Limitations to the 6-Minute Walk Test in Interstitial Lung Disease and Pulmonary Hypertension in Scleroderma

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ABSTRACT. ***Objective.*** To determine factors that influence 6-minute walk distance (6MWD) in patients with scleroderma (systemic sclerosis, SSc)-interstitial lung disease (ILD), SSc-pulmonary hypertension (PH), and idiopathic pulmonary fibrosis (IPF).

Methods. We retrospectively evaluated all patients with SSc or IPF who performed a 6-minute walk test (6MWT) at a university hospital between 1999 and 2003. Chi-square, ANOVA, simple linear regression, and backwards elimination multivariable regressions were performed.

Results. Forty-eight consecutive IPF patients with 6MWT were compared to 33 patients with SSc-ILD, 13 with SSc-PH, 19 with both SSc-ILD and SSc-PH (SSc-Both), and 15 with SSc without ILD or PH (SSc-Neither). Mean 6MWD did not differ between groups. Limitations to 6MWT trended toward dyspnea in IPF and lower extremity pain in SSc. SSc-Both had dyspnea limitation more than other SSc subgroups ($p = 0.017$). Percentage predicted forced vital capacity (FVC%) and percentage predicted carbon monoxide diffusing capacity (DLCO%) were more strongly predictive of 6MWD in IPF than in SSc; however, exclusion of SSc subjects with pain limitation improved the predictive value. Significant correlates of 6MWD in multivariable analysis differed between subgroups.

Conclusion. Pain limitations confound the utility of the 6MWT, particularly in SSc. Pain may cause failure to reach a dyspnea limitation during 6MWT, especially in SSc patients without both ILD and PH. Correlates of 6MWD differ between SSc subgroups and IPF; therefore, the 6MWT distance is not always reflective of the same physiological process. 6MWT interpretation should include consideration of vascular, pulmonary, and musculoskeletal exercise limitations. (First Release Jan 15 2009; J Rheumatol 2009;36:330–6; doi:10.3899/jrheum.080447)

Key Indexing Terms:
SCLERODERMA SYSTEMIC SCLEROSIS INTERSTITIAL LUNG DISEASE
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Pulmonary disease is the most common cause of death in patients with scleroderma (systemic sclerosis, SSc)[1]. The 2 most frequent pulmonary complications in patients with scleroderma are interstitial lung disease (ILD) and pulmonary hypertension (PH)[2]. The importance of pulmonary complications and their associated morbidity and mortality in this patient population has led to an increase in the numbers of clinical trials conducted to evaluate treatments for both PH and ILD in SSc.

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Exercise testing is a common endpoint used in clinical trials evaluating treatments for pulmonary diseases. The 6-minute walk test (6MWT) is a simple way to measure submaximal exercise tolerance[3] that has been used as a primary endpoint in clinical trials for treatment and prognosis of idiopathic pulmonary fibrosis (IPF)[4], and is the most commonly used endpoint in clinical trials for pulmonary arterial hypertension (PAH)[5-8]. Six-minute walk distance (6MWD) has been shown to correlate with mortality in IPF[9] and idiopathic PAH[10], but may have less value as a surrogate endpoint in patients with systemic diseases such as SSc. The musculoskeletal manifestations of SSc are well described, and include joint pain and inflammation[11], muscle pain and weakness[12], and peripheral vascular disease[13,14]. Although patients with SSc lung disease have been shown to have decreased exercise capacity[15,16], systemic manifestations of SSc may influence the walk distance and complicate interpretation of the test.

Recently, Villalba and colleagues[17] found the 6MWD in SSc to correlate with age, dyspnea index, fibrosis on the chest radiograph, systolic pulmonary arterial pressure (sPAP), and oxygen desaturation, but not with percentage predicted forced vital capacity (FVC%) or findings on chest computed tomography (CT). Oxygen desaturation was found to be a better surrogate endpoint than 6MWD, correlating with dyspnea index, FVC%, fibrosis on chest radiograph, ground-glass or reticular opacities on chest CT, and sPAP. Another study found the 6MWD had test-retest reliability, but only a weak correlation with the Borg Dyspnea Index and FVC%, and no correlation with percentage predicted carbon monoxide diffusing capacity (DLCO%)[18]. These results suggest that the 6MWD may be influenced by factors other than lung disease in patients with SSc.

