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Six Minute Walk Test (6MWT) in The Assessment of Severity of Interstitial Lung Disease Secondary to Systemic Sclerosis

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Abstract

***Background:** Interstitial lung disease (ILD) and pulmonary artery hypertension account for 60% of systemic sclerosis (SSc) related deaths. Impaired gas exchange that worsens with exercise is central to the pathophysiology of SSc-related ILD (SSc-ILD). Six minute walk test (6MWT) is a simple and cost-effective tool to assess lung function and has been proven to be reproducible. It has the potential to be employed as a tool to assess and monitor severity of pulmonary involvement in SSc.*

***Aims and objectives:** This study evaluates the correlation between 6MWT results with the other parameters of disease severity like forced vital capacity (FVC), diffusion capacity of lung for carbon monoxide (DLCO) from pulmonary function tests, right ventricular systolic pressure (RVSP) by echocardiography, HRCT findings like pulmonary artery dilatation and honeycombing and clinical findings like modified Rodnan skin score (mRSS) in patients of SSc-ILD.*

***Materials and methods:** 30 patients with SSc-ILD were subjected to two 6MWTs. Six minute walk distance (6MWD) < 400 m and fall in saturation during 6MWT ($\triangle$Sat) $\geq$ 4% were considered abnormal. 6MWD of the two tests were compared. If the variability was more than 15%, a third test was planned. The two tests with 6MWD within 15% variability were considered for our studies. Then, 6MWD and $\triangle$Sat were compared with FVC, DLCO, RVSP, HRCT and clinical findings like mRSS.*

***Results:** There was no statistically significant correlation between 6MWD and $\triangle$Sat (p = 0.51). On univariate analysis, there was no statistically significant correlation of 6MWD < 400 m with mRSS(p = 0.07), %FVC (p = 0.59), %DLCO (p = 0.68), RVSP (p = 0.35) and pulmonary artery dilatation on HRCT (p = 0.713). There was statistically significant positive correlation between 6MWD < 400 m and pre-test Borg index (p = 0.04) and post-test Borg score (p = 0.02). On multi-variate logistic analysis, no parameters had statistically significant correlation with 6MWD < 400 m. However, on univariate analysis, there was statistically significant negative correlation of $\triangle$Sat $\geq$ 4% on 6MWT with % FVC (p = 0.04) and % FEV1 (p = 0.027) and statistically significant positive correlation pre-test Borg score (p = 0.02), post-test Borg dyspnoea score (p < 0.0001), honey combing on HRCT (p = 0.044) and pulmonary artery dilatation on HRCT (p = .01). There was no statistically significant correlation between $\triangle$Sat $\geq$ 4% and % DLCO (p = 0.24), RVSP (p = 0.74) or mRSS (p = 0.79). On multivariate logistic analysis, only pulmonary artery dilatation on HRCT had statistically significant positive correlation with $\triangle$Sat $\geq$ 4% (p = 0.04).*

***Conclusions:** 6MWT is a highly reproducible test. Desaturation during 6MWT is more reflective of pulmonary involvement and is an adjunct to pulmonary function tests in evaluation of patients with SSc-ILD. 6MWD is subjective and depends on patient motivation.*

Introduction

Systemic sclerosis is a multisystem disorder with varying manifestations. There is a strong female preponderance in SSc with female: male ratio of 3:1[1]. Pulmonary involvement remains the most common cause of morbidity and mortality in cases of SSc. SSc-ILD and pulmonary artery hypertension (PAH) account for 60% of deaths related to SSc[2].

Early diagnosis and regular follow-up is the keystone to prevent the morbidity and mortality associated with these diseases. Central to the pathophysiology of SSc-ILD is the impaired gas exchange that worsens with exercise[3]. Interstitial lung disease can be assessed with high resolution computed tomography (HRCT) and pulmonary function test including diffusion study. HRCT chest is the reference tool to detect pulmonary abnormalities in SSc[4]. Additionally, it provides an accurate assessment of the extent of lung involvement. Evaluation of PAH, which is also a marker of disease severity in SSc-ILD, requires right heart catheterisation or an echocardiography. However, these modalities require expertise and specialised equipment. This demands for a simple, cost-effective and reproducible test that may help to study the disease severity.

