The Correlation Between the Six Minute Walk Test and Spirometric Parameters in Patients with Systemic Lupus Erythematosus

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A R T I C L E   I N F O

A B S T R A C T

Introduction: Systemic Lupus Erythematosus (SLE) is an autoimmune disease affect nearly every organ system. Pulmonary involvement, which is a common manifestation of SLE, can remain undiagnosed if asymptomatic. This study aimed to evaluate the efficiency of spirometric findings in early detection of silent pulmonary involvement and examine its correlation with the six minute walk test in SLE patients.

Materials and Methods: In this cross-sectional study fifty patients, who met the American College of Rheumatology criteria for SLE, were recruited from the outpatient rheumatology clinic at the Imam Reza Hospital of Mashhad between July 2013 and September 2014. First, a checklist including demographic information and previous medical documents was completed. Then, spirometry and 6MWT was performed to evaluate subclinical pulmonary involvement and assess patients' exercise capacity.

Results: Based on the results of pulmonary function tests, patients were divided into two groups. A total of 40 patients with normal pattern were placed in one group and 10 patients with restrictive pattern in the other. The difference between SLE patients with and without abnormal spirometry were statistically significant in regard to anti-RNP positivity but total distance walked in six minute, was not significantly different between two groups (p=0.356). Additionally, there were no significant correlations between 6MWD and FVC in SLE patients in the either group as determined by Pearson's correlation coefficient testing. (R=0.439,P=0.205 in SLE patients with normal spirometry and R=0.191,P=0.237 in those with abnormal pattern)

Conclusion: Considering the impact of anti-U1RNP positivity with restrictive pattern on spirometry, it can be deemed as a pulmonary involvement predictor in SLE patients. However, lack of correlation between 6MWT and spirometric parameters is suggestive of restrictive lung involvement, which in turn, demonstrates a multifactorial basis for limited exercise capacity in patients with SLE. Thus, the application of the 6MWT as a measure of pulmonary function is called into question.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease which may affect many organ systems (1). Pulmonary involvement is frequently observed in SLE (1). Common

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pulmonary manifestations in these patients include pleuritis with or without pleural effusion, alveolitis, interstitial lung disease, lupus pneumonitis, pulmonary hemorrhage, pulmonary arterial hypertension, and thromboembolic disease (2, 3).

In most cases, pulmonary involvement in SLE is mild and asymptomatic, therefore, it goes undiagnosed by physicians at times (4).

Pulmonary function tests (PFTs) are the most available measurement tools applied for assessing lung involvement in SLE (4). The results of lung function tests in SLE patients without clinical symptoms can demonstrate various patterns (4–6).

Generally, the main focus of the most previous studies has been evaluation of symptomatic patients using forced vital capacity (FVC) with simple spirometry. However, the available evidence concerning the relationships among lung function test, performance status and functional exercise capacity in the lupus patients are contradictory (7–9).

The six minute walk test (6MWT) is actually an easy and cost-effective test of submaximal exercise capacity, already validated for assessing several cardiopulmonary disorders, and is a good index of functional capacity in patients with cardiac disease (10).

The aim of this study was to determine the role of spirometry in early detection of unnoticed pulmonary involvement in asymptomatic SLE patients and to establish its correlation with the 6MWT in these patients.

Materials and Methods

This study was carried out on 50 patients with SLE, who were recruited from the outpatient rheumatology clinic at the Imam Reza Hospital of Mashhad between July 2013 and September 2014, using the criteria defined below.

Inclusion criteria: all the patients meeting the 1982 revised criteria of the American College of Rheumatology (ACR) for diagnosis of systemic lupus erythematous (11), without evidence of other connective tissue diseases.

Patients were excluded if they had the following conditions:
- Left heart disease,
- Pregnancy,
- History of unstable angina or a heart attack during the previous months,
- Resting tachycardia (heart rate ≥120 beats/min),
- Uncontrolled hypertension ≥ 180/100,
- History of cardiac arrhythmia,
- Arthritis and other musculoskeletal diseases.