Disagreement concerning acceptable endpoints for clinical trials in patients with SSc continues due to the multisystem expression of the disease and the inadequacy of traditional outcome measures, resulting in debate concerning the best endpoints. Progress has been made in the development of a core set of measures to be used in clinical trials, but further study is still required[19-21].

Our objectives were to evaluate the limitations to 6MWT in patients with SSc compared to IPF, a disease whose predominant feature is ILD, and to assess differences in physiologic measures between these 2 groups. We further hypothesized that the utility of the 6MWD will differ between SSc subgroups. Differences in symptom limitations to 6MWT and physiologic variables may further define exercise limitations and inform the design of future clinical trials.

MATERIALS AND METHODS

Patient population. We retrospectively evaluated all adult patients with American College of Rheumatology-defined SSc or American Thoracic Society (ATS)-defined IPF seen at the Medical University of South Carolina from 1998 to 2003 who performed a 6MWT. The SSc group (All SSc) was prospectively subdivided into SSc with ILD (SSc-ILD), SSc with PH (SSc-PH), SSc with both ILD and PH (SSc-Both), and SSc with neither ILD nor PH (SSc-Neither). The 6MWT was performed in accord with ATS guidelines[22]. There were no requirements concerning gender, limited versus diffuse SSc, overlap with other connective tissue diseases, or disease severity or duration. To be diagnosed with SSc-associated PH, a subject had elevated pulmonary artery pressures by echocardiogram (sPAP > 40 mm Hg) or right-heart catheterization (mean PAP > 25 mm Hg). IPF and SSc-associated ILD were diagnosed by any ground-glass or reticular opacities on high resolution chest CT with slice thickness 0.6–1.0 mm. The 6MWT was oxygen supplemented in some patients, although the 6MWT was not stopped at any level of oxygen desaturation. Each subject's 6MWD, pre-walk and post-walk Borg dyspnea scores, resting oxygen saturation (SpO_2), and minimum SpO_2 during 6MWT were recorded. After the 6MWT, each subject was asked, "What prevented you from walking farther?" and the answer was recorded as the patient-reported limitation to the 6MWT. Answers were characterized into one of 6 categories: (1) dyspnea, (2) lower extremity pain, (3) generalized fatigue, (4) chest pain or tightness, (5) lightheadedness or dizziness, or (6) no limitation. In addition, FEV1/FVC, FVC%, and DLCO% within 3 months of 6MWT were recorded, performed by ATS standards[23] and assessed by standards of Crapo, *et al*[24] with hemoglobin adjustment according to Cotes, *et al*[25].

Statistical analysis. Categorical data were compared using chi-square tests and continuous data were compared using analysis of variance (ANOVA) and Tukey's multiple comparison test. Simple linear regression was used to determine whether physiologic variables correlated with 6MWD. Backwards elimination multivariable regression was used to determine the patient characteristics and physiologic variables correlated with 6MWD. We limited each model to one predictor per 10 subjects. Variables included age, gender, pre- and post-walk Borg dyspnea score, resting SpO_2, minimum SpO_2 during 6MWT, FVC%, DLCO%, FEV1/FVC, and reported limitation to 6MWT, and sPAP. P value ≤ 0.05 was considered significant. Continuous data are reported as mean and 95% confidence interval (95% CI) or 25%–75% range as specified. Categorical data are reported by frequency.

RESULTS

Between 1998 and 2003, 80 patients with SSc and 48 patients with IPF underwent 6MWT. Baseline characteristics of the IPF and SSc groups, with SSc broken down by pulmonary diagnosis, are shown in Table 1. These characteristics agree with the known demographics of SSc, a disease that tends to occur in younger women, and IPF, a disease that occurs more often in older individuals. Of the 80 subjects with SSc, missing data included 5 subjects who had not been asked their limitation to the 6MWT and one subject whose walk distance was not recorded. Seven subjects with IPF and 13 with SSc had no spirometry recorded within 3 months of the 6MWT. Three subjects in each group who underwent spirometry did not have a concurrently recorded DLCO%.