Six minute walk test (6MWT) is a simple tool that does not need sophisticated equipment or training and has been validated in various respiratory diseases. It has been suggested that 6MWT can be used to assess the central

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pathophysiological mechanism in SSc which is the impairment of gas exchange that worsens with exercise[3]. Desaturation at the end of 6MWT is as informative as the decrease in walk distance for pulmonary involvement in SSc[5]. However, 6MWT has not been validated in SSc in Indian patients. In this study, we evaluated the utility of 6MWT as a measure of disease status in SSc-ILD.

Material and Methods

A cross-sectional observational study was done in a teaching hospital in New Delhi. The study included patients above 18 years of age with SSc-ILD. All patients were first subjected to detailed history, examination and laboratory investigations. SSc was diagnosed based on ACR/EULAR criteria and ILD on HRCT. HRCT chest is the reference tool to detect the pulmonary abnormalities in SSc[4]. Additionally, it provides an accurate assessment of the extent of the lung involvement. Pulmonary artery hypertension (PAH) was diagnosed on echocardiography. Right ventricular systolic pressure (RVSP) of 40 mm Hg or more was used as the diagnostic criterion for PAH. Pulmonary artery dilatation on HRCT was defined by the ratio of diameter of main pulmonary artery to ascending aorta greater than one. This radiological sign of PAH was also compared with 6MWT results.

Then, they were subjected to pulmonary function test (PFT) with diffusion capacity of lungs for carbon monoxide (DLCO) and echocardiography. Those patients with forced vital capacity (FVC) < 40%, DLCO < 40% and RVSP > 50 mm Hg, SpO2 < 84% were excluded from our study as they had severely compromised cardiopulmonary functions. These subjects may develop life-threatening complications during 6MWT. Patients with history of pulmonary tuberculosis (fibrotic changes in lungs secondary to tubercular sequelae may affect the 6MWT results), severe musculoskeletal problems (unable to perform 6MWT), non-steady or inadequate SpO_2 (due to Raynaud's phenomenon in SSc) were excluded from our study as they may give spurious 6MWT results despite a normal pulmonary function. Patients with contraindications to 6MWT were also excluded. Thus, a total of 30 SSc-ILD patients were included in our study.

The patients were then classified into diffuse and limited SSc variants. Clinical features, antibody profile, HRCT, echocardiographic, and PFT findings were studied.

Six minute walk test (6MWT)

A seldom travelled 100 feet long straight hallway with hard surface was chosen. Patients were asked to wear comfortable clothes and shoes. They were allowed to use their walking aids and usual medications. Repeat test was done about the same time of the day and in the same location. The patients were asked to sit at rest in a chair at the starting point for at least 10 minutes before the test starts. Baseline heart rate, blood pressure were measured. Pulse oximetry was done. Baseline dyspnoea index and fatigue were rated using the Borg scale.

Patients were asked to walk as far as possible for 6 minutes. They could walk back and forth the hallway and that they are permitted to slow down, stop and to rest as necessary and can resume walking as soon as they are able to do so. Distance covered in 6 minutes, post-walk heart rate, oxygen saturation and blood pressure, post-test Borg dyspnoea index and fatigue were noted. 6MWT was terminated before 6 minutes if the patient got exhausted, develop chest pain or intractable leg cramps.

Two 6MWTs were performed between a minimum of 2 hours and a maximum of 4 weeks interval. To ensure the consistency of the tests, 6MWD of the two 6MWTs was required to be within 15% of each other. In the event of >15% variability, a third test was done, to be within 15% variability of the first or the second 6MWT or the patient was excluded. The results of the 6MWT with the best 6MWD were considered for all analyses.

Statistical analysis

For the purpose of analysis, desaturation was defined as $\triangle$Sat $\geq$ 4% from baseline and 6MWD was considered abnormal when it was < 400 m. These cut-off values for 6MWT were considered as predictors of severe pulmonary involvement. These were set based on prior studies as the one by Villaba *et al*[5]. We then divided patients into two categories: a) 6MWD $\geq$ 400 m and 6MWD < 400 m and b) $\triangle$Sat $\geq$ 4% and $\triangle$Sat < 4%.

