Role of pulmonary function tests in screening pulmonary arterial hypertension in scleroderma

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Introduction Pulmonary arterial hypertension (PAH) is a life-threatening complication of scleroderma. Its prevalence is estimated to be between 12 and 29%. The symptoms are usually nonspecific and overlooked in those patients already limited by other complications of their condition. It is recommended to perform noninvasive screening for scleroderma patients for early detection of PAH, which has a significant impact on treatment strategy and clinical outcomes.

Aim of the study The aim of this study was to assess the role of certain pulmonary function parameters [forced vital capacity (FVC), diffusion capacity of the lung for carbon monoxide (DLCO), FVC/DLCO] in the early prediction of PAH in scleroderma patients.

Patients and methods This prospective study was conducted on 30 scleroderma-diagnosed patients; all patients were subjected to routine laboratory investigations, plain chest radiographic posteroanterior view, computed tomography of the chest, transthoracic echocardiography, spirometry, and DLCO.

Results The echocardiographic results showed pulmonary artery systolic pressure greater than 35 mmHg in eight patients, which led to suspect a possibility of pulmonary hypertension (PH) in those patients. On comparing patients with suspected PH and others, we found significant differences in the values of FVC% and DLCO%, which was significantly lower in patients with suspected PH ($P < 0.05$), and FVC%/DLCO% was significantly higher in those patients ($P < 0.05$). The best cutoff value of FVC/DLCO for predicting suspected PH among the studied cases was a value greater than 1.91, with a sensitivity of 87.5% and a specificity of 100%.

Conclusion Assessment of pulmonary functions is an easy and helpful tool in screening pulmonary vasculopathy in scleroderma patients. It helps to suspect patients with early PH, which can be subsequently confirmed with further appropriate tests. *Egypt J Broncho* 2015 9:287–292

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Keywords: diffusion capacity of the lung for carbon monoxide, pulmonary arterial hypertension, pulmonary function tests, scleroderma

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Introduction

Scleroderma, also known as systemic sclerosis, is a multisystem autoimmune connective tissue disorder characterized by microvascular damage and fibrosis in multiple organs, which leads to significant morbidity and mortality [1]. Pulmonary involvement in systemic sclerosis is common; it most often comprises fibrosis or interstitial lung disease, and pulmonary vascular disease leading to pulmonary arterial hypertension (PAH) [2]. Pulmonary complications are usually associated with unfavorable prognosis and considered the leading cause of disease-related morbidity and mortality in scleroderma patients [2]. PAH is a progressive vasculopathy that is advanced by the time symptoms develop. As symptoms are nonspecific, continued progression toward end-stage disease occurs for an average of 2 years between symptom onset and diagnosis, and usually this is associated with high mortality despite therapy [3]. Therefore, there is an urgent need for earlier diagnosis, which may have a significant impact on the treatment strategy and clinical outcome [4]. Quality of life and prognosis are substantially improved with early diagnosis and treatment, and the outcomes are clearly better [5].

It is recommended to screen patients with systemic sclerosis without clinical signs and symptoms of pulmonary hypertension (PH) with a two-step approach using clinical assessment for the presence of telangiectasia and anticentromere antibodies, pulmonary function tests and single-breath diffusion capacity of the lung for carbon monoxide assessment (DLCO-SB) measurements, ECG in the initial stage, followed by echocardiography and consideration of right heart catheterization in patients with abnormal findings [5].

Aim of the study

The aim of this study was to assess the role of certain pulmonary function parameters in the early prediction

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of PAH in scleroderma patients, which are as follows: forced vital capacity (FVC) % of the predicted value, DLCO-SB% of the predicted value, and FVC/DLCO%.

Patients and methods

This prospective study was conducted on 30 patients diagnosed with scleroderma, recruited from the Rheumatology Department of Ain Shams University Hospital. For all patients, the following were performed and documented: detailed medical history, thorough clinical examination, full laboratory investigations, chest radiographic posteroanterior view, computed tomography of the chest with high resolution and without contrast, transthoracic echocardiography, spirometric study, and DLCO. Exclusion criteria were as follows: patients with concurrent lung diseases, patients with occupational history predisposing to lung disorders, smokers, patients who cannot undergo spirometry and DLCO, patients complaining of moderate or severe dyspnea, patients with clinical or laboratory evidence of other collagen vascular diseases or evidence of parenchymal abnormality on high resolution computed tomography chest, and cardiac patients. All patients provided consent to participate and the study was approved by the institutional ethical committee.

