Review

Usefulness of six-minute walk test in systemic sclerosis

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ABSTRACT

The 6-minute walk test (6MWT) is a standardised, feasible and reliable measure of sub-maximal exercise capacity that has never been fully validated in systemic sclerosis (SSc). A variety of data suggest that many non-pulmonary aspects of SSc contribute to the test results, thus blunting the ability of the 6MWT to measure changes in lung function. Sources of variability are a training effect, technician experience, subject encouragement, medication, other activities on day of testing, deconditioning and the effects of musculoskeletal conditions and pain. Another cause of variability is the anatomical site the probe is attached to: a forehead probe is preferable to a finger or earlobe sensor. The indiscriminate use of the 6MWT for all SSc patients is not useful. It should be used in patients with pulmonary involvement, combined with diffusion capacity of the lung for carbon monoxide (DLCO) and its components (membrane diffusion and capillary volume) or the Scleroderma Health Assessment Questionnaire Disability Index. The use of these combined parameters may indicate the onset of pulmonary hypertension.

Recent studies suggest two alternatives to the 6MWT: maximal cardiopulmonary exercise testing and DLCO testing during effort. However, their use must still be validated.

Introduction

Systemic sclerosis (SSc) is a systemic autoimmune disease causing tissue fibrosis that leads to vascular injury, skin fibrosis, and the involvement of the heart, lungs, kidneys, and gastrointestinal tract. It is characterised by three distinct pathophysiological processes: cellular and humoral autoimmunity, vascular injury, and tissue fibrosis. Functional and structural vascular injury is frequently the earliest sign and may occur years before the other manifestations, although it is frequently associated with fibrosis due to the excessive accumulation of collagen and extracellular matrix components. Genetic factors may also play a role in the pathogenesis of the disease by affecting host susceptibility or modifying its clinical presentation and organ damage (1).

The symptoms of patients with SSc often include dyspnea upon exertion, fatigue, and reduced exercise tolerance, which are frequently due to the involvement of the musculoskeletal system, lungs, heart, chest wall, and pulmonary vasculature. SSc patients are at particular risk of developing pulmonary arterial hypertension (PAH) or interstitial lung disease (ILD) with pulmonary hypertension (PH) which, if untreated, may lead to right ventricular failure and early death (2).

ILD and PH are leading causes of disease-related morbidity and mortality (3); the frequency of kidney-related deaths has significantly decreased from 42% to 6%, but the proportion of deaths due to ILD and PAH has increased to respectively 33% and 28% (4). A European Sclerodermia Trials and Research (EUSTAR) group analysis of a cohort of 3656 SSc patients found that ILD was present in 53% of those with diffuse and 35% of those with limited cutaneous SSc (5). The cumulative survival of SSc patients five and ten years after diagnosis is respectively 84.1% and 74.9% (6); the reported survival of SSc-ILD patients is similar to that of patients without ILD after five years, but significantly lower after 10 years (29% in SSc without ILD *vs*. 69% in SSc with ILD) (7).

Autopsy studies have found that up to 100% of patients have parenchymal

involvement (6), and high-resolution computed tomography has shown that as many 90% have interstitial abnormalities (8); pulmonary function is altered in 40-75% (9). This means that the early detection and management of pulmonary and cardiac involvement is required, as well as accurate means of measuring therapeutic outcomes.

SSc patients have reduced exercise capacity, especially those with pulmonary involvement (10, 11). A simple means of evaluating sub-maximal exercise capacity is the 6-minute walk test (6MWT), a safe, non-invasive and reproducible test that reflects the effort required for daily physical activities (12). Originally developed to study patients with heart failure and pulmonary disease, the 6MWT had been increasingly used as an outcome measure in clinical SSc trials (13, 14), but its usefulness is questioned because of the difficulties in obtaining good oximetry measurements (15) and the variety of pathophysiological alterations causing vascular injury and pulmonary disease. SSc patients and patients with idiopathic pulmonary fibrosis often have similar 6MWT results, and there is no consensus concerning the cut-off value indicating certain organ involvement.