The study protocol was approved by the local institutional ethics committee of Mashhad University of Medical Sciences. Additionally, informed written consents were obtained from all the participants before entering the study.

The following steps were taken for all the patients:

1. Completion of a checklist including the patients' demographic information, medication history and previous medical documents.

2. Pulmonary function tests (spirometric tests) to evaluate subclinical pulmonary involvement.

3. The 6MWT to assess exercise capacity.

Checklist

A questionnaire surveying the patients' demographic information and past medical history, regarding autoantibodies: rheumatoid factor (RF), anti-U1RNP and anti-phospholipid antibodies (APL), at any time during the course of disease and treatment, was employed.

Pulmonary function tests

According to the standards of American Thoracic Society (ATS) spirometry was performed by a technician at the time of examination (12).

To ensure reproducibility of the test, spirograms were repeated until three acceptable FVC maneuvers were performed (13). Subsequently, FVC and forced expiratory volume in 1 second (FEV1) were measured.

These values were matched for age, gender and height of participants and the results were presented as percent of predicted values.

According to the standards of ATS, pulmonary function parameters below 80% of predicted value were considered abnormal (12). Additionally, values below 70% of FEV1/FVC ratio and below 80% of predicted FEV1 were defined as obstructive pattern and FVC values less than 80% of predicted value with normal or above normal FEV1/FVC ratio were considered as restrictive pattern (14, 15). Measurements were obtained without bronchodilator administration and the subjects were tested in the sitting position.

The Six Minute Walk Test (6MWT)

The 6MWTs were performed on all patients, according to the standard protocol of the ATS, to estimate patients' exercise capacity (16). This test is easy to administer with good reproducibility. Moreover, it is well-tolerated by the patients with respiratory symptoms, also, it adequately reflects the patients' daily living activities better than other exercise tests.

The 6MWT was performed indoor in a corridor, with a 30m walking course. In case the patients needed rest, some chairs were placed

alongside the area.

The patients were advised to use appropriate clothing and footwear, and walking aids if they needed any. The instructions were made clear to the patients, e.g., the objective of the test is to walk as far as possible for six minutes and that they are allowed to slow down or stop and rest, and resume whenever they are ready.

Patients on bronchodilator therapy were advised to use their medication as they were prescribed. The Borg scale for scoring dyspnea and fatigue was explained to the patients and the baseline scores were recorded. A demonstration lap was performed by a nurse and queries from the patients were responded to.

The pulse oximeter and heart rate monitor were attached to the participants and the countdown timer was set to six minutes and started with the patients commencing the test. The patients were informed the remaining time minute by minute, and 15 seconds before the end of the test.

The completed laps and additional distance were measured at the final partial lap (if there were any), subsequently, they were calculated and entered into a worksheet. The modified Borg dyspnea and fatigue scores were recorded post-exercise after we made sure that the patient was feeling comfortable at end of the test (17).

The modified Borg scale is a descriptive 10 point-scale and the adjectives used in this scale assist patients to determine intensity of dyspnea and fatigue.

The recorded data included:
- Total distance walked (meters) in six minutes,
- Pre and post-exercise Borg dyspnea and fatigue scores,
- Oxygen saturation (%).

Statistical analysis

Data were analyzed using SPSS, version 20.

Descriptive statistics: quantitative variables were represented by mean±SD and qualitative variables, were represented by numbers and percentages.

Group comparison: comparisons between the groups were made using Mann-Whitney (for comparing the means of quantitative variables) and Wilcoxon Signed Ranks (for comparing means in correlated groups) tests. Chi-squared (x2) and two-tailed Fisher's exact tests were used to compare frequencies (numbers and percentages) for qualitative variables.

Correlations: The correlation between 6MWD and FVC, was evaluated using Pearson's coefficient. *P*-value<0.05 was considered significant.

