Performance capacity evaluated using the 6-minute walk test: 5-year results in patients with diffuse systemic sclerosis and initial interstitial lung disease

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ABSTRACT

Objective. *To identify factors indicating exercise-induced oxygen desaturation during the 6-minute walk test (6MWT) in patients with diffuse systemic sclerosis (SSc) and initial interstitial lung disease (ILD).*

Methods. *The study involved 121 consecutive adult anti-Scl 70 autoantibody-positive SSc patients with initial ILD, 93 of whom were followed up for five years. Before enrolment and then annually, the patients underwent high-resolution computed tomography (HRCT), functional lung tests, with carbon monoxide diffusion capacity of the lung (DLCO) and its components (alveolar-capillary membrane [Dm] and pulmonary blood volume [Vc]), the evaluation of dyspnea before and after the 6MWT using the Borg scale, and transthoracic echocardiography. A decrease in peripheral capillary oxygen saturation (SpO_2) of ≥4% during the 6MWT was used to define desaturation, the appearance of which led to the patient being withdrawn from follow-up.*

Results. *There were no significant differences in HRCT score during the follow-up, but 32 patients (35%) desaturated during the 6MWT, including 12 (37%) who experienced a severe decrease SpO_2 to ≤88%, indicating a high risk of mortality. At baseline, there was no statistically significant difference in any considered clinical characteristics between the desaturating and non-desaturating patients but, at the time of desaturation, the desaturators had lower minimum SpO_2% levels during the 6MWT ($p<0.0001$), and lower DLCO ($p<0.0001$) and Dm ($p<0.0001$).*

Comparison of the desaturators defined on the basis of a reduction in SpO_2 to ≤88% and those defined on the basis of a decrease in SpO_2 of ≥4% showed that, at baseline, the former had lower minimum SpO2% levels during 6MWT ($p<0.001$), lower DLCO ($p=0.01$), a lower DLCO/VA ratio ($p=0.05$), lower Dm ($p<0.005$) and Vc values ($p<0.5$), and higher RVsystP ($p=0.01$).

At the time of desaturation, the desaturators' minimum SpO_2 levels during the 6MWT correlated with their DLCO ($r=0.78$; $p<0.001$), Dm ($r=0.65$; $p<0.01$), Vc ($r=0.52$;$p<0.05$) and RVsystP values ($r = -0.53$; $p<0.05$).

Conclusion. *Our data seem to confirm the close interdependence between pulmonary diffusion and oxygen desaturation during exercise. In SSc combined 6MWT, DLCO and its components may indicate patients at increased risk of developing pulmonary hypertension.*

Introduction

Systemic sclerosis (SSc) is unique insofar as it is characterised by the features of 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, and fibrosis due to the excessive accumulation of collagen and extracellular matrix components is frequently encounterd. Genetic factors may play a role in the pathogenesis of the disease by affecting host susceptibly 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 with lung involvement are at particular risk of developing pulmonary hypertension which, if it is untreated, may lead to right ventricular failure and early death (2).

The six-minute walk test (6MWT) is a simple, efficient and inexpensive

means of evaluating performance during sub-maximal exercise that can be safely used in the case of patients with advanced lung disease (3-5), and oxygen desaturation during the 6MWT correlates with the single-breath carbon monoxide diffusion capacity of the lung (DLCO) (6, 7). SSc patients with lung involvement have impaired DLCO and pulmonary arterial hypertension (8), and a DLCO of ≤50% of the predicted value indicates a high risk of mortality (9). It has also been shown that oxygen desaturation measured by means of pulse oximetry (SpO_2 ≥4%) during the 6MWT correlates with age, the dyspnea index, positive anti-Scl 70 autoantibodies, forced vital capacity (4) and a reduced DLCO (10, 11).

The aim of this study was to identify factors indicating exercise-induced oxygen desaturation during the 6MWT in patients with diffuse SSc and initial interstitial lung disease (ILD).

Methods

One hundred and twenty-one consecutive anti-Scl70 autoantibody-positive patients with diffuse SSc defined according to the extent of skin involvement, characterised by sclerotic lesions extending above the elbows and the knees, and initial or early onset of ILD diagnosed by means of high-resolution computed tomography (HRCT) were enrolled at the Rheumatology Department of L. Sacco University Hospital in Milan, Italy, between January 2007 and December 2008 (12, 13). Twenty-eight were excluded from the study because of articular disabilities, severe cough, heart failure, back pain, an inadequate pulse oximetry signal (Raynaud's phenomenon, RP), resting SpO_2 levels of <90%, or oxygen desaturation during the 6MWT (a decrease in SpO_2 of ≥4%); the remaining 93 were followed up for up to five years.