The aim of this review is to consider the usefulness of 6MWT in SSc patients by reviewing papers published over the last ten years in order to clarify when it is indicated and how its results should be interpreted.

The six-minute walk test (6MWT)

Lipkin first introduced the 6MWT as a simple a practical means of evaluating functional capacity in 1986 (16).

Indications and limitations

The strongest indication for the 6MWT is the need to evaluate the response of patients with moderate or severe heart or lung disease to medical interventions, but it has also been used as a one-time measure of functional status, and a predictor of morbidity and mortality. However, the fact that investigators have used the 6MWT in these settings does not prove that it is the best means of determining functional capacity or intervention-induced changes in functional capacity in such patients as it does not determine peak oxygen uptake, diagnose the cause of dyspnea on exertion, or evaluate the causes or mechanisms of exercise limitation (17). The information provided by the 6MWT should be considered complementary to the results of cardiopulmonary exercise testing rather than a replacement for it because, despite their differences, some good correlations between them have been reported for patients with end-stage lung disease (12). In some clinical situations, the 6MWT may even provide information that is a better index of the patient's ability to perform daily activities than peak oxygen uptake: *i.e.* the results correlate better with formal measures of quality of life (18).

Contraindications

Absolute contraindications for 6MWT are a history of unstable angina or heart attack during the previous month; relative contraindications include resting tachycardia (heart rate >120 beats/minute) or uncontrolled hypertension (systolic blood pressure >180 mmHg; diastolic blood pressure >100 mmHg). Patients with any of these findings should be referred to the physician ordering or supervising the test for an individual clinical assessment before executing the test, and the findings of a resting electrocardiogram done during the previous six months should be reviewed.

Stable exertional angina is not an absolute contraindication, but patients with these symptoms should perform the test using their anti-angina medication, and rescue nitrate medication should be readily available.

Technical aspects of 6MWT

The primary measurement is the total distance walked (6MWD); secondary measures can include fatigue and dyspnea measured using a modified Borg scale or visual analogue scale. The American Thoracic Society (ATS) 6MWT guideline (12) suggests that pulse oximetry during testing is optional but, if used, recommends baseline oxygen saturation values rather than constant monitoring. However, concerns regarding the safety of significant oxygen desaturation in patients with an underlying chronic lung disease have led to suggestions that the guidelines should be modified to include continuous pulse oximetry during 6MWT (19), also given the availability of fourth-generation pulse oximeters specifically designed to compensate for motion artefacts.

The 6MWT should be performed indoors along a long, flat, straight, enclosed corridor with a hard surface that is seldom travelled. The walking course must be 30 metres in length, and marked every three metres. The turning points should be marked with a cone. A starting line marking the beginning and end of each 60-metre lap should be marked on the floor using brightly coloured tape (12). During the test, physicians should not walk with the patients because, even if they remain behind, it will alter the patient's pace. An oval or circular track should not be used. Standardised phrases must be used when speaking to the patient because the amount of encouragement and enthusiasm expressed can make a difference of up 30% in the distance. The laps should be counted using a lap counter (20).

It is not necessary for a physician to be present, but it is recommended that the people administering the test are certified in cardiopulmonary resuscitation and that medications are available to treat angina, bronchospasm, and severe shortness of breath.

In order to interpret 6MWT results, it is recommended to calculate the predicted distance using equations from a published study of healthy people in the same age group. The 6MWD of a healthy subject ranges from 400 to 700 metres, but the few published studies have all used different methods and the predicted distances differ by up to 30% (21-23). Oxygen desaturation during 6MWT is defined as a 4% decrease in the pre-test value measured at rest (24).