Limitations to 6MWT. There was no significant difference in mean 6MWD between the IPF and the SSc subgroups (p = 0.14; Table 2). Dyspnea was reported as an exercise limitation more often in subjects with IPF (67%) than SSc (57%), although this was not statistically significant (p = 0.30; Figure 1). Dyspnea comparisons between IPF (67%) and SSc-ILD (48%) were not statistically different (p = 0.11). Lower extremity pain was the primary limitation to walk distance for 20% of subjects with SSc compared to 15% of subjects with IPF (p = 0.40; Figure 1). Pain was the limitation in 23% of the SSc-ILD subjects, but this was also not significantly different from the IPF group (p = 0.51). The SSc subgroups differed on the primary limitation to 6MWT distance. Almost all subjects with both ILD and PH report-

Table 1. Baseline subject characteristics for idiopathic pulmonary fibrosis (IPF) and scleroderma (SSc), then with SSc broken down by pulmonary disease groups. Continuous data are reported as mean (25%–75% range), categorical data are reported as frequency (%).

	Characteristic	
	Age, yrs	Female, %
IPF (n = 48)	63 (53–73)	24 (50)
SSc (n = 80)	52 (46–60)	62 (78)
p	< 0.001	0.001
SSc-ILD (n = 33)	48 (45–54)	21 (64)
SSc-PH (n = 13*)	57 (53–62)	10 (77)
SSc-Both (n = 19**)	53 (46–60)	17 (89)
SSc-Neither (n = 15)	56 (50–66)	14 (93)
p	0.038	0.05

* N = 1 without right-heart catheterization; ** N = 3 without right-heart catheterization. SSc-ILD: SSc with interstitial lung disease; SSc-PH: SSc with pulmonary hypertension; SSc-Both: SSc with both ILD and PH; SSc-Neither: SSc with neither ILD nor PH.

Table 2. Mean 6-minute walk distance (6MWD), resting, minimum, and drop in oxygen saturation (SpO_2), percentage predicted forced vital capacity (FVC%), and percentage predicted carbon monoxide diffusing capacity (DLCO%) compared by ANOVA between idiopathic pulmonary fibrosis (IPF) and scleroderma (SSc)-interstitial lung disease (ILD) (Table 2A); and between SSc subgroups (Table 2B). All data reported as mean (95% CI).

Table 2A.

	IPF, n = 46	ILD, n = 27	p
6MWD, m	379 (347–411)	349 (308–391)	0.27
Resting SpO_2, %	96 (95–96)	97 (97–98)	0.003
Minimum SpO_2, %	87 (86–89)	92 (90–94)	0.002
Drop in SpO_2	8 (6–9)	6 (4–8)	0.07
FVC%	75 (69–81)	64 (57–71)	0.02
DLCO%	46 (41–52)	44 (38–51)	0.68

Table 2B.

	ILD, n = 27	PAH, n = 12	Neither, n = 13	Both, n = 17	p	Tukey Results
6MWD, m	349 (302–397)	315 (243–387)	313 (244–382)	312 (251–372)	0.7029	NA
Resting SpO_2, %	97 (97–98)	97 (97–99)	98 (97–99)	96 (95–97)*	0.2191	NA
Minimum SpO_2, %	92 (89–94)	92 (88–95)	94 (90–97)	87 (84–90)	0.0129	Both different from ILD and Neither
Drop in SpO_2, %	6 (3–8)	5 (1–8)	4 (1–7)	9 (7–12)	0.0633	NA
FVC%	64 (58–69)	96 (87–106)**	91 (83–99)	62 (55–69)	< 0.0001	ILD and Both different from PAH and Neither
DLCO%	44 (37–51)***	58 (46–70)†	62 (52–72)	37 (28–46)††	0.0017	Both different from PAH, ILD, and Neither; ILD different from Neither

* n = 18; ** n = 10; *** n = 26; † n = 9; †† n = 16. SSc-ILD: SSc with interstitial lung disease; SSc-PH: SSc with pulmonary hypertension; SSc-Both: SSc with both ILD and PH; SSc-Neither: SSc with neither ILD nor PH.