Before enrolment and then annually, the patients underwent HRCT, functional lung tests, the measurement of DLCO and its components (alveolar-capillary membrane [Dm] and pulmonary blood volume [Vc]) (VMax 227 Autobox, Sensormedics, Yorba Linda, CA, USA), the 6MWT using a forehead sensor (Nonin 2500, Nonin Medical INC, Plymouth, MN, USA), dyspnea evaluations before and after the 6MWT using the Borg scale (14), and transthoracic echocardiography (IE33 Echocardiography System, Philips, Amsterdam, The Netherlands).

Lung volume, dynamic spirometry parameters and DLCO were measured in accordance with the criteria of the European Respiratory Society (ERS) and American Thoracic Society (ATS) (15-18); the DLCO and volume ventilated ratio (DLCO/VA) was considered as representing diffusion because the transfer factor is clearly related to the available lung surface represented by VA. Single-breath DLCO was adjusted for the level of carboxyhaemoglobin as measured using a blood gas analyser (Critical Care Laboratory Systems 35, Instrumentation Laboratory, Paderno Dugnano, Italy) (19), and DLCO Dm and Vc were calculated using the equation of Roughton and Foster (20).

The 6MWT was carried out in accordance with a protocol adapted from the ATS guideline (21) using a straight and level 45-metre course in an enclosed corridor that was marked with cones at either end. Standardisation instructions were read aloud to each patient before the test (22) and, at the end of each minute, he or she was informed of the elapsed time and given standard encouragement. Respiratory frequency was measured before and immediately after the end of the 6MWT.

We avoided using a fingertip sensor to measure oxygen saturation because digit circulation is often deteriorated in SSc patients to the extent that SpO_2 cannot by measured during the 6MWT.

A forehead sensor may overcome these difficulties because capillary perfusion of the forehead by the supraorbital artery is less susceptible to vasoconstriction (23) and forehead sensor are less susceptible to motion artefact as they are fletter and can be secured more affectively.

Consequently, oxygen saturation was recorded by means of pulse oximetry after a 5-minute rest before the test, throughout the test itself, and immediately afterwards.

In order to evaluate the degree of ILD and its evolution, the patients underwent HRCT before enrolment and then annually. Thin sections separated by three minutes were acquired between the apices and bases of the lungs using a CT scanner with the patients in a supine position, and then recontructed using a high-resolution algorithm. The scans were analysed for the presence or absence of a pattern consistent with ILD by an experienced radiologist who was blinded to the clinical data. ILD was defined as the presence of characteristic multifocal or diffuse abnormalities (subpleural opacities, parenchymal bands, thickened interlobular septae, an irregular pleural interface, honeycomb lung) if they were bilateral and at multiple levels. Disease severity was semiquantitatively graded using a 5-point scale: grade 0=0% involvement of lung parenchyma; grade 1=1-15%; grade 2=15-30%; grade 3=30-50%; and grade 4=>50% (24). The American Thoracic Society classification was used in order to exclude other forms of ILD (25).

All of the patients underwent transthoracic echocardiography in the left lateral decubitus position. Left ventricular end-diastolic and end-systolic diameters were determined by means of M-mode echocardiography, and the left ventricular ejection fraction (EF) was calculated using a modified version of Simpson's formula. Right ventricular systolic pressure (RVsystP), which reflects systolic pulmonary artery pressure, was estimated on the basis of tricuspid regurgitating velocity as measured by means of tissue Doppler echocardiography following Bernoulli's principle (26, 27).

The patients were followed up for five years or until the appearance of desaturation (defined as a ≥4% decrease in SpO_2) led to the patient being transferred to the desaturator group.

The study protocol was approved by our local ethics committee and conducted in accordance with the ethical guidelines of the 1975 Helsinki Declaration. Informed consent was obtained from all of the subjects before they underwent any of the study procedures.

