (p = 0.054).

Table 3. Multivariate analyses for 6MWT considered as a categorical variable.

Factor	OR (95% CI)	p
FVC, % predicted	1.02 (0.98–1.06)	0.368
DLCO/VA, % predicted	1.01 (0.96–1.06)	0.641
Baseline heart rate, bpm	0.96 (0.92–1.00)	0.067
Exercise desaturation, n (%)	0.46 (0.07–2.90)	0.409
Minimal saturation < 90%	0.22 (0.03–1.74)	0.152
CRP, mg/l	0.92 (0.85–1.00)	0.044
Anti-topoisomerase I antibody, n (%)	1.24 (0.27–5.78)	0.784
Medsger severity scale class 3–4	3.79 (0.44–32.22)	0.223
European activity score	0.85 (0.52–1.39)	0.510

For abbreviations, see Table 1.

Table 4. Multivariate analyses for the 6MWD considered as a continuous variable.

Factor	p
FVC, % predicted	0.922
DLCO/VA, % predicted	0.3254
CRP	0.054
Exercise desaturation	0.119
Minimal saturation < 90%	0.668
PAH by right-heart catheterization	0.608
Acroosteolysis	0.699
Calcinosis	0.044
ESSG disease activity score > 3	0.291
Medsger severity scale > 2	0.209
sHAQ > 1	0.097

6MWD: 6-min walking distance; ESSG: European Spondylarthropathy Study Group. For other abbreviations see Table 1.

Table 2. 6MWT as a categorical variable: univariate analyses.

Factor	SSc Patients with Normal 6MWT, n = 61	SSc Patients with Abnormal 6MWT, n = 26	p
Disease duration, yrs	7.7 ± 7.9	6.3 ± 6.6	0.436
FVC, % predicted	104.3 ± 20.5	81.2 ± 27.7	< 0.001
DLCO/VA, % predicted	69.6 ± 19.6	52.5 ± 24.3	0.002
Baseline heart rate, bpm	82.1 ± 15.7	91.7 ± 12.5	0.005
Exercise desaturation, n (%)	12 (20)	12 (46)	0.023
Minimal saturation < 90%, n (%)	6 (9.8)	11 (42.3)	< 0.001
CRP, mg/l	4.5 ± 6.0	14.4 ± 19.3	0.001
Anti-topoisomerase I antibody, n (%)	14 (23)	13 (50)	0.025
Medsger severity scale class 3–4	18 (30)	16 (62)	0.010
European activity score	1.44 ± 1.22	2.56 ± 2.2	0.032

6MWT: 6-min walk test. For other abbreviations see Table 1.

DISCUSSION

The main results of our study indicate that the 6MWD is associated with several types of organ damage and biomarkers in SSc. From these, only CRP and calcinosis were independently associated with the changes in 6MWD.

The 6MWT evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism[4]. It is a feasible and well tolerated test reflecting daily living activities[18]. Although originally developed for testing patients with congestive heart failure and pulmonary diseases, the 6MWT has recently found favor in the investigation of idiopathic PAH, as it was shown to be an independent predictor of mortality and a reliable tool in clinical trials[19,20]. In the specific context of SSc, 6MWD has been widely used in recent years[1,7-10,21], particularly in PAH, as it may be a marker of heart and lung involvement. However, several aspects of SSc unrelated to PAH may influence this test. To clarify this issue, we performed a prospective study of unselected patients with SSc and evaluated relationships between the 6MWD and organ damage and indexes of SSc.

Our cohort reflects patients usually followed in tertiary centers. Importantly, 7 patients (7/94) were not able to perform the 6MWT, because of muscle weakness or articular pain, highlighting one of the limits of this test. This supports the lack of content validity of the 6MWT, which does not cover the whole range of the disease.