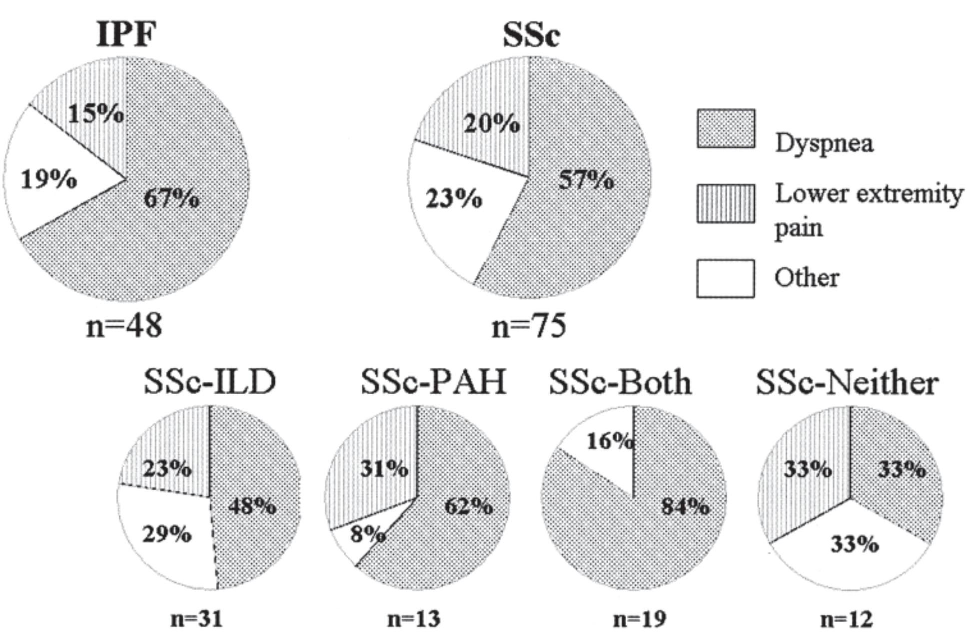

Figure 1. Patient-reported limitations to 6-minute walk test (6MWT) in idiopathic pulmonary fibrosis (IPF) and scleroderma (SSc) subgroups. ILD: interstitial lung disease; PAH: pulmonary arterial hypertension.

ed a dyspnea limitation to 6MWD, whereas fewer than half in the subgroup with neither ILD nor PH had dyspnea (p = 0.017; Figure 1). SSc subjects with both ILD and PH never reported lower extremity pain as their primary limitation, but lower extremity pain was reported as a limitation in patients in each of the SSc-ILD, SSc-PH, and SSc-Neither subgroups (p = 0.014; Figure 1).

Although sample sizes were too small to make meaningful statistical comparisons, the distribution of reported dyspnea limitation did not vary by gender in IPF, SSc, or any of the SSc subgroups. Women tended to report "other" limitations including chest tightness or dizziness more often than men (p = 0.29). Pain appeared to be a limitation more often in older subjects across IPF and all SSc subgroups, especially in the SSc-Neither subgroup, when age was analyzed as a dichotomous variable, > 55 versus ≤ 55 years old (p = 0.07).

Predictors of 6MWT distance. The correlation coefficients between both FVC% and DLCO% and 6MWD were significant in IPF but not in SSc (Figure 2A, 2B). Association of DLCO% but not FVC% with 6MWD in SSc became weakly significant with exclusion of patients who reported either lower extremity pain or "no limitation" as their limitation to the 6MWT (Figure 2C, 2D). The correlation between 6MWD and FVC% was much stronger for SSc subjects with severe lung disease (FVC% ≤ 60%, N = 17; $R^2 = 0.205$, p = 0.03) than subjects with less severe disease (FVC% > 60%, N = 49; $R^2 < 0.001$, p = 0.86). 6MWD was not correlated with sPAP in subjects with sPAP < 45 (N = 19, R^2 = 0.069, p = 0.227), but was significantly correlated with sPAP ≥ 45 (N = 14; $R^2 = 0.383$, p = 0.018). 6MWD was not correlated with DLCO for those with DLCO ≤ 60% (N = 49; $R^2 = 0.0146$, p = 0.41) or DLCO > 60% (N = 14; inversely related). Significant multivariable correlates of 6MWD differed between subjects with IPF and those with SSc (Table 3). The correlates of 6MWD in IPF were DLCO% and gender; the correlates in all SSc patients were pre-walk Borg score, minimum SpO_2, resting SpO_2, and gender; the correlates in SSc-ILD were DLCO%, minimum SpO_2, and pre-walk Borg score; the strongest correlate in SSc-PH was post-walk Borg score; the strongest correlate in SSc-Both and SSc-Neither was minimum SpO_2. Exclusion of SSc subjects with pain limitation improved model fit, increasing the percentage of explained variability from 26% in the full group to 36% in the limited group (Table 3). When only age, gender, DLCO%, and FVC% were included in the model,