6MWT in systemic sclerosis

Changes in distance walked

An improvement in 6MWT is usually expressed and analysed as the absolute change in distance; there are no data concerning clinically minimally im-

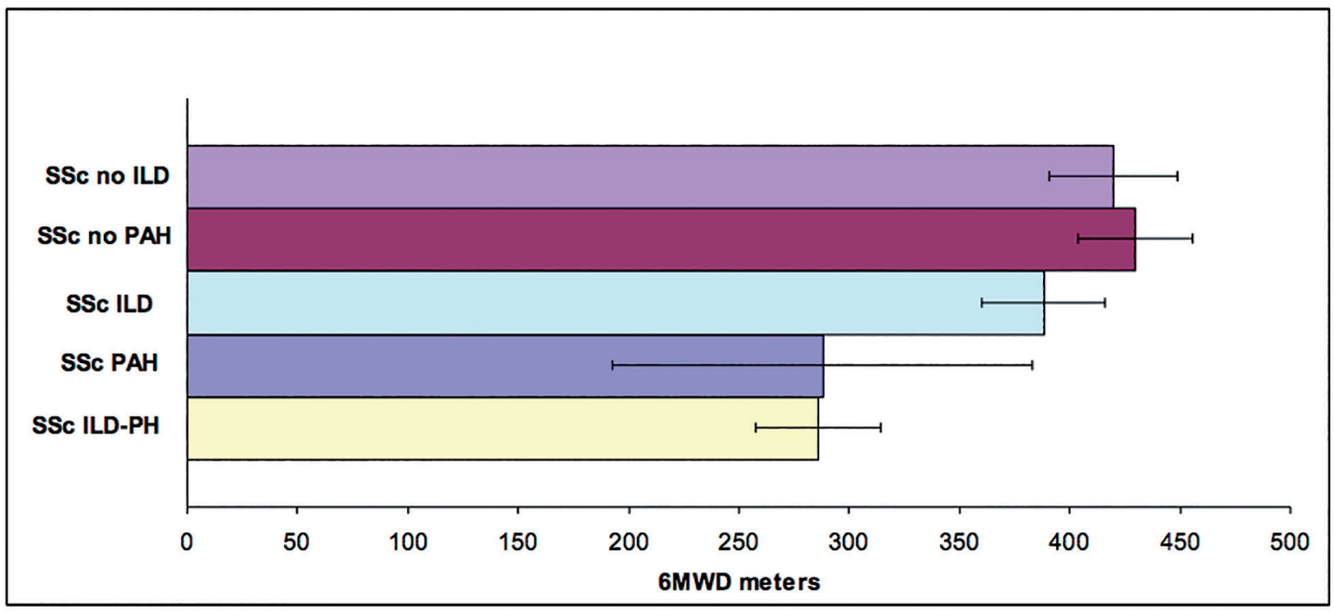

Fig. 1. 6MWD in systemic sclerosis subgroups of pulmonary involvement.
Six minute walking test distance (6MWD) as reported in a meta-analysis by Vandecasteele *et al*. (28) (43 studies, 3185 SSc patients). The pooled mean distance of 725 SSc-PAH patients was significantly lower than the pooled mean of 412 SSc-noPAH patients ($p<0.001$). Ninety-five SSc-ILD-PH patients walked significantly less than 328 SSc-ILD patients ($p<0.001$), and significantly less than 86 SSc-noILD patients ($p<0.008$). The mean 6MWD of the SSc-PAH and SSc-ILD-PH subgroups was comparable.
SSc: systemic sclerosis; ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; ILD-PH: pulmonary hypertension related to ILD.

portant difference in SSc patients (*i.e.* the level of change leading to a subjective benefit perceived by a patient). In patients with other diseases, this minimal difference correlates with patient-related outcomes (25, 26) such as functional class or survival, but nothing is known in relation to SSc (27).

Distance walked discriminating ILD and PAH in SSc

Many factors can influence the distance walked: the possible sources of variability are a training effect, technician experience, patient encouragement, medication, other activities on the day of testing, deconditioning, and the effect of musculoskeletal conditions.