Spirometry

FVC, forced expiratory volume in 1 s (FEV_1), FEV_1/FVC, and maximum midexpiratory flow (MMEF) were measured using the spirometry system (Masterscreen 2001, version 4.5; Erich Jaeger GmbH, Friedberg, Germany). Readings were recorded in triplicate, with the highest values recorded and expressed as a percentage of the predicted value according to the guidelines of the American Thoracic Society (ATS) [6].

Single-breath diffusion capacity of the lung for carbon monoxide

Carbon monoxide diffusing capacity single-breath method (DLCO-SB) was measured using the system (Masterscreen 2001, version 4.5; Erich Jaeger GmbH) according to the ATS guidelines [7]. The following activities were avoided before the test: vigorous exercise within 30 min of the test, consumption of a large meal within 2 h of testing, and inhalation of supplemental oxygen within 10 min before the test.

The procedure of DLCO-SB was performed as follows:

The equipment was calibrated with a 3-l syringe.

The tests were well explained to the patients.

The weight and height were recorded.

The patient was in a sitting position with the head slightly elevated.

The mouthpiece was placed, and the patient was instructed to close his lips around the mouthpiece.

Tidal breathing was carried out for a sufficient time to ensure that the patient was comfortable with the mouthpiece.

Deep inspirations had to be avoided during this period, as they could increase subsequent CO uptake.

The DLCO maneuver began with unforced exhalation to residual volume.

At residual volume, the patient's mouthpiece was connected to a source of test gas and the patient inhaled rapidly to total lung capacity.

The patient was asked to hold his/her breath by maintaining full inspiration using only the minimal effort necessary. The breath-hold time was for about 10 s, after which the patient exhaled maximally.

Standard criteria checked for DLCO testing are as follows:

Use of a proper quality-controlled equipment.

Inspired volume of 85% of largest vital capacity in 4 s.

A stable calculated breath-hold for 10 s, with no evidence of leaks, or Valsalva or Mueller maneuvers.

Expiration in 4 s with appropriate clearance of dead space (VD) and proper sampling/analysis of alveolar gas.

Statistical analysis

Data were collected, tabled, and statistically analyzed using SPSS, (Chicago, IL, USA) version 15.

(1) Parametric data were expressed as minimum, maximum, and mean ± SD.
(2) Nonparametric data were expressed as number and percentage.
(3) Comparison between parametric data of the two groups was made using the unpaired *t*-test.
(4) Comparison between nonparametric data of two groups was made using the χ^2-test.
(5) Pearson's correlation was used to study the correlation between two parameters: direct (+) correlations for two variables that move in the same direction and indirect (–) or inverse correlation for two variables that move in the opposite directions.

Receiver operating characteristic (ROC) curve represents a sensitivity/specificity pair corresponding to a particular decision threshold. The area under the ROC curve is a measure of how well a parameter can distinguish between two diagnostic groups (diseased/normal). ROC curve was determined using Medcalc software, version 15.2.2.

Two-tailed *P* value greater than 0.05 was considered nonsignificant, *P* value of 0.05 or less was considered significant, and *P* value of 0.01 or less was considered highly significant.

Results

The study included 30 patients with scleroderma, four were male (13.3%) and 26 were female (86.7%). The age of the studied patients ranged from 28 to 60 years with a mean age of 42.06 ± 8.88 years (Table 1). As regards the anthropometric measures, the mean weight of the studied cases was 73.33 ± 11.89, the mean height was 162.9 ± 6.01, and the mean BMI was 27.58 ± 3.89 (Table 2).

As regards the results of pulmonary function tests, the mean FVC% was 81.27 ± 13.47, the mean FEV_1% was 77.88 ± 13.06, the mean FEV_1/FVC% was 83.44 ± 8.46, the mean maximum midexpiratory flow was 66.86 ± 23.05, the mean DLCO% was 59.41 ± 19.82, the mean carbon monoxide transfer coefficient (KCO) was 76.77 ± 22.92, and the mean FVC%/DLCO% was 1.49 ± 0.47 (Table 3).

As regards the transthoracic echocardiographic findings of the studied patients, the mean pulmonary artery systolic pressure (PASP) was 27.56 ± 8.87, the mean right ventricular systolic pressure (RVSP) was 29.83 ± 9.42, and the mean ejection fraction % was 59.05 ± 5.5 (Table 4). According to the value of PASP (≥35 mmHg) as a cutoff for suspecting a potential or early-developing pulmonary vasculopathy (PH) [8], the prevalence of patients with suspected PH among the studied cases was 8/30 (26.7%).