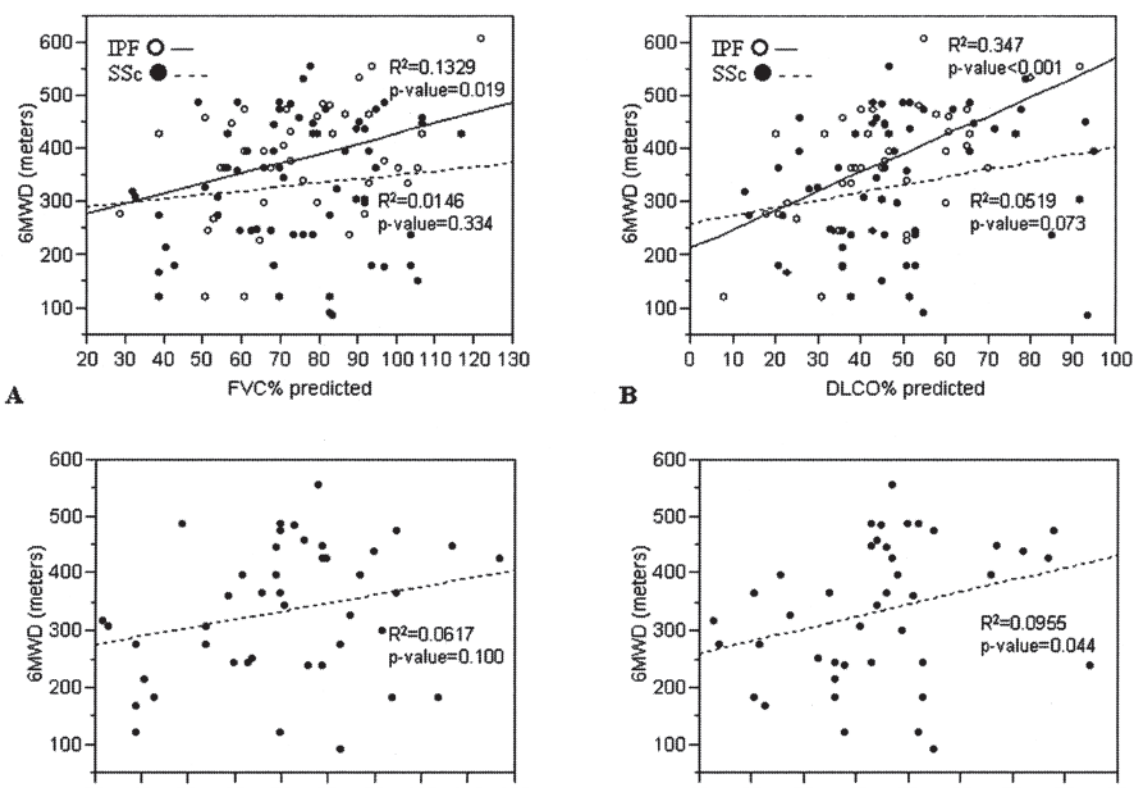

Figure 2. A, B. Percentage predicted forced vital capacity (FVC%) and percentage predicted carbon monoxide diffusing capacity (DLCO%) compared with 6-minute walk distance (6MWD) in subjects with idiopathic pulmonary fibrosis (IPF) and scleroderma (SSc). (A: IPF n = 41, SSc n = 66; B: IPF n = 38, SSc n = 63) C, D. Comparison between FVC% (n = 45) or DLCO% (n = 43) and 6MWD in SSc subjects who reported a limitation to walk distance other than pain or "no limitation."

Table 3. Predictors of 6-minute walk distance (6MWD) by multivariable regression.