As shown in Figure 1, a meta-analysis of 43 studies with 3185 SSc patients has studied exercise capacity in SSc patients with and without PAH or ILD with PH, and concluded that SSc-PAH patients walk less than SSc-noPAH patients, and that SSc-ILD-PH patients walk less than SSc-ILD and SSc-noILD patients, whereas the distance is comparable in patients with SSc-PAH or SSc-ILD-PH (28).

SSc patients without cardiac or pulmonary disease not only have reduced peak oxygen consumption (peak VO_2) but also reduced metabolic equivalent at peak VO_2 (10). Although not directly measured, this implies that muscle perfusion is an unrecognised factor affecting exercise capacity in SSc.

Studies of PAH have shown that patients with PAH secondary to SSc cover a shorter distance than patients with idiopathic PAH. A controlled trial involving patients with PAH secondary to SSc showed a significant increase in 6MWD after bosentan therapy, but the increase was lower than in the patients with idiopathic PAH patients (29). A placebo-controlled study of the efficacy of 12 months' treatment wih bosentan in SSc-ILD-PH patients found no difference in 6MWD (30) and, although trials of sitaxentan and ambisentan showed a significant effect on 6MWD, the magnitude of the response was much less than in patients with other forms of PAH (31, 32).

It has been introduced that the 6MWD is highly reproducible in SSc-ILD patients (15), but the weak correlation between 6MWD and other physiological parameters such as forced vital capacity (FVC), pulmonary diffusing capacity for carbon monoxide (DLCO) and Borg's dyspnea index suggests that the limited exercise capacity of SSc patients has a multifactorial basis (Fig. 2).

How 6MWD and oxygen desaturation correlate with other variables

The preferred method of monitoring oxygen desaturation in SSc patients is to use a forehead probe because the presence of Raynaud's phenomenon make finger and earlobe sensors unreliable (33). Some authors have indicated the usefulness of oxygen desaturation in studies of pulmonary functioning, and concluded that stratifying patients by the degree of desaturation during a 6MWT is important when interpreting serial changes in patients with parenchynal lung disease (Table I) (34, 35).

Analysis of the BUILD-2 data concerning only placebo-treated patients showed a significant difference between those with limited and diffuse SSc (36): in the former, there was a significant correlation between 6MWD, baseline and 12-month DLCO and the baseline Borg dyspnea index, whereas there was no significant correlation between 6MWD, Borg dyspnea index, FVC, DLCO at baseline, but a signifi-

cant correlation between 6MWD, Borg dyspnea index and FVC at follow-up.

The relationships between 6MWT, and objective and subjective measures of pulmonary function (FVC, DLCO, the modified Rodnan skin score (mRSS), Borg's dyspnea index, and the Scleroderma Health Assessment Questionnaire Disability Index (SHAQ-DI)) were analysed at baseline in SSc patients randomised to the placebo arm (36, 37). The 6MWD significantly correlated with all of the other variables except DLCO and mRSS, although most of the correlations were very low (ranging from r=0.26 for FVC to r=-0.48 for SHAQ-DI). As SHAQ-DI is a measure of functional ability and reflects everyday living activities, it is not surprising that it correlated more closely than the other variables with the 6MWD, which is a measure of the sub-maximal exercise level characterising most of these activities.

One study of the severity of pulmonary disease in patients with SSc used an oxygen desaturation cut-off value of ≥4% during the 6MWT and a 6MWD cut-off value of <400 metres. The results showed that age, Borg's dyspnea index, chest X-ray fibrosis, PAH of ≥30 mmHg and oxygen desaturation of ≥4% were statistically associated with 6MWD, and that age, anti-Scl-70 autoantibody positivity, Borg's dyspnea index, chest X-ray fibrosis, an FVC of <80% of predicted, PAH of ≥30 mmHg, and ground glass or reticular opacities revealed by high-resolution computed tomography (HRCT) were associated with desaturation. A 6MWD of <400m was more frequent among African-Americans (among whom women had more severe disease, an earlier disease onset and a worse survival rate) (35), and correlated with aspecific variables such as an older age and dyspnea. Oxygen desaturation of ≥4% correlated with age and dyspnea but, more interestingly, also with an FVC pf <80% of predicted and anti-Scl70 autoantibody positivity (which are associated with exercise-induced oxy-haemoglobin desaturation) and the more frequent development of ILD and PH (38).