Statistical analysis

The data were analysed using Statistical Package for the Social Sciences software, version 2.0 (IBM SPSSC

Statistics 2.0, 2011) and are expressed as mean values and standard deviation. The Borg scale scores, respiratory function, and the 6MWT and echocardiographic parameters of the desaturators and non-desaturators were compared using an unpaired Student's *t* test. Spearman's rank correlation was used as appropriate. A *p*-value of <0.05 was considered significant.

Results

Of 121 SSc patients enrolled 28 were excluded: 20 for unadequate pulse oximetry signal (72%), 3 for back pain (10%), 2 for severe cough (8%) and 3 for articular disabilities (10%).

The remaining 93 patients (age 65±3 y, 10 m, 83 f) were all anti-Scl70 autoantibody positive, affected by diffuse SSc (duration disease 9±3 y) with initial lung involvement, and being treated with corticosteroids (mean dose 5 mg; range 2.5-10 mg). Eighty nine (96%) were also taking azathioprine (AZA) at a mean dose of 150 mg/day (range 50-200 mg), ten (9%) cylophosphamide and five (4.5%) mycophenolate mofetil, and seventy-seven (82%) were receiving low-dose nifedipine (30 mg/day) because of Raynaud Phenomena (RP). None of the patients suffered from cardiovascular disease or any other complication. All of the patients were antinuclear antibodies (ANA) positive. Table I shows the patients' characteristics at the beginning of follow-up.

There were no statistically significant differences in HRCT scores during the follow-up, but 32 patients (35%) desaturated during the 6MWT (a ≥4% decrease in SpO_2), including 12 (37%) who were severely desaturated (SpO_2 ≤88%). There was no statistically significant difference in any of the considered characteristics of the two groups at baseline (Table II) but, at the time of the exit from the study, the desaturators had a longer disease duration (13.5±1.5 *vs*. 10±2 years; $p<0.0001$), lower minimum SpO_2% levels during the 6MWT (90.3±1% *vs*. 94.2±0.4%; $p<0.0001$), lower DLCO (41.6±11% *vs*. 64.2±13% of predicted; $p<0.0001$), a lower DLCO/VA ratio (66.3±10% *vs*. 76.4±16% of predicted; $p=0.05$) and lower Dm values (10±3 *vs*. 14.9±2.8 mL/min/mmHg; $p<0.0001$) (Table III). Comparison of the desaturators defined on the basis of a reduction in SpO_2 to ≤88% and those defined on the basis of a decrease in SpO_2 of ≥4% showed that, at baseline, the former had lower minimum SpO2% levels during 6MWT (86.3±1% *vs*. 90.5±1%; $p<0.001$), lower DLCO (37±10% *vs*. 46±9% of predicted: $p=0.01$), a lower DLCO/VA ratio (63±8% *vs*. 70±10% of predicted; $p=0.05$), lower Dm (7±4

Table I. Characteristics of 93 patients with systemic sclerosis.

Gender (M/F)	11%/89%
Age (years)	65 ± 3
SpO_2% at rest	94.3 ± 2
Duration disease (y)	9 ± 3
HRCT rate	2.8 ± 0.7
VC (% predicted)	88 ± 18
FEV_1 (% predicted)	91 ± 21
TLC (% predicted)	84 ± 16
RV/TLC (% predicted)	95 ± 14
DLCO (% predicted)	68.5 ± 16
DLCO/VA (% predicted)	78.6 ± 16
Dm (ml/min/mmHg)	15.3 ± 3
Vc (ml)	74 ± 18
SpO_2 during 6MWT	94.3 ± 0.8
Breath rate before 6MWT (n°/min)	21 ± 4
Breath rate at 6MWT end (n°/min)	26 ± 5
Borg scale before 6MWT	2 ± 1
Borg scale at 6MWT end	5 ± 2
6MWT distance (m)	403 ± 134
RVsystP (mmHg)	29.7 ± 8.3
EF (%)	74 ± 5

6MWT: six-minute walk test; SpO_2: oxygen saturation by pulse oxymeter; VC: vital capacity; FEV_1: forced expiratory volume in one second; TLC: total lung capacity; RV: residual volume; DLCO: diffusion capacity of thr carbon monoxide; VA: alveolar volume; Dm: alveolar-capillary membrane; Vc: pulmonary blood volume; HRCT: hight-resolution computed tomography; RVsystP: right ventriculars systolic pressure; EF: left ventricular ejecton fraction. *SD: standard deviation

Table II. Characteristics of 61 future non desaturators and 32 future desaturators at baseline.