Bland Altman plot was used to find the difference in measurement of 6MWD and $\triangle$Sat at two different time intervals. Multivariate logistic regression was used to find the independent risk factors predicting the change in 6MWD and $\triangle$Sat.

The relationship between various 6MWT parameters like 6MWD, $\triangle$Sat, pre-test and post-test Borg dyspnoea index were analysed. The relation of 6MWT parameters with PFT parameters like DLCO, FVC, the echocardiographic parameter RVSP, HRCT findings and clinical findings like mRSS were analysed.

Results

Majority of our patients, 29 out of 30 (96.67%) were females (This may be attributed to the strong female preponderance of SSc[1]). The mean age of our study population was 38.03 ± 11.28 years. Majority of them

(56.67%) were below 40 years of age. The median disease duration was 5.5 years (6 months to 30 years). The majority of our patients (76.67%) had localised systemic sclerosis (LSSc). Out of these LSSc, two had LSSc-Rheumatoid arthritis overlap. Three of the patients had combined SSc-ILD-PAH (10%). mRSS was higher in the 6MWD < 400 m and △Sat ≥ 4% group.

Anti-nuclear antibody (ANA) was positive in 20 out of 30 patients (66.67%). Anti Scl-70 antibodies were positive in 13 patients (43.33%). Anti-centromere antibodies (ACA) were positive in 5 patients (16.67%). Antibodies like PM-Scl (10%), anti SSA/Ro (30%), anti SSB/La (30%), anti U1RNP (13.33%), anti Ku (3.33%) were also seen in our study population. Out of the 13 patients positive for anti-Scl-70 antibody, six had PSS and the rest had LSSc.

All our patients had ILD diagnosed on HRCT. The common findings in HRCT were ground glass opacities (86.67%), interlobar septal thickening (76.67%) and honeycombing (13.33%). ILD pattern on HRCT was non- specific interstitial pneumonia (NSIP) in 86.67% (26) and usual interstitial pneumonia (UIP) in the rest. Of the patients with UIP, two had progressive systemic sclerosis (PSS) and the other two had RA-LSSc overlap. Pulmonary artery dilatation, another useful sign of PAH was present in 13 (43%) of our study population.

3 out of 30 (10%) had echocardiographic evidence of pulmonary artery hypertension. Of the 13 who had CT evidence of PAH, only two had PAH by echocardiography.

DLCO < 50% was present in 33.33% (10) of our population; all of them except three had pulmonary artery dilatation on HRCT. This however did not have a statistical significance. PAH by echocardiography did not correlate with DLCO. Reduced DLCO without any other abnormalities was the only abnormality detected in 3 (10%) of our patients; the spirometry, RVSP and 6MWT were normal in them.

6MWT is a highly reproducible test. Bland Altman plot was used to find out the difference in measurement of 6MWD and △Sat of the two 6MWTs. We had done a third 6MWT in three of our patients. This was due to lack of steady SpO_2 reading secondary to Raynaud's phenomenon (during winter months) in all of them when the second 6MWT was done. However, the third 6MWT done later in the absence of Raynaud's phenomenon was within 15% variability of the first. The two 6MWTs within 15% variability were named 6MWT1 and 6MWT2 for study purpose. Only 6MWD1 and 6MWD2 (Fig. 1), also △Sat1 and △Sat2 (Fig. 2) did not exceed the maximum allowed difference between the two test results (i.e., within mean ± 1.96 SD) and hence the two 6MWT results were in agreement and could be used interchangeably.