A retrospective comparison of 6MWT results in SSc patients *versus* patients affected by idiopathic pulmonary fibrosis did not reveal any important differences, even though their physiological pulmonary abnormalities were similar. The 6MWD correlated significantly with FVC and DLCO in the patients with idiopathic pulmonary fibrosis but not in those with ILD. The authors concluded that the 6MWD does not reflect the same physiological process in each disease as it is influenced by dyspnea in the patients with pulmonary involvement, and by lower extremity pain in patients with SSc without ILD or PH (39) (Fig. 2).

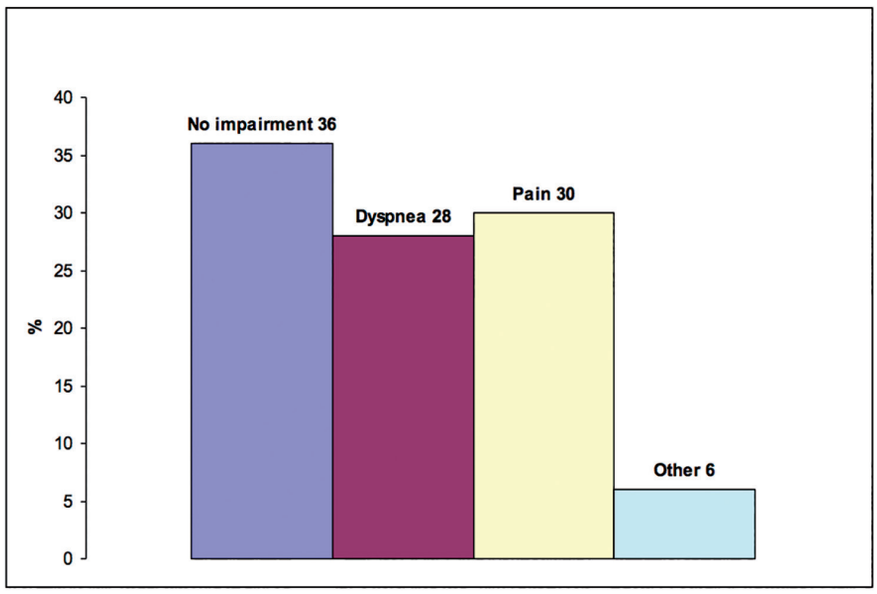

Fig. 2. Patient reported limitations of 6MWD in 394 SSc patients.
Data from: Wilsher *et al*. (33); Garin *et al*. (39); Schoindre *et al*. (40); Deutsche *et al*. (41).

Wilsher *et al*. (33) have suggested that measuring oxygen desaturation might improve the usefulness of the 6MWT, and their results demonstrating moderate and significant correlations between forehead oxygen desaturation and HRCT abnormalities, FVC and DLCO seem to support this idea.

One study of the reproducibility of the 6MWT in a small cohort of SSc patients with a FVC of ≤77% and a DLCO of ≤65% of predicted showed that 6MWT is feasible and reliable, and that forehead oximetry should be used. The test measurements correlated reasonably but variably with functional and morphological measures of disease severity (24).

Schoindre *et al*. in a French cohort (40) categorised 6MWD in normal or abnormal on the basis of the reference equation of Enring and Sherill (22). Correlations were found between the 6MWD and predicted FVC and DLCO levels but, as C-reactive protein levels and calcinosis were the only independent variables associated with an abnormal 6MWD, the authors raised doubts about the specificity of the 6MWD in SSc.