Gender (M/F)	Non desaturators 20%/80%	desaturators 19%/81%	*p*-values ns
Age (years)	64 ± 4	65 ± 2	ns
SpO_2% at rest	96.5 ± 3	95 ± 3	ns
Duration disease (y)	9 ± 3	10 ± 2	ns
HRCT rate	2.8 ± 0.5	2.9 ± 0.7	ns
VC (% predicted)	90 ± 20	84 ± 15	ns
FEV_1 (% predicted)	92 ± 23	88 ± 16	ns
TLC (% predicted)	85 ± 12	83 ± 14	ns
RV/TLC (% predicted)	97 ± 16	94 ± 14	ns
DLCO (% predicted)	70 ± 16	64.2 ± 13	ns
DLCO/VA (% predicted)	80.3 ± 15	76.4 ± 16	ns
Dm (ml/min/mmHg)	16 ± 2.7	14.9 ± 2.8	ns
Vc (ml)	77 ± 16	72 ± 18	ns
SpO_2% during 6MWT	95.3 ± 2	94.5 ± 2.5	ns
Breath rate before 6MWT (n°/min)	20 ± 6	22 ± 4	ns
Breath rate at 6MWT end (n°/min)	25 ± 4	26 ± 6	ns
Borg scale before 6MWT	2 ± 1	2 ± 2	ns
Borg scale at 6MWT end	4 ± 3	5 ± 2	ns
6MWT distance (m)	410 ± 96	396 ± 111	ns
RVsystP (mmHg)	28.4 ± 9.1	31.2 ± 8	ns
EF (%)	74 ± 6	74 ± 4	ns

6MWT: six-minute walk test; SpO_2: oxygen saturation by pulse oxymeter; VC: vital capacity; FEV_1: forced expiratory volume in one second; TLC: total lung capacity; RV: residual volume; DLCO: diffusion capacity of thr carbon monoxide; VA: alveolar volume; Dm: alveolar-capillary membrane; Vc: pulmonary blood volume; HRCT: hight-resolution computed tomography; RVsystP: right ventriculars systolic pressure; EF: left ventricular ejecton fraction. *SD: standard deviation.

Table III. 32 patients will be desaturators at the start of follow-up *vs*. at the desaturation time.

	At the start of follow-up	At desaturation time	*p*-values
SpO_2% at rest	94 ± 3	93 ± 2.5	ns
Duration disease (y)	10 ± 2	13.5 ± 1.5	0.0001
HRCT rate	2.9 ± 0.7	3.3 ± 1.5	ns
VC (% predicted)	84 ± 15	79 ± 17	ns
FEV_1 (% predicted)	88 ± 16	84 ± 18	ns
TLC (% predicted)	83 ± 14	77 ± 16	ns
RV/TLC (% predicted)	94 ± 14	90 ± 17	ns
DLCO (% predicted)	64.2 ± 13	41.6 ± 11	0.0001
DLCO/VA (% predicted)	76.4 ± 16	66.3 ± 10	0.05
Dm (ml/min/mmHg)	14.9 ± 2.8	10 ± 3	0.0001
Vc (ml)	72 ± 18	67 ± 17	ns
SpO_2% during 6MWT	94.5 ± 2.5	90 .± 3	0.01
Breath rate before 6MWT (n°/min)	22 ± 4	24 ± 5	ns
Breath rate at 6MWT end (n°/min)	26 ± 6	29 ± 7	ns
Borg scale before 6MWT	2 ± 2	3 ± 3	ns
Borg scale at 6MWT end	5 ± 2	6 ± 3	ns
6MWT distance (m)	396 ± 111	378 ± 96	ns
RVsystP (mmHg)	31.2 ± 8	33 ± 9	ns
EF (%)	74 ± 4	73 ± 5	ns

6MWT: six-minute walk test; SpO_2: oxygen saturation by pulse oxymeter; VC: vital capacity; FEV_1: forced expiratory volume in one second; TLC: total lung capacity; RV: residual volume; DLCO: diffusion capacity of thr carbon monoxide; VA: alveolar volume; Dm: alveolar-capillary membrane; Vc: pulmonary blood volume; HRCT: hight-resolution computed tomography; RVsystP: right ventriculars systolic pressure; EF: left ventricular ejecton fraction. *SD: standard deviation.