Group	Predictors	p	Model Fit (R^2)
IPF, n = 40	DLCO%	< 0.001	0.46
	Gender	0.019	
All SSc, n = 75	Pre-walk Borg score	0.007	0.26
	Minimum SpO_2	0.021	
	Resting SpO_2	0.026	
	Gender	0.015	
All SSc without pain, n = 52	Pre-walk Borg score	0.005	0.36
	Minimum SpO_2	0.015	
	Resting SpO_2	0.009	
	Gender	0.007	
SSc-ILD, n = 31	DLCO%	0.013	0.46
	Minimum SpO_2	0.035	
	Pre-walk Borg score	0.049	
SSc-PH, n = 13	Post-walk Borg score	0.019	0.41
SSc-Both, n = 17	Minimum SpO_2	0.026	0.29
SSc-Neither, n = 14	Minimum SpO_2	0.027	0.32

IPF: idiopathic pulmonary fibrosis; SSc: scleroderma; SSc-ILD: SSc with interstitial lung disease; SSc-PH: SSc with pulmonary hypertension; SSc-Both: SSc with both ILD and PH; SSc-Neither: SSc with neither ILD or PH.

47% of the variability in IPF (n = 37) and 41% of the variability in SSc-ILD (n = 26) was explained.

Physiologic measures. Physiologic measures such as minimum SpO_2 during 6MWT, FVC%, and DLCO% may indicate the severity of pulmonary interstitial or vascular disease. The 6MWD was statistically equal between the IPF and SSc-ILD groups; however, the IPF group had a significantly lower resting SpO_2, lower minimum SpO_2, and greater drop in SpO_2. In contrast, the FVC% was lower in the SSc-ILD group compared to the IPF group.

DISCUSSION

Our goal was to better inform future decisions concerning preferred endpoints in clinical trials. The absence of a clearly superior primary endpoint for clinical trials in patients with SSc has led to controversy concerning the best surrogate outcome measures in this patient population[19]. Although pulmonary disease is the leading cause of death in SSc, physiologic endpoints such as the 6MWT that are sensitive to disease in multiple organ systems may fail to specifically evaluate lung disease.

We found that the causes of limitation to the 6MWT differ between SSc subgroups and IPF. Walk distance alone is unable to distinguish between subjects with ILD or PH and subjects without clinically evident pulmonary disease. The 6MWT is therefore sensitive to some other disease manifestations of SSc that limit the 6MWD.

The correlates of 6MWD vary between SSc subgroups and between SSc-ILD and IPF. In IPF, a single predictor, DLCO%, explained a large percentage (37%) of the variability in 6MWT distance. Similarly in the SSc-ILD cohort, DLCO% was a strong predictor of 6MWD, but other variables such as minimum SpO_2 were significant predictors. However, in the entire SSc population, the picture was much more mixed, with several predictors contributing to the model, with measured variables accounting for a smaller percentage of the variability in 6MWD. Interestingly, the model was improved with exclusion of subjects who reported pain as a limitation to the walk test.

Subjects with SSc have varying degrees of musculoskeletal and peripheral vascular involvement, including arthralgia, myopathy, and claudication[11-14]. In addition to myositis, alterations in small blood vessels in the skeletal muscles may influence cellular oxygen delivery and contribute to an early transition to anaerobic metabolism. Therefore, removing SSc patients who reported pain allowed stronger correlations between measures of lung disease and the 6MWD. The extent to which this improvement is due to joint, muscle, and/or circulatory limitations remains unknown.

Sensitivity of the 6MWD to pain does not necessarily make the endpoint inadequate for all clinical trials. If the goal of a study is to improve the overall well-being of a patient, without the need to distinguish between pulmonary and musculoskeletal disease, the 6MWT may be adequate. However, in SSc, where pulmonary disease is the main cause of mortality, clinical trials for medical therapies would be amiss to ignore the importance of evaluating pulmonary disease severity. If the musculoskeletal disease and peripheral vascular involvement remain stable, changes in pulmonary disease may be detected. Future studies of SSc pulmonary disease should exclude patients with unstable lower extremity pain limitation if 6MWT is used.