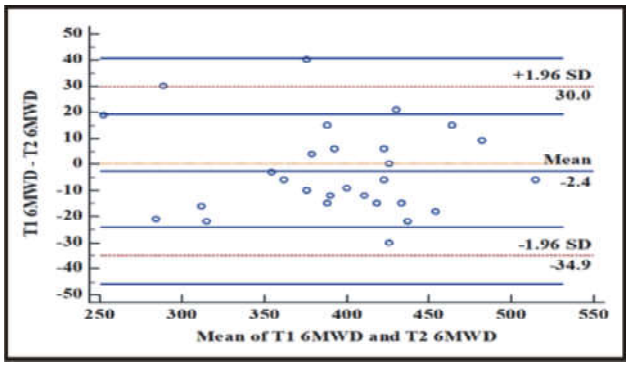

Fig. 1: *Bland Altman plot for 6MWD1 and 6MWD2.*

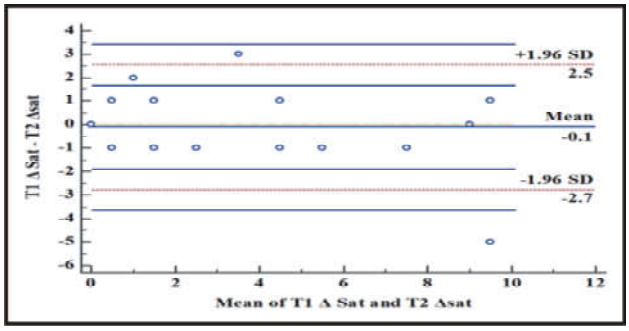

Fig. 2: *Bland Altman plot for △Sat 1 and △Sat 2.*

The mean 6MWD in our study was 400.97 ± 57.77 m. 50% had 6MWD < 400 m. The mean 6MWD in the group with △Sat ≥ 4% was 387.75 ± 45.99 m (304 to 441 m) and that in △Sat < 4% group was 407.59 ± 58.87 m (262 to 518 m).

8 out of 30 (26.67%) patients had desaturation during the 6MWT. The mean △Sat in our study population is 2.07 ± 3.03%. The mean △Sat in the group with 6MWD < 400 m was 2.4 ± 3.01% and that in 6MWD ≥ 400 m group was 1.73 ± 2.91%.

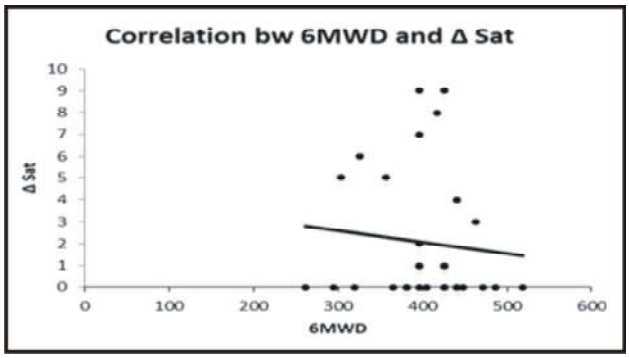

Fig. 3: *Correlation between 6MWD and △Sat.*

Fig. 3 shows the correlation between 6MWD and △Sat. There was no statistically significant correlation between the two variables (p = 0.5058).

Age and disease duration were lower, mRSS and weight were higher in the 6MWD < 400 m group. % FVC, % DLCO and % RVSP were lower in this group. On univariate analysis (Table I), there was no statistically significant correlation between 6MWD < 400 m and % FVC, % DLCO, RVSP or other parameters discussed above. There was statistically significant correlation between 6MWD < 400 m and pre-test Borg index and post-test Borg score. On multi-variate logistic analysis, none of the above parameters had a statistically significant correlation with 6MWD < 400 m.

Table I: Variables associated with 6MWD.

Variable	Mean value in 6MWD < 400 m	Mean value in 6MWD ≥ 400 m	P value in univariate analysis	Odds Ratio
Weight (Kg)	50.4 ± 7.47	49.4 ± 7.9	0.713	1.018
mRSS	23.27± 7.43	18.67 ± 5.27	0.077	1.129
FVC (%)	59.88 ± 11.61	62.99 ±20.15	0.595	0.988
FEV1 (%)	62.15 ± 12.77	65.12 ± 20.22	0.621	0.989
DLCO (%)	64.08 ± 19.32	67.49 ± 26.09	0.676	0.993
RVSP (mm Hg)	27.73 ± 8.46	30.47 ± 7.55	0.347	0.956
Pre-Borg dyspnoea index (n)	2.33±1.19	1.27±1.18	0.036	2.079
Post-Borg dyspnoea index (n)	5.47± 1.45	3.33±2.12	0.016	1.879
Honeycombing on HRCT (n)	2	2	1.00	1.00
Pulmonary artery. dilatation on HRCT (n)	6	7	0.713	0.762