Table IV. 20 patients desaturators for a fall of SpO_2% ≥4% during 6MWT *vs*. 12 patients desaturators for a SpO_2% ≤88% during 6MWT.

	Fall of SpO_2% ≥4%	SpO_2% ≤88%	*p*-values
Gender (m/f)	18%/82%	19%/81%	ns
Age (y)	64.3 ± 3	65.2 ± 3.3	ns
SpO_2% at rest	93.3 ± 2.6	92.8 ± 3	ns
Duration disease (y)	13.4 ± 2.8	13.6 ± 3	ns
HRCT rate	2.9 ± 0.8	3.6 ± 0.7	ns
VC (% predicted)	83 ± 15	76 ± 16	ns
FEV_1 (% predicted)	86 ± 14	81 ± 15	ns
TLC (% predicted)	79 ± 13	73 ± 16	ns
RV/TLC (% predicted)	94 ± 15	91 ± 17	ns
DLCO (% predicted)	46 ± 9	37 ± 10	0.01
DLCO/VA (% predicted)	70 ± 10	63 ± 8	0.05
Dm (ml/min/mmHg)	11 ± 3	7 ± 4	0.005
Vc (ml)	71 ± 16	59 ± 15	0.05
SpO_2% during 6MWT	90.5 ± 1	86.3 ± 1	0.001
Breath rate before 6MWT (n°/min)	22.4 ± 4	25 ± 3	ns
Breath rate at 6MWT end (n°/min)	28 ± 4	32 ± 6	0.05
Borg scale before 6MWT	2 ± 1	2 ± 2	ns
Borg scale at 6MWT end	4 ± 1	6 ± 3	0.01
6MWT distance (m)	384 ± 103	363 ± 112	ns
RVsystP (mmHg)	30.8 ± 7	38.9 ± 8	0.01
EF (%)	73.8 ± 4	71 ± 3	ns

6MWT: six-minute walk test; SpO_2: oxygen saturation by pulse oxymeter; VC: vital capacity; FEV_1: forced expiratory volume in one second; TLC: total lung capacity; RV: residual volume; DLCO: diffusion capacity of thr carbon monoxide; VA: alveolar volume; Dm: alveolar-capillary membrane; Vc: pulmonary blood volume; HRCT: hight-resolution computed tomography; RVsystP: right ventriculars systolic pressure; EF: left ventricular ejecton fraction. *SD: standard deviation.

vs. 11±3 mL/min/mmHg; $p<0.005$) and Vc values (71±16 *vs*. 59±15 mL; $p<0.5$), and higher RVsystP (38.9±8 *vs*. 30.8±7 mmHg: $p=0.01$). At the end of the 6MWT, these patients also had a higher respiratory rate (32±6 *vs*. 28±4 breaths/min; $p<0.05$) and higher Borg scale scores (6±3 *vs*. 4±1; $p=0.05$) (Table IV).

At the time of desaturation, the desaturators' minimum SpO_2 level during the 6MWT correlated with their DLCO (r=0.78; $p<0.001$), DLCO/VA ratio (r=0.64; $p<0.01$), Dm (r=0.65; $p<0.01$) and Vc (r=0.52; $p<0.05$), and RVsystP values (r=-0.53; $p<0.05$) (Table V).

Discussion

It has been reported that the percentage of predicted DLCO is one of the predictors of 6MWT distance (8) and oxygen desaturation during the 6MWT (10) in SSc patients with ILD. Pimenta *et al*. (28) have demonstrated that the desaturation: distance ratio during the 6MWT closely correlates with DLCO, and so oximetry may more accurately reflect the diffusion capacity of the alveolar/capillary membrane, which is reduced in patients with ILD due to impaired gas exchange (reflected by DLCO) (29). It has also been found that exercise-induced oxygen desaturation in patients with advanced idiopathic interstitial pneumonia correlates with walking speed, DLCO and arterial oxygen pressure at rest (29). Exercise-induced oxygen desaturation is an important factor limiting exercise in patients with interstitial lung disease, who have a reduced DLCO due to a decrease in alveolar volume and the involvement of alveolar/capillary membranes, which reduces the distance and minimum SpO_2 levels during the 6MWT because of disturbed gas exchange. A reduction in SpO_2 to ≥88% during the 6MWT indicates a high risk of mortality and is a sign of progression in patients with idiopathic interstitial lung disease (27, 30).