Furthermore, Schoindre *et al*. (40) found an association between oxygen desaturation during 6MWT and a SHAQ score of >1 and, using multivariate logistic regression, identified a significant model for predicting 6MWD consisting of the SHAQ score and DLCO. They found that the 6MWD was less in PAH patients, and correlated (weakly to moderately) with predicted FVC, forced expiratory volume in the first second, total lung capacity, DLCO, and nutrition status.

Deuschle *et al*. with a multivariate analysis showed that the SHAQ score and predicted DLCO were the best predictors of 6MWD, and that a cut-off distance of 473 metres best discriminated SSc patients with and without PAH with moderate sensitivity and specificity that could help for risk stratification (41).

A cohort of 121 anti-Scl-70 autoantibody-positive patients with diffuse SSc and initial ILD were studied for five years in an attempt to identify factors indicating exercise-induced oxygen de-

Table I. Studies investigating correlations between 6MWD and other variables.

Authors	Population	6MWD (metres)	Correlated parameters
Wilsher et al. (2012) (33)	30 SSc (17 SSc diffuse + 13 SSc limited) with and without ILD and PAH	502 (435-547)	FEV_1 FVC DLCO
Garin *et al*. (2009) (39)	80 SSc: 33 SSc ILD 13 SSc PAH 19 SSc ILD-PH 15 SSc	 319 (302-397) 315 (243-387) 312 (251-372) 313 (244-382)	FVC DLCO (only in SSc ILD)
Schiopu *et al*. (2007) (36)	65 SSc ILD (36 SSc diffuse + 29 SSc limited)	408 (87)	DLCO (only in SSc ILD limited)
Impens *et al*. (2007) (37)	86 SSc-ILD (47 SSc diffuse + 39 SSc limited)	404 (86)	FVC Borg dyspnea score SHAQ-DI
Villalba *et al*. (2007) (38)	110 SSc of which 33 SSc ILD (78 SSc limited + 32 SSc diffuse)	450 (150-660)	Age Borg dyspnea score Fibrosis at chest X-ray PAP ≥30 mmHg SaO_2 decrease ≥4%
Schoindre *et al*. (2009) (40)	87 SSc (36 SSc diffuse + 51 SSc limited) with and without ILD or PAH	461 (103)	PCR FVC DLCO
Deuschle *et al*. (2011) (41)	115 SSc (34 SSc diffuse + 61 SSc limited)	491 (86-664)	FVC FEV_1 TLC DLCO SHAQ-DI Nutrition status

SSc: systemic sclerosis; ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; ILD-PH: pulmonary hypertension related to ILD; 6MWD: 6 minute walking test distance; FEV_1: forced expiratory volume 1st sec.; FVC: forced vital capacity; TLC: total lung capacity; DLCO: diffusion capacity carbon monoxide; SHAQ-DI: Sclerodermia Health Assessment Questionnaire Disability Index; PAP: pulmonary arterial pressure; SaO_2: oxygen saturation. Interquartile ranges and standard deviations given in brackets as appropriate.

saturation during the 6MWT (42). During the follow-up, 32 patients (35%) desaturated during during the test, 12 of whom (37%) experienced a severe decrease in saturation (≤88%), indicating a high risk of developing PH and mortality. In these patients, a decrease in DLCO of <65% of predicted due to a decrease in the membrane component (Dm) decreased exercise capacity because of effort-induced hypoxaemia. A greater reduction in DLCO due to a decrease in both Dm and the capillary volume component (Vc) may also increase pulmonary pressure. The authors concluded that the combined execution of a 6MWT and evaluation of DLCO and its components (Dm and Vc) during follow-up could identify the anti-Scl-70 autoantibody-positive patients with diffuse SSc and initial ILD who are at greater risk of developing PH.

Clinical features

Published data confirm that the 6MWT is reliable and reproducible as it reflects the effort required for everyday physical activities by patents with SSc, whose exercise capacity is reduced especially if they have pulmonary involvement. However, SSc is a multifaceted and complex disease, and it is likely that the 6MWT and its outcome measure of the total distance walked are affected by other variables whose impact varies with the specific classification of SSc and the different types of pulmonary involvement.