Studying the difference between patients with suspected PH and those with no suspected PH showed no significant association between PH and the sociodemographic distribution of the patients ($P > 0.05$) (Table 5).

Studying the difference between patients with no suspected PH and those with suspected PH as regards anthropometric measures showed no significant association between PH and the anthropometric measures of the patients ($P > 0.05$) (Table 6).

A comparison of the results of patients with no suspected PH and those with suspected PH as regards pulmonary function tests showed significant differences with respect to FVC%, FEV_1%, DLCO%, and carbon monoxide transfer coefficient (KCO),

Table 1 Sociodemographic data of the studied cases

Sex [*N* (%)]	
Male	4 (13.3)
Female	26 (86.7)
Age	
Range	28–60
Mean ± SD	42.06 ± 8.88

Table 2 Anthropometric measures of the studied cases

Weight (kg)	
Range	55–108
Mean ± SD	73.33 ± 11.89
Height (cm)	
Range	155–175
Mean ± SD	162.9 ± 6.01
BMI	
Range	21–36.1
Mean ± SD	27.58 ± 3.89

Table 3 Pulmonary function test results

Pulmonary function test	Range (mean ± SD)
FVC%	45–103.9 (81.27 ± 13.47)
FEV_1%	41–99 (77.88 ± 13.06)
FEV_1/FVC%	64.3–99.53 (83.44 ± 8.46)
MEEF	23.2–120 (66.86 ± 23.05)
DLCO%	20–85.3 (59.41 ± 19.82)
KCO	19.9–112 (76.77 ± 22.92)
FVC%/DLCO%	1.1–2.63 (1.49 ± 0.47)

DLCO, diffusion capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

Table 4 Echocardiographic findings in the studied cases

Echocardiography finding	Range (mean ± SD)
PASP (mmHg)	16–45 (27.56 ± 8.87)
RVSP (mmHg)	18–48 (29.83 ± 9.42)
EF%	50.2–70.2 (59.05 ± 5.5)

EF, ejection fraction; PASP, pulmonary artery systolic pressure; RVSP, right ventricular systolic pressure.

Table 5 Differences between patients with no suspected pulmonary hypertension and patients with suspected pulmonary hypertension as regards sociodemographic data

Sociodemograhic data	Patients with no suspected PH (*n* = 22)	Patients with suspected PH (*n* = 8)	*P*
Sex			
Male	4	0	0.1
Age			
Range	28–60	35–50	0.6
Mean ± SD	42.5 ± 9.88	40.9 ± 5.6	

PH, pulmonary hypertension.

with values significantly lower among patients with suspected PH. However, FVC%/DLCO% was significantly higher among patients with suspected PH ($P < 0.05$). There were no significant differences between the two groups as regards FEV_1/FVC% and maximal expiratory flow (MEEF) ($P > 0.05$) (Table 7).

As regards the echocardiographic findings of the studied patients, there was a highly significant difference between patients with suspected PH and the others as regards the mean RVSP, which was higher among patients with suspected PH. However, the mean ejection fraction was lower among patients with suspected PH ($P < 0.01$) (Table 8).

Table 6 Differences between patients with no suspected pulmonary hypertension and patients with suspected pulmonary hypertension as regards anthropometric measures

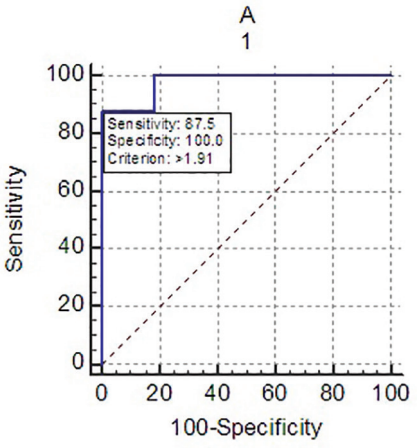
Anthropometric measures	Patients with no suspected PH (n = 22)	Patients with suspected PH (n = 8)	t	P
Weight (kg)				
Range	55–108	56–82	1.27	0.2
Mean ± SD	75 ± 12.5	68.8 ± 9.3		
Height (cm)				
Range	155–175	155–170	1.67	0.1
Mean ± SD	164 ± 5.9	159.9 ± 6		
BMI				
Range	21–63.1	23.3–32	0.55	0.5
Mean ± SD	27.8 ± 4.1	26.9 ± 3.2		

PH, pulmonary hypertension.