Bichile *et al*. (32) found an association between initial high-resolution CT grading and improved post-6MWT oxygen saturation, which predicts a good outcome in treated patients with moderate ILD. Decreasing serial FVC and DLCO measurements have a negative impact on prognosis (33) and, importantly, even small changes in FVC and DLCO within the first 6-12 months of observation may translate into major survival differences during long-term follow-up over five and 10 years.

The impaired DLCO of SSc patients (28, 29) may be caused by two distinct mechanisms: pulmonary capillary dysfunction, or pulmonary fibrosis decreasing alveolar volume and directly affecting CO uptake. The latter is par-

Table V. Spearman's rank correlation in patients desaturators during 6MWT.

SpO2 during 6MWT	versus	DLCO	r 0.78	$p<0.001$
		DLCO/VA	r 0.64	$p<0.01$
		Dm	r 0.65	$p<0.01$
		Vc	r 0.52	$p<0.05$
		RVsystP	e -0.55	$p<0.05$

6MWT: six-minute walk test; SpO_2: oxygen saturation by pulse oxymeter; DLCO: diffusion capacity of thr carbon monoxide; VA: alveolar volume; Dm: alveolar-capillary membrane; Vc: pulmonary blood volume; RVsystP: right ventriculars systolic pressure.

ticularly common in patients with diffuse SSc in whom the impairment is often due to ILD, and so impaired DLCO may reflect an underlying pulmonary vasculopathy (31). DLCO impairment has also been observed in association with altered nail fold capillary microscopy findings in SSc patients with RP (32).

We chose to enrol anti-Scl70 positive SSc patients in this study because the presence of these auto-antibodies is not only related to a greater likelihood of exercise-induced oxy-haemoglobin saturation (4) but also to the more frequent development of ILD and pulmonary hypertension (33).

Our data show that 32 of our 93 patients (35%) became desaturators during the five-year follow-up period, 12 of whom (37%) had SpO2 levels of ≤88% during the 6MWT, a level that may also represent a negative prognostic index (27, 31). A reduction in DLCO due to decrease in its Dm component seems to be the determining cause of reduced oxy-haemoglobin saturation during execrcise. As our patients showed no worsening in the degree of ILD as evaluated on the basis of their HRCT scores, the reduction in Dm could have been due to an erythrocytic haemorheological alteration (34). If, in addtion to the reduction in DLCO and Dm, where is also a reduction in the second component (Vc), exercise induces a greater decrease in SpO_2% and an increase in pulmonary pressure, probably because of vascular destruction in the fibrotic areas of the lung and latent pulmonary vessel disease (35).

The fact that the degree of lung involvemennt indicated by the HRCT score remains unchanged confirms the greater sensitivity of DLCO in revealing the progression of ILD in SSc patients (36).

Conclusions

Studying oxygen saturation during the 6MWT is a simple, reproducible and less-time consuming method of diagnosing and monitoring SSc patients with ILD that can be recommended as a means of prognosticating pulmonary morbility. Further studies of the routine use of this test in a large cohort a patients attending a scleroderma clinic are therefore warranted.

It is worth highlighting two aspects: the first is the need to monitor patients with diffuse SSc and initial ILD because approximately one-third will develop a major exercise limitation in the form of oxygen desaturation during the following five years; the second is the role of studying DLCO and its components in the follow-up of SSc patients, particularly if they are anti-Scl70 positive.

A reduction in DLCO to <65% of the predicted value due to a decrease in Dm may indicate decreased exercise capacity due to effort-induced hypoxemia, and a greater reduction in DLCO due to a decrease in both components may also increase pulmonary pressure. In 2008 Ovebeek *et al*. (37) denied the usefulness of Dm and Vc when sceening SSc patients for pulmonar hypertension. We believe that the combination of 6MWT, DLCO and its components during following up SSc patients could identify those with at greater risk of developing pulmonary hypertension, but further studies are necessary to clarify this point.