The 6MWD is not reflective of the same physiological process in each disease or each SSc subgroup. Although each group had statistically the same mean 6MWD, the ILD subgroups clearly had more severe lung disease as assessed by FVC%, DLCO%, and minimum SpO_2. The association between FVC% and DLCO% with 6MWD is improved with exclusion of pain, but pain may not be the only confounding limitation in SSc. The interesting group of SSc patients with neither PH nor ILD on routine testing likely sheds some light on additional 6MWT limitations in SSc. After excluding patients with pain, this group had a mean 6MWD of 340 m. These patients had similar degrees of O_2 desaturation, FVC%, and DLCO% abnormalities compared to the group with SSc-PH. These similarities suggest a vascular limitation to exercise that could be due to small-vessel disease in the muscles or to exercise-induced PH, a diagnosis that would require exercise echocardiography or exercise right-heart catheterization to detect.

Less severe pulmonary disease may be missed by the 6MWD. Detection and evaluation of early stages of pulmonary disease will become more important as better medical therapies for ILD and PH are developed. For this reason, other measures of lung disease should be considered as endpoints in studies of subjects with early pulmonary disease. For example, measuring oxygen desaturation may improve the 6MWT utility[17,26]. In our study, minimum SpO_2 is one of the strongest correlates of 6MWD in almost every subgroup of SSc and SSc as a whole.

Our SSc results are similar but not identical to those of Villalba and colleagues[17]. In univariate analysis we found a correlation between 6MWD and diminished SpO_2 ($p = 0.033$) and pre-walk Borg dyspnea score ($p = 0.041$), with no correlation to gender or FVC%. In contrast, we did not find 6MWD correlated with age, either as a continuous variable or a dichotomous variable. Similarly to Villalba, *et al*[17] we found SpO_2 decline correlated with 6MWD and FVC% ($p = 0.027$) but not gender. In contrast to the previous study, the drop in SpO_2 was not correlated with Borg dyspnea score or age. The differences between the studies are likely due to different age distribution and populations. Further, Villalba, *et al*[17] did not specify whether the dyspnea score was pre- or post-walk, which may explain the discrepancy with our results.

Limitations of our study include missing data, a problem common to all retrospective studies. Subjects in the PH subgroup were diagnosed by either right-heart catheterization or echocardiogram with sPAP > 40 mm Hg. Because some subjects did not have right-heart catheterization close to the time of the 6MWT, some of these individuals may not have World Health Organization Group I PAH. Further, we defined SSc-ILD very sensitively, with any ground-glass opacity on chest CT regardless of FVC%, a categorization that is different from some studies. The 6MWD was measured on supplemental oxygen for some patients, which may have altered our ability to measure distance or desaturation. Some SSc groups had very small numbers, limiting our analytic abilities. Therefore, our results should be validated in a larger prospective study. A strength of our study was the comparison of subjects with SSc-pulmonary disease to those with IPF. A limitation was the lack of an idiopathic PAH comparator group due to the small number of patients with idiopathic PAH at our center. A future study may provide more insight into mechanisms of exercise intolerance in SSc. Unfortunately, our database did not contain other disease features such as skin extent, disease duration, arthritis, or myositis. Information on these factors would be extremely valuable in a future study to elucidate the specific variables that confound the association between 6MWD and pulmonary disease measures. Finally, few of the IPF subjects underwent echocardiogram or right-heart catheterization, so these patients could have undetected cor pulmonale, which could confound the results.

Our study reveals that the 6MWT is influenced by many factors that affect the specificity for pulmonary disease; however, these factors may not affect the sensitivity of the test. Two important future studies remain to be done in this area. The first would be to determine the responsiveness of the 6MWD and desaturation to changes in disease state for the different SSc lung disease phenotypes. An important longterm project would define the prognostic value of a low 6MWD between subgroups.

Limitations due to pain confound the utility of the 6MWT, particularly in SSc. 6MWT interpretation should include consideration of vascular, pulmonary, and musculoskeletal limitations to exercise. Sensitivity of the 6MWD to these various organ-system disease processes may necessitate exclusion of subjects with pain or the use of multiple endpoints to fully improve sensitivity of the outcome measures to pulmonary disease[19]. Continued investigation of how to use the 6MWT in the clinical care and research of patients with SSc is warranted.