Results

This study was carried out on 50 patients, previously diagnosed with SLE according to the revised ACR classification criteria.

These SLE patients were divided into two groups based on spirometric results:
- Group I: included 10 SLE patients with abnormal spirometry.
- Group II: included 40 SLE patients with normal spirometry.

Demographic data, clinical/paraclinical features, 6MWT in SLE patients and comparisons between the two groups (the patients with pulmonary involvement and those without it, based on spirometry) are summarized in Table 1.

The study group comprised of 50 patients, 48 females and 2 males, with a mean age of 29.1±5.5 years that ranged from 21 to 48 years and mean disease duration was four years (range 1-17) years. Comparison of lupus patients with normal spirometry and those with abnormal spirometry, showed no significant differences regarding age distribution and body mass index (BMI) between the two groups (p=0.676). However, male gender was significantly associated with pulmonary involvement in spirometry (p=0.037). Patients with abnormal PFT had relatively longer disease duration in comparison to the patients with normal PFT but this difference was not statistically significant. (p=0.369). None of the patients participating in our study were smokers.

Past medical history of these patients revealed that none of them had chronic respiratory symptoms, but 12 patients (24%) had previously undergone immunosuppressive therapy for sever organ involvement. Also, 50% of SLE patients had abnormal PFT, while 17.5% of them had normal PFT. Thus, the frequency of immunosuppressive therapy was significantly higher in patients whose spirometry was consistent with restrictive pattern. Furthermore, immunosuppressive therapy was also associated with occurrence of restrictive pattern in SLE (OR=4.71, p=0.04) (Table 2).

Anti-U1RNP in 17 patients (34%), rheumatoid factor in 7 patients (14%) and antiphospholipid antibodies in 11 patients (22%) were positive. SLE patients with abnormal spirometry showed significantly higher numbers of positive anti-U1RNP cases in comparison to SLE patients with normal spirometry (p=0.001), while this was not true with other autoantibodies such as RF and APL. Anti-U1RNP, was also associated with increased odds ratio (OR =13.77), therefore, it can be considered as a significant predictor of restrictive pattern in SLE patients (p =0.001) (Table 2).

Table 1. Comparison of clinical and paraclinical parameters in SLE patients with normal and abnormal spirometry

parameter	Total SLE patients† N=50	SLE patients with abnormal spirometry† N=10	SLE patients with normal spirometry† N=40	P-value*
Age	29.10±5.53	29.30±4.49	29.05±5.80	0.676
Gender (F:M)	48:2 (96:4)	8:2	40:0	0.037
BMI	23.46±3.2	23.6±3.4	23.4±3.1	0.676
Disease duration	4.14±2.80	5.5±4.6	3.8±2.0	0.369
Smoking Hx	0	0	0	---
Immunosuppressive Tx	12(24)	5(50)	7(17.5)	0.046
Rheumatic Factor	7(14)	3(30)	4(10)	0.133
Anti RNP	17(34)	8(80)	9(22.5)	0.001
APL Ab	11(22)	3(30)	8(20)	0.382
FEV1 (% predict)	80.7±9.3	66.5±8.2	84.3±5.4	0.000
FEV1 (L)	2.76±0.46	2.3±0.5	2.8±0.3	0.006
FVC (% predict)	82.9±10.2	66.9±8.4	86.9±5.8	0.000
FVC (L)	3.1±0.5	2.7±0.6	3.2±0.4	0.007
FEV1/FVC	88.1±4.5	86.6±4.0	88.5±4.5	0.225
MWD (m) ⸙	480.6±49.9	487.3±70.8	478.9±44.3	0.356
Borg dyspnea scale BT.	0	0	0	---
Borg dyspnea scale AT.	1.37±0.72	1.25±0.54		0.711
Borg fatigue scale BT,	0	0	0	---
Borg fatigue scale AT.	1.49±0.84	1.70±0.82	1.43±0.84	0.331
O_2 desaturation > 4%	0	0	0	---

†values expressed as mean±standard deviation or counts and percentages.
* P-value calculated through Mann Whitney U test / Fisher's exact test 2 sided for comparison between groups of SLE patients with and without PAH.
BMI, Body Mass Index; RNP, Ribo Neucleo Protein; APL Ab, Anti PhosphoLipid Antibody; FEV1, Forced Expiratory volume in 1 second; FVC, Forced Vital Capacity; 6MWT, 6 Minute Walk Test; BT, Before Test; AT, After Test.