Study limitations

We did not evaluate pulmonary pressure by means of cardiac catheterisation because we did not think it ethical to submit the patients to such an invasive procedure many times during the follow-up period. An important limitation of this study is the use of the 6-MWT that has been widely accepted and is recommended in the assessment of SSc, for prognosing and monitoring the efficacy of the therapy. However, confounders and co-morbidities, such as pain and musculoskeletal disorders, can reduce the reliability and validity of this test in SSc. Furthemore, the absence of second experienced radiologist for assesing the presence or absence of a pattern consistent with ILD could be a further limitation.

References

1. VARGA J, KORN JH: Pathogenesis of systemic sclerosis: emphasis on human data. *In*: CLEMENTS PJ, FURST DE (Eds.) *Systemic Sclerosis*. 2nd ed. Philadelphia, PA: *Lippincott, Williams and Wilkins,* 2004; pp 63-88.
2. MUKERJEE D, ST GEORGE D, COLEIRO B, KNIGHT C *et al*.: Prevalence and outcome in systemic sclerosis associated pulmonary hypertension: application of a registry approach. *Ann Rheum Dis* 2003; 62: 1088-93.
3. TOLLE JJ, WAXMAN AB, VANHORN TL, PAPPAGIANOPOULOS PP, SYSTROM DM: Exercise-induced pulmonary arterial hypertension. *Circulation* 2008; 118: 2183-9.
4. VILLALBA WO, SAMPAIO-BARROS PD, PEREIRA MC *et al*:. Six-minute walk test for evaluation of pulmonary disease severity in sclerodermia patients. *Chest* 2007; 131: 217-22.
5. JENKINS S, CECINS N: Six minute walk test: observed adverse events and oxygen desaturation in a large cohort of patients with chronic lung disease. *Intern Med J* 2011; 41: 416-22.
6. WALLAERT B, WEMEAU-STERVINOU L, SALLERON J, TILLIE-LEBLOND I, PEREZ T: Do we need exercise test to detect gas exchange impairment in fibrotic idiopathic interstitial pneumonias? *Pulm Med* 2012; 12: 657180.
7. WEMEAU-STERVINOU L, PEREZ T, MURPHY C, POLGE A-S,WALLAERT B: Lung capillary blood volume and membrane diffusion in idiopathic interstitial pneumonia. *Resp Med* 2012; 106: 564-70.
8. ALKOTOB ML, SOLTANI P, SHEATT MA *et al*.: Reduced exercise capacity and stress-induced pulmonary hypertension in patients with sclerodermia. *Chest* 2006; 130: 176-81.
9. TRAD S, HUONG DLT, FRANCES C *et al*.: Impaired carbon monoxide diffusing capacity as a marker of limited systemic sclerosis. *Eur J Intern Med* 2011; 22: e80-e6.
10. SOMEYA F, MUGII N, HASEGAWA M, YAHATA T, NAKAGAWA T: Predictors of exercise-induced oxygen desaturation in systemic sclerosis patients with interstitial lung disease. *Respiratory Care* 2014; 59: 75-80.
11. GUARNIERI G, ZANATTA E, MASON P *et al*.: Determinants of impairment in lung diffusing capacity in patients with systemic sclerosis. *Clin Exp Rheumatol* 2015; 33 (Suppl. 91): S80-86.
12. REED J, POPE JE: A comparison between general rheumatologists and scleroderma experts