The best cutoff value of FVC%/DLCO% for detecting a suspicion for PH among the studied cases was a value greater than 1.91 and area under the curve of 0.977, with a P value of 0.0001, a sensitivity of 87.5%, and a specificity of 100% (Table 9 and Fig. 1).

Among the studied patients there were highly significant direct correlations between FVC/DLCO and each of PASP and RVSP (Table 10 and Figs 2 and 3).

Fig. 1



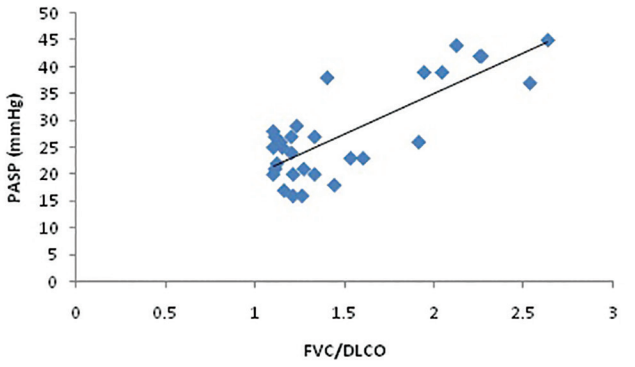
ROC curve of FVC%/DLCO% in detecting a risk for pulmonary hypertension. DLCO, diffusion capacity of the lung for carbon monoxide; FVC, forced vital capacity; ROC, receiver operating characteristic.

Table 7 Differences between patients with no suspected pulmonary hypertension and patients with suspected pulmonary hypertension as regards pulmonary function test results

Pulmonary function test	Patients with no suspected PH (n = 22)	Patients with suspected PH (n = 8)	t	P
FVC%				
Range	70.2–103.9	45–87.2	4.05	0.0004**
Mean ± SD	86.1 ± 9.1	67.9 ± 15		
FEV_1%				
Range	59.9–99	41–85.6	3.21	0.003**
Mean ± SD	81.9 ± 9.8	66.8 ± 15.1		
FEV_1/FVC%				
Range	64.3–99.53	78.2–91.3	0.4	0.6
Mean ± SD	83.05 ± 9.5	84.5 ± 5.1		
MEEF				
Range	34.2–120	23.2–96.6	1.45	0.15
Mean ± SD	70.5 ± 22.5	56.9 ± 22.8		
DLCO%				
Range	45.1–85.3	20–50.1	7.57	0.0001**
Mean ± SD	69 ± 11.6	32.9 ± 11.4		
KCO				
Range	70.5–112	19.9–87.4	6.14	0.0001**
Mean ± SD	87.1 ± 11	48.5 ± 23.7		
FVC%/DLCO%				
Range	1.1–1.91	1.4–2.63	7.3	0.0001**
Mean ± SD	1.3 ± 0.2	2.1 ± 0.4		

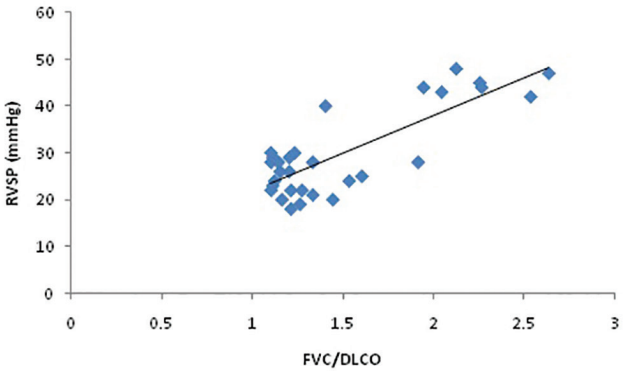
DLCO, diffusion capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PH, pulmonary hypertension; **$P \leq 0.01$, highly significant.

Fig. 2



Direct correlation between FVC%/DLCO% and PASP. DLCO, diffusion capacity of the lung for carbon monoxide; FVC, forced vital capacity; PASP, pulmonary artery systolic pressure.

Fig. 3



Direct correlation between FVC%/DLCO% and RVSP. DLCO, diffusion capacity of the lung for carbon monoxide; FVC, forced vital capacity; RVSP, right ventricular systolic pressure.