Table 2. Analysis of factors associated with abnormal forced vital capacity in SLE patients

Variable	Odds ratio	95%Confidence interval	P-value*
Immunosuppressive Tx	4.71	1.06-20.78	0.046
Rheumatic Factor	3.85	0.70-21.15	0.133
Anti RNP	13.77	2.47-76.79	0.001
APL Ab.	1.71	0.36-8.14	0.671

* P-value calculated by Fisher's exact test 2 sided.
RNP, Ribo Neucleo Protein; APL Ab, Anti Phospholipid Antibody.

The spirometric evaluation of these patients revealed that the majority of them (80%) presented with normal pattern, with FVC of 82.9±10.2% of predicted value. All the patients with abnormal spirometry (20%) showed restrictive pattern. Percent predicted value of FEV1 and FVC were significantly different between the two groups (p=0.000, p=0.007), but FEV1/FVC ratio did not show any significant differences (p=0.225).

All the 50 SLE patients performed 6MWT in this study and all of them (100%) were able to complete the test successfully. The mean distance walked in 6MWD was 480m (range 335–562 m) and oxygen desaturation>4% did not occur in any

of the patients following the test. The mean total distance walked by the patients within six minutes in the two groups, i.e., patients with normal spirometry and those with abnormal pattern, was not significantly different (p=0.356).

The pre-exercise Borg dyspnea and fatigue scores were zero in all patients. The mean Borg dyspnea score post-exercise was 1.37 and the mean Borg fatigue score post-exrcise was 1.49. The Borg dyspnea and fatigue scores pre- and post-exercise, also were not significantly different between patients in the group with normal pulmonary function and those with abnormal pattern (p=0.711, p=0.331).(Table 2)

No significant correlation was found between

6MWD and FVC in either group of patients as determined by Pearson's correlation coefficient testing. (r=0.439, p=0.205 in SLE patients with normal spirometry and r=0.191,p=0.237 in those with abnormal pattern)

Discussion

The 6MWT is a practical and simple tool that provides a global assessment of functional capacity of patients with cardiopulmonary disorders. Moreover, it can aid with monitoring the response to therapy (18). This test is capable of evaluating the integrated responses of blood, muscle metabolism and the respiratory, cardiovascular and neuromusculoskeletal systems (19).

The 6MWT can be influenced by the individual's age, gender and BMI (20). In 2002, the ATS approved of 6MWT as a standard test for clinical pulmonary function laboratories (21), and it's correlation with pulmonary function tests, in patients with respiratory disorders, makes this test an efficient tool for assessing the status of diseases (19).

Since this test is underutilized by the clinicians in daily practice, we aimed to perform a study to evaluate the correlation between 6MWT and spirometric parameters in SLE patients. Similar studies have been conducted worldwide, assessing the exercise capacity and the correlation of 6MWT with spirometric and clinical parameters in different respiratory disorders (19, 21, 22-26). Nevertheless, such studies have rarely taken pulmonary involvement in SLE into account.

FVC seems to be the gold standard measure of ILD (22). In this study, FVC values below the lower limit of normal range, along with simultaneous reduction in FEV1 and a normal FEV1/FVC ratio, which is suggestive of a restrictive defect, were detected in 10 out of 50 patients. Therefore, SLE patients were classified into two groups based on these spirometric results, patients with normal spirometry and those with abnormal pattern.