The first part of the analysis considered the 6MWD as a binary variable (normal or abnormal). In univariate analysis, a large number of clinical or biological measures and indexes were significantly associated with abnormal 6MWD. In multiple logistic regression analysis, CRP was the only independent measure modestly associated with abnormal 6MWT. To our knowledge, this association has never been reported in SSc. Our group has previously shown an association between CRP and arthritis[22]. Thus, the association between CRP and abnormal 6MWD could reflect the influence of articular involvement on the 6MWD despite the exclusion of the patients with more severe arthritis unable to perform the walking test. In addition, muscle weakness with potential involvement of lower limbs or respiratory muscles, which was not systematically assessed in our study, may also influence walking capacity. More consistently, CRP is an acute-phase reactant and it should be remembered that erythrocyte sedimentation rate, another acute-phase reactant, is part of the European activity score[14]. Although the European activity score was not independently associated with the 6MWT in our series, CRP should be further investigated as an outcome measure of SSc. Indeed, our results are in accord with published data on 110 SSc patients, showing the association between a 6MWD < 400 m and multiple SSc-related organ manifestations[23].

The second part of our analysis considered the 6MWD as a continuous variable, and again many measures were associated with the 6MWD in univariate analyses. The presence of calcinosis was found to be an independent factor affecting 6MWD in multivariate analysis. A previous study showed that calcinosis is associated with a history of digital ulcers, suggesting that calcinosis could relate to or be linked with vascular involvement[22]. Nevertheless, no vascular complication including digital ulcers was identified as an associated factor in our study.

Our analyses clearly support that 6MWD in SSc is influenced by multiple disease-specific confounding factors, such as primary myocardial involvement[24], pulmonary fibrosis[23], osteoarticular/soft tissue involvement[22], and general bad health, and cannot solely be used to evaluate PAH. Moreover, a recent study showed that selected SSc patients without evidence of pulmonary/cardiac involvement, myositis, or anemia have a lower aerobic capacity resulting in a reduced exercise capacity, questioning the role of peripheral vascular abnormalities or subclinical muscle involvement[25]. All these data suggest that the comorbidities reported here may, independently or together, be sources of reduction in exercise capacity in patients with SSc, which should modify the content validity and discrimination of this test. Thus, the 6MWT might not be suitable for the assessment of a specific organ-damage treatment in SSc and this may contribute to the differences observed between patients with CTD (mostly with SSc) and the idiopathic PAH population in the recent metaanalysis assessing the effects of oral treatments on exercise capacity in PAH-SSc[11].

Another concern related to the 6MWT is the absence of its clear validation in PAH related to SSc, according to the Outcome Measures in Rheumatology (OMERACT) filter. Reliability and reproducibility of this test have not yet been assessed, such as the evaluation of construct/criterion validity (the 6MWD has not yet been correlated with right-heart catheterization, the "gold standard"). In the absence of clear validation, this outcome is now only recommended by an expert group, after a recent Delphi consensus, to be used as an interim tool[3].

The 6MWT is also used in SSc in the specific situation of SSc-ILD, in which it has been evaluated as a measure of response in a systematic review performed at the OMERACT 6 workshop on Outcome Measure Development for Clinical Trials in SSc. This item was only partially validated and was therefore judged to be "not ready for use in clinical trials in SSc patients"[26]. This is supported by a recent study that reported a nonsignificant correlation between 6MWD and FVC, which is the main assessment tool of SSc-ILD[27], concluding that the 6MWT has neither content nor criterion validity in SSc-ILD[21].

Our study has several limitations including a small sample size, a small number of patients with PAH, and a cross-sectional design. Thus, larger prospective studies assessing

changes in cardiopulmonary status together with changes of 6MWT will be required to clarify the usefulness of this test in SSc.

Our study confirms that the 6MWT is not a discriminant outcome measure in SSc. In the specific situation of PAH-SSc, this may partly explain the apparent lack of efficacy of some new oral treatments for PAH and the differences between patients with PAH-SSc and idiopathic PAH[11]. Until now, the only endpoint used in clinical trials and validated according to the criteria of the OMERACT filter is right-heart catheterization, which is invasive and therefore not suitable for repeated measures[4]. Although they need to be formally validated, oxygen saturation before/during/after exercise and echocardiography are among the measurement tools recommended at this time by the recent Delphi consensus study[2]. Other outcome measures, such as N-terminal pro-brain natriuretic peptide or exercise echocardiography, might be considered in the future and should be investigated.

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