with respect to following systemic sclerosis guidelines. *Clin Exp Rheumatol* 2015; 33 (Suppl. 91): S40-46.
13. BARSOTTI S, BELLANDO RANDONE S, GUIDUCCI S, DELLA ROSSA A: Systemic sclerosis: a critical digest of the recent literature. *Clin Exp Rheumatol* 2014; 32 (Suppl. 86): S194-205.
14. BORG G: Psychophysical basis of perceived exertion. *Med Sci Sparts Exerc* 1982; 14: 377-81.
15. MILLER MR, HANKINSON J, BRUSASCO V *et al*.: ATS/ERS Task force standardisation of spirometry. *Eur Respir J* 2005; 26: 319-38.
16. WANGER J, CLAUSEN JL, COATES A *et al*.: Standardisation of the measurements of lung volumes. *Eur Respir J* 2005; 26: 511-22.
17. MACINTYRE N, CRAPO RO, VIEGI G *et al*.: Standardisation of the single breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 2005; 26: 720-35.
18. PELLEGRINO R, VIEGI G, BRUSASCO V *et al*.: Interpretative strategies for lung function test. *Eur Respir J* 2005; 26 (Vol.): 948-68.
19. MOHSNIFAR Z, TASKIN DP: Effects of carboxyhemoglobin on single breath diffusing capacity: derivation of an empirical correction factor. *Respiration* 1979; 37: 158-91.
20. ROUGHTON FJW, FOSTER RE: Relative importance of diffusion and chemical reaction rates in determining rate of exchange of gases in the human lung, with special reference to true diffusing capacity of pulmonary membrane and volume of blood in the capillaries. *J Appl Physiol* 1957; 11: 277-89.
21. AMERICAN THORACIC SOCIETY: ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; 166: 111-17.
22. CAMARRI R, EASTWOOD PR, CECINS NM, THOMPSON PJ, JENKINS S: Six-minute walk distance in healthy subjects aged 55-75 years. *Resir Med* 2006; 100: 658-63.
23. MACLEOD DB, CORTINEZ LI, KEIFER JC: The desaturation response time of finger pulse oximeters during mild hypothermia. *Anaesthesia* 2005; 60: 65-71.
24. MALERBA M, RADAELI A, RAGNOLI B *et al*.: Exahaled nitric oxide levels in systemic sclerosis with and without pulmonary involvement. *Chest* 2007; 132 (Vol.): 575-80.
25. American Thoracic Society/European Respiratory Society International Multidisclinary Consensus Classification of the Idiopatic Interstitial Pneumonias. *Am J Respir Crit Care Med* 2002; 165: 277-304.
26. MEUNE C, AVOUAC J, WAHBI K *et al*.: Cardiac involvement in systemic sclerosis assessed by tissue-Doppler echocardiography during routine care: a controlled study of 100 consecutive patients. *Arthritis Rheum* 2008; 58: 1803-9.
27. SCHACHNA L, WIGLEY FM, CHANG B, WITH B, WISE RA, GELBER AC: Age and risk of pulmonary arterial hypertension in scleroderma. *Chest* 2003; 124: 2098-104.
28. PIMENTA SP, BARBOSA DA ROCHA R, BALDIB. G, DE MELO KAWASSAKI A, ADIB KAIRALLA R, RIBEIRO CARVALHO CR: Desaturation – distance ratio: a new concept for a functional assessment of interstitial lung disease. *Clnics Science* 2010; 65: 841-6.
29. LAMA VN, FLAHERTY KR, TOEWS GB *et al*.: Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. *Am J Resp Crit Care Med* 2003; 168: 1084-90.
30. HALLSTRAND TS, BOITANO LJ, JOHSON WC, SPADA CA, HAYES JG, RAGHUG: The timed walk test as a measure of severity and survival in idiopathic pulmonary fibrosis. *Eur Respir J* 2005; 25: 96-103.
31. BICHILE I, BICHILE T, EHSAN A, KHARAJE J: Six minute walk test as an assessment tool in systemic sclerosis. *Internet Journal of Rheumatology* 2008; 6.
32. BOUROS D, WELLS AU, NICHOLSON AG, COLBY TV *et al*.: Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. *Am J Respir Crit Care Med* 2002; 165: 1581-6.
33. WALKER UA, TYNDALL A, CZIRJAK I *et al*.: EUSTAR Co-authors: Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. *Ann Rheum Dis* 2007; 66: 754-63.
34. SPENGLER ML, SVETAZ MJ, LEROUX MB, LEIVA ML, BOTTAI HM: Association between capillaroscopy, haemorheological variables and plasma proteins in patients bearing Raynaud's phenomenon. *Clin Hemorheol Microcirc* 2004; 30: 17-24.
35. HUEZ S, ROUFUSSE F, VACHIERY JL *et al*.: Isolated right ventricular dysfunction in systemic sclerosis: latent pulmonary hypertension? *Eur Respir J* 2007; 30: 928-38.
36. DIOT E, BOISSINOT E, ASQUIER E *et al*.: Relationship between abnormalities on high-resolution CT and pulmonary function in systemic sclerosis. *Chest* 1998; 114: 1623-9.
37. OVERBEEK MJ, GROEPENHOFF H, VOSKUYL AE *et al*.: Membrane diffusion and capillary blood volume measurements are not useful as sceening tools for pulmonary arterial hypertension in systemic sclerosis: a case control study. *Respir Res* 2008; 9: 68-75.