There were no significant differences between the two groups regarding age distribution, BMI and disease duration. Additionally, male gender and history of previous immunosuppressive therapy were significantly associated with abnormal spirometric pattern. Quite in line with our results, Hisham Habib et al. reported that an increased risk for abnormal FVC<80%, was significantly associated with immunosuppressive therapy (27).

SLE patients with abnormal spirometry showed significantly higher number of cases with positive anti-U1RNP in comparison to SLE patients with normal spirometry (P>0.05).

Nonetheless, this was not true with other autoantibodies such as RF or APL.

Hisham et al. also reported that both anti-phospholipid and anti-RNP, were associated with an increased risk of abnormal FVC<80% (OR=2.34 and OR = 4.43, respectively) (27). In our study, on the other hand, only anti-U1RNP was significantly associated with reduced lung volume in lupus patients (OR= 13.77). Similarly, in a study conducted by Groein et al., anti-U1RNP was reported to be associated with a higher prevalence of restrictive defects among patients with SLE (28).

The patients with restrictive pattern in spirometry, as compared to those with normal pattern, did not show a significant difference in total distance walked within six minutes. Thus, the 6MWT can not give useful information about respiratory compromise in SLE patients with no clinically relevant respiratory symptoms.

Furthermore, this study failed to demonstrate any correlations between the 6MWT and pulmonary function parameters (R=0.439, P=0.205 in SLE patients with normal spirometry and R=0.191,P=0.237 in those with abnormal pattern). These results are in agreement with the results of a study carried out by Buch et al., in which 163 patients with interstitial lung disease secondary to scleroderma, had performed a 6MWT and a PFT (22). Based on the results, only a weak correlation was observed between 6MWT and percent predicted value of FVC (22). Also, a study conducted by Tashkin et al. supports these findings (24). They have reported little changes of FVC despite improvement in exercise capacity of patients with scleroderma and NSIP (24).

In a relatively similar study, conducted on 45 SLE patients in Brazil, two main variables were defined for dividing the patients into groups: walking distance < 400 m and a fall in O_2 saturation≥ 4% from baseline (20). Considering the cut-off value of 400 m distance, the two groups showed no significant differences concerning age, height, disease duration, FVC, FEV1, FEV1/FVC, Δsat, and Borg scale value (20). However, the distance walked by the patients in the two groups was significantly different (P<0.001) (20). Moreover, no associations were found regarding a FVC value less than the lower limit of predicted value (20).

Also, with placing the participants into groups according to the presence of de saturation≥ 4 at the end of the test, no differences were observed between the two groups, concerning age, height, disease duration, FVC, FEV1, FEV1/FVC, Δsat and Borg scale value (20), while the walked distance showed a significant difference (p=0.029) (20). Additionally, a FVC value below the lower limit of normal predicted value was significantly

associated with desaturation (p=0.027) (20). They concluded that, desaturation was a better indicator of the compromised respiratory function indices as compared to 6MWT (20).

Limitations

There were some limitations in our study. Many eligible patients refused to take part in the study due to various reasons including active disease, lack of interest in participating in research studies, inconvenience, distance required to commute to the center and work commitments. Our assessment can possibly be biased as a result of this non-participation. Moreover, female patients outnumbered males. A possible reason for this might be less prevalence of this disorder in males. Small sample size due to paucity of time and financial resources was also another limitation of our study.

Conclusion

Given the substantial effect of anti-U1RNP positivity with restrictive pattern on spirometry in the current study, it can be considered as a predictor of pulmonary involvement in SLE patients.

Lack of correlation between 6MWT and spirometric parameters is suggestive of restrictive lung involvement and indicates a multifactorial basis for limited exercise capacity in patients with SLE. Therefore, the efficiency of the 6MWT as a measure of pulmonary function is called into question.

In a nutshell, in order to prove the efficiency of 6MWT in assessing pulmonary involvement, further studies should be conducted for determining the variables limiting exercise capacity.

Conflict of Interest

The authors declare no conflict of interest.

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