In addition to the test conditions themselves, the 6MWT is influenced by the status of all of the organ systems involved in exercise. The skin and musculoskeletal components of SSc can lead to ineffective performance, and multisystem disease and inactivity can lead to deconditioning and reduced cardiopulmonary capacity. The changes in the cardiac physiology of SSc patients have not yet been fully clarified, and the same is true of the effects of left ventricular systolic or diastolic dysfunction on exercise capacity and the importance of right ventricular diastolic dysfunction. The 6MWT does not provide specific information regarding the relative contributions of each of these systems or the mechanisms underlying exercise limitations. Moreover, even using oxygen desaturation during 6MWT together with 6MWD does not reflect the severity of SSc-associated parenchymal lung disease in case series of undifferentiated SSc patients.

It is therefore possible that the indiscriminate use of the 6MWT in all SSc patients is of only relative significance. Desaturation provides additional information regarding the severity of dis-

ease in SSc patients with pulmonary involvement, and would appear to be a more specific measure of lung function, but it is recommended that a forehead probe be used in order minimise interference with the detection of the oximetry signal from Raynaud's phenomenon, which is often present in SSc patients.

We believe that the 6MWT should be used with an assessment of the degree of oxyhaemoglobin desaturation by measuring DLCO in order to stratify SSc patients with ILD during follow-up, especially if they are anti-Scl-70 autoantibody positive. Such patients may be affected by sometimes very severe exertional desaturation (≤88%) which, when associated with a reduction in DLCO (<65%) can predict the presence of PH.

Alternatives to the 6MWT

Given the doubts concerning the use of the 6MWT in SSc patients, it can be wondered whether there are more reliable tests for identifying the early evolution to ILD or even PAH in SSc patients, and two recent studies suggest promising alternatives.

Boutou *et al*. (43) have shown that maximal cardiopulmonary exercise testing (CPET) on a cycle ergometer can provide useful data when assessing the main cause of exercise limitation. Their study included a large number of clinically stable patients with diffuse or limited SSc and perceived exertional dyspnea or decreased physical performance. Using a modified algorithm (44), it was possible to categorise the patients into four subgroups: those whose exercise capacity was normal or subnormal but not limited by evident heart or lung disease (32%), and those whose exercise capacity was limited by respiratory limitations (10%), left ventricular dysfunction (26%), or pulmonary vasculopathy (32%). As expected, the extent of fibrosis revealed by HRCT helped to identify the patients with respiratory limitations, but it must be pointed that most of the patients with left ventricular dysfunction were anti-Scl-70 autoantibody positive and 40% also had extensive fibrosis.

Legnani *et al*. (45) measured DLCO during cycle ergometry in a small cohort of patients with limited SSc and found that a moderate effort revealed a latent impairment in gas diffusion through the alveolar/capillary membrane, thus confirming that exertional DLCO can identify lung damage at an earlier stage than resting DLCO.

Conclusions

The indiscriminate use of the 6MWT in all SSc patients has only relative significance, but the test has the advantage that can be used in all conditions and does not require dedicated training.

Stratifying SSc patient with lung involvement on the basis of the degree of desaturation during a 6MWT is important when interpreting serial changes. It is likely that CPET and DLCO measured during exercise provide more opportunities for diagnosing lung involvement early and stratifying patients on the basis of its severity, however, both tests are more complex to perform and interpret, and require greater patient compliance than the 6MWT; moreover, their repeatability in SSc patients has not yet been assessed (46, 47). Consequently, although the early indications are very interesting, it is not possible to completely shelve the 6MWT in favour of these methods.

The 6MWT accompanied by an evaluation of other parameters such as DLCO and its components (Dm and Vc) and SHAQ scores may be indicated in the follow-up of patients with SSc-ILD, especially if they are anti-Scl-70 autoantibody positive in order to identify those at greater risk of developing PH.

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