Table 8 Echocardiographic findings in the studied cases

Echocardiography finding	Patients with no suspected PH (n = 22)	Patients with suspected PH (n = 8)	t	P
RVSP (mmHg)				
Range	18–30	40–48	13.3	0.0001**
Mean ± SD	24.6 ± 3.8	44.1 ± 2.6		
EF (%)				
Range	51.6–70.2	50.2–59.6	3.93	0.0005**
Mean ± SD	61 ± 4.7	53.7 ± 3.8		

EF, ejection fraction; PH, pulmonary hypertension; RVSP, right ventricular systolic pressure; $^{**}P \leq 0.01$, highly significant.

Table 9 Reliability for prediction of a suspected pulmonary hypertension using forced vital capacity/diffusion capacity of the lung for carbon monoxide

Best cutoff point for FVC/DLCO	
Area under the curve	0.977
SE	0.025
Significance (P)	<0.0001**
Confidence interval (95%)	
Lower bound	0.845
Upper bound	1

DLCO, diffusion capacity of the lung for carbon monoxide; FVC, forced vital capacity; $^{**}P \leq 0.01$, highly significant.

Table 10 Correlations of forced vital capacity/diffusion capacity of the lung for carbon monoxide among all cases

Echocardiography finding	r	P
PASP (mmHg)	0.799	0.0001**
RVSP (mmHg)	0.812	0.0001**

PASP, pulmonary artery systolic pressure; RVSP, right ventricular systolic pressure; $^{**}P \leq 0.01$, highly significant.

Discussion

PAH is a serious complication of scleroderma and the most frequent cause of death in this disease [9]. The recent advances in PH therapies have led to a remarkable improvement in patient survival, but survival benefits are greatest for those diagnosed at earlier stages [10]. Several studies have indicated that early treatment of PAH can improve hemodynamics, exercise capacity, and survival [11,12].

The assessment of PASP with transthoracic echocardiography is currently regarded as the most useful noninvasive method of screening of PAH [13]. The results of our study showed that eight out of 30 studied patients had a PASP of 35 mmHg or greater, and it has been demonstrated that patients presenting these values should be suspected as developing early PH [8].

On comparing the results of patients with no suspected PH and those with suspected PH as regards pulmonary function tests, we found significant differences in terms of FVC%, FEV_1%, and DLCO%, with values significantly lower among patients with suspected PH, and FVC%/DLCO% was significantly higher among patients with suspected PH ($P < 0.05$). These results are in accordance with the results of Thakkar *et al.* [13], who demonstrated that patients who had DLCO less than 70.3% and higher FVC/DLCO ratio were regarded as having a 'positive' screen for PAH. The best cutoff value of FVC%/DLCO% in our study for detecting a suspected PH was a value greater than 1.91, with a sensitivity of 87.5% and a specificity of 100%, whereas Thakkar and colleagues reported FVC%/DLCO% of 1.82 or greater, with a sensitivity of 50.0% and a specificity of 100%.

The retrospective study by Steen and Medsger [14] found that a decreasing DLCO is an excellent predictor of the subsequent development of isolated PH in limited scleroderma. They demonstrated that DLCO may decrease for many years before the diagnosis of PH. Our results also showed a significant difference in DLCO values between patients with suspected PH and the others.

In contrast, other authors [15] did not report DLCO to be a useful method for identifying patients with early pulmonary vasculopathy associated with systemic sclerosis. Our results demonstrated the reliability of DLCO and DLCO/FVC in suspecting PH, correlating these results with echocardiographic findings.

Among the studied patients there were highly significant direct correlations between FVC/DLCO and each of PASP and RVSP. This is in disagreement with the results of Nathan *et al.* [16], who found no significant correlation between FVC%, DLCO%, and the ratio of the two with mean pulmonary artery pressure, but this study differs from ours in being a retrospective study that examined the ability of pulmonary function tests to predict PH in idiopathic pulmonary fibrosis patients.

Right heart catheterization remains the gold standard for determining the presence of PH, although the latest (5th) World Symposium guidelines have abandoned the need for vasoreactivity testing, as 'responders' are exceedingly rare in patients with scleroderma associated PAH [17]. From the results of our study, we conclude that pulmonary function tests and FVC/DLCO ratio can be very useful for screening and early suspicion of PH in patients with scleroderma; it is an easy, cost-effective, and noninvasive approach, and suspected patients are recommended to undergo further appropriate diagnostic testing for confirmation of PH.

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Conflicts of interest
There are no conflicts of interest.

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