REFERENCES

1. Steen VD, Medsger TA. Severe organ involvement in systemic sclerosis with diffuse scleroderma. Arthritis Rheum 2000;43:1074-84.
2. Silver RM. Scleroderma. Clinical problems. The lungs. Rheum Dis Clin North Am 1996;22:825-40.
3. Guyatt GH, Sullivan MJ, Thompson PJ, et al. The 6-min walk: a new measure of exercise capacity in patients with chronic heart failure. Can Med Assoc J 1985;132:919-23.
4. Collard HR, Anstrom KJ, Schwarz MI, Zisman DA. Sildenafil improves walk distance in idiopathic pulmonary fibrosis. Chest 2007;131:897-9.
5. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. N Engl J Med 1996;334:296-301.
6. Simonneau G, Barst RJ, Galie N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: A double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med 2002;165:800-4.
7. Oudiz RJ, Schilz RJ, Barst RJ, et al. Treprostinil, a prostacyclin analogue, in pulmonary arterial hypertension associated with connective tissue disease. Chest 2004;126:420-7.
8. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 2002;346:896-903.
9. Lederer DJ, Arcasoy SM, Wilt JS, D'Ovidio F, Sonett JR, Kawut SM. Six-minute-walk distance predicts waiting list survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2006;174:659-64.
10. Miyamoto S, Nagaya N, Satoh T, et al. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. Am J Respir Crit Care Med 2000;161:487-92.
11. Baron M, Lee P, Keystone EC. The articular manifestations of progressive systemic sclerosis (scleroderma). Ann Rheum Dis 1982;41:147-52.
12. Tager RE, Tikly M. Clinical and laboratory manifestations of systemic sclerosis (scleroderma) in Black South Africans. Rheumatology Oxford 1999;38:397-400.
13. Norton WL. Comparison of the microangiopathy of systemic lupus erythematosus, dermatomyositis, scleroderma, and diabetes mellitus. Lab Invest 1970;22:301-8.
14. Veale DJ, Collidge TA, Belch JJ. Increased prevalence of

symptomatic macrovascular disease in systemic sclerosis. Ann Rheum Dis 1995;54:853-5.
15. Morelli S, Ferrante L, Sgreccia A, et al. Pulmonary hypertension is associated with impaired exercise performance in patients with systemic sclerosis. Scand J Rheumatol 2000;29:236-42.
16. Sudduth CD, Strange C, Cook WR, et al. Failure of the circulatory system limits exercise performance in patients with systemic sclerosis. Am J Med 1993;95:413-8.
17. Villalba WO, Sampaio-Barros PD, Pereira MC, et al. Six-minute walk test for the evaluation of pulmonary disease severity in scleroderma patients. Chest 2007;131:217-22.
18. Buch MH, Denton CP, Furst DE, et al. Submaximal exercise testing in the assessment of interstitial lung disease secondary to systemic sclerosis; reproducibility and correlation of the 6-min walk test. Ann Rheum Dis 2007;66:169-73.
19. Furst D, Khanna D, Matucci-Cerinic M, et al. Systemic sclerosis — continuing progress in developing clinical measures of response. J Rheumatol 2007;34:1194-200.
20. Matucci-Cerinic M, Steen VD, Furst DE, Seibold JR. Clinical trials in systemic sclerosis: lessons learned and outcomes. Arthritis Res Ther 2007;9 Suppl 2:S7.
21. Khanna D, Lovell DJ, Giannini E, et al. Development of a provisional core set of response measures for clinical trials of systemic sclerosis. Ann Rheum Dis 2008;67:703-9.
22. American Thoracic Society Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement; guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-7.
23. American Thoracic Society. Standardization of spirometry, 1994 update. Am J Respir Crit Care Med 1995;152:1107-36.
24. Crapo RO, Morris AH, Gardner RM. Reference spirometric values using techniques and equipment that meet ATS recommendations. Am Rev Respir Dis 1981;123:659-64.
25. Cotes JE, Dabbs JM, Elwood PC, Hall AM, McDonald A, Saunders MJ. Iron-deficiency anaemia: its effect on transfer factor for the lung and ventilation and cardiac frequency during sub-maximal exercise. Clin Sci 1972;42:325-35.
26. Paciocco G, Martinez FJ, Bossone E, Pielsticker E, Gillespie B, Rubenfire M. Oxygen desaturation on the six-minute walk test and mortality in untreated primary pulmonary hypertension. Eur Respir J 2001;17:647-52.