Age, weight, disease duration, mRSS were higher in the group with △Sat ≥ 4%. %FVC, %DLCO and 6MWD were lower and RVSP was higher for the group with △Sat ≥ 4%. On univariate analysis (Table II), △Sat ≥ 4% had statistically significant correlation with %FVC, pre-test Borg score and post-test Borg dyspnoea score. Honey combing on HRCT and pulmonary artery dilatation on HRCT also had significant correlation with △Sat ≥ 4%. There was no statistically significant correlation between △Sat ≥ 4% and % DLCO or RVSP. On multivariate logistic analysis, only pulmonary artery dilatation on HRCT had statistically significant correlation with △Sat ≥ 4% (p = 0.04).

Of the three cases of PAH diagnosed on echocardiography, one had △Sat ≥ 4% with 6MWD ≥ 400 m. One had both △Sat and 6MWD normal as per our set criteria. Third patient had 6MWD < 400 m with △Sat < 4%. RVSP had no statistically significant correlation between either of the 6MWT parameters.

In our study, almost all cases with pulmonary artery dilatation in HRCT had reduced % DLCO. So, we analysed its correlation with RVSP and % DLCO. There was no statistically significant correlation between pulmonary artery dilatation and the above two parameters.

Table II: Variables and △Sat.

Variable	Mean value in △Sat ≥ 4%	Mean value in △Sat < 4%	P value in univariate analysis	Odds ratio
Weight	54.25 ± 6.98	48.32 ± 7.29	0.069	1.112
mRSS	21.5 ± 7.1	20.77 ± 6.77	0.79	1.016
%FVC	50.72 ± 10.69	65.33 ± 16.32	**0.044**	0.923
%FEV1	51.69 ± 12.53	67.98 ± 16.06	**0.027**	0.914
%DLCO	57.68 ± 19.02	68.73 ± 23.49	0.243	0.975
RVSP (mm Hg)	29.88 ± 8.31	28.82 ± 8.07	0.745	1.017
Pre-Borg dyspnoea scale(n)	3 ± 0.87	1.36 ± 1.15	**0.016**	4.00
Post-Borg dyspnoea scale(n)	6.75 ± 0.83	3.54 ± 1.75	**<0.0001**	51.32
Honeycombing on HRCT(n)	3	1	**0.044**	12.6
Pulmonary artery dilatation on HRCT(n)	7	1	**0.012**	18.67

Discussion

Lung involvement is a leading cause of morbidity and mortality in SSc patients. The prevalence of ILD in SSc is difficult to predict as patients are asymptomatic earlier in the disease. Early screening for pulmonary involvement and follow-up in initial years prevents morbidity. 6MWT is a submaximal exercise test that can be used to monitor disease progression in SSc-ILD. This cost-effective test can be handy especially in a low resource country.

The study characteristics of our study population and HRCT findings were similar to studies conducted earlier by Villaba *et al*[5]. Majority of our population were females (29 out of 30). This is attributed to the female preponderance of SSc (female: male ratio of 3:1)[1]. Most of them were below 40 years of age and had disease duration of 5.5 years. Organ involvement in SSc occurs within the first 4 years of the disease.

Extent of disease by HRCT is a marker of disease severity, so is honeycombing pattern. Honeycombing was present in 4 of our patients. UIP pattern in our PSS cases may be due to the more extensive disease that takes on a characteristic reticulo-nodular appearance and associated with fine honeycomb airspaces and ultimately large airspaces[6].

PAH as defined by echocardiography was present in three

of our patients but when defined by HRCT, it was present in thirteen. The dilatation of pulmonary artery trunk is one among the CT findings in PAH. This is also a marker of severity of lung disease. Distal main pulmonary artery dilatation exceeding that of aorta has a positive predictive value of › 95% and a specificity of more than 90% for the diagnosis of PAH[7,8].

DLCO was reduced in almost all patients with other PFT abnormalities in our study. This is in agreement with the study by Bourous *et al*[9]. Of the four patients with FVC > 80%, three had DLCO < 80%. Thus, reduced DLCO was the only abnormality in 10% of our study population. This is similar to the study by Steen *et al*[10] wherein isolated reduction in DLCO was present in 19% of their study population. Thus, low DLCO without reduced FVC is the earliest and most sensitive pulmonary functional abnormality in systemic sclerosis.

The two 6MWTs were highly reproducible both in terms of 6MWD and desaturation when compared using the Bland Altman plot. This is in agreement to studies by Gregory Pugnet *et al*[11] and Buch *et al*[12]. Thus, 6MWT is a highly reproducible test.

Clinical findings like extent of skin involvement as calculated by modified Rodnan Skin Score, HRCT findings like honeycombing and pulmonary artery dilatation, PFT parameters like % FVC, % FEV1 and % DLCO, echocardiographic parameter RVSP, etc., are also measures of disease severity in SSc-ILD. 6MWT being a simple easily reproducible tool to assess the cardiopulmonary function, we assessed the correlation between the two 6MWT results with the various other parameters of disease severity.

% FVC and % FEV1 had statistically significant correlation with △Sat. There were trends that % DLCO was lower and RVSP was higher in the △Sat ≥ 4% group. But, there was no statistical significance. This may be due to the small sample size. Thus, △Sat is not completely reflective of DLCO and hence 6MWT may not be able to identify SSc-ILD in the initial stages. More studies with large sample size may be needed to establish this relation.

Of the other parameters analysed, honeycombing and pulmonary artery dilatation on HRCT and Borg dyspnoea index (both pre- and post-test) too had statistically significant correlation with △Sat.

Reduced DLCO may be the initial manifestation of pulmonary involvement in SSc-ILD. But, none of the 6MWT parameters has a correlation with % DLCO. In our study, PAH by echocardiography neither correlated with % DLCO nor with △Sat. Almost all cases of pulmonary artery dilatation had reduced DLCO and vice-versa. However, there was no statistically significant correlation between %DLCO and pulmonary artery dilatation. This may be due to the small sample size and hence, more studies need to be conducted to fully validate this.

Pulmonary artery dilatation was the only parameter which had a statistically significant relation with △Sat on multivariate analysis. Thus, pulmonary artery dilatation on HRCT is more predictive of % DLCO and △Sat than echocardiographic evidence of PAH. None of the previous studies had looked into this finding. Since we did not perform right heart catheterisation (RHC) to diagnose PAH in these cases, more studies need to be done to prove the superiority of CT over echocardiography to diagnose PAH.

The mean desaturation was higher in the 6MWD < 400 m group and the mean 6MWD was lower for △Sat ≥ 4% group. But, there was no statistically significant correlation between 6MWD and △Sat, unlike the study by Villaba *et al*[5].

There were trends that higher disease activity as indicated by mRSS and lower PFT values were associated with 6MWD <400. But, none of the PFT parameters or RVSP on echocardiography had a statistical significance when compared with 6MWD <400 m.

It was also noted that the highest and the lowest 6MWD is recorded in the group with △Sat ≥ 4%. Systemic sclerosis being a multisystem disease, the various non-pulmonary aspects like musculoskeletal pain can affect 6MWD. Thus, 6MWD is more subjective than △Sat and depends on patient motivation.

Of the two 6MWT parameters, △Sat is more correlating to PFT parameters than 6MWD. Musculoskeletal involvement does not affect the △Sat. Thus, △Sat is more predictive of pulmonary involvement than 6MWD. The drawbacks of our study were the small sample size. We did not confirm PAH by RHC.

Conclusion

6MWT is a highly reproducible test and can be used in the follow-up of patients with SSc-ILD. Of the two 6MWT parameters, 6MWD is more subjective. △Sat is more predictive of lung involvement and can be used to assess the progression of disease and aids in further evaluation and treatment modification. Being simple and cost effective, 6MWT can be used to detect trends in disease progression. However, more studies have to be done to fully validate its usefulness in SSC-ILD.

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