Original article

Evaluation of respiratory impairment in patients with systemic lupus erythematosus with the six-minute walk test

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A B S T R A C T

Objective: Evaluate SLE stable patients, without overt respiratory compromise, by means of 6MWT.

Causuistic and methods: Forty-five stable SLE patients were enrolled. The ATS/ERS protocol for 6MWT, was used and two parameters with cut-off points were chosen.

Results: Forty-two patients were women. The mean age was 39 ± 11.4 years; mean duration of disease, 121 ± 93.1 months; mean value of MRC, 2 ± 0; mean FVC, 85.9 ± 34.2%; mean FEV1, 67.5 ± 21.6%; mean MIP, 82 ± 58.4%; mean MEP, 78 ± 37.3%; mean heart rate at rest, 75 ± 12.8 bpm; mean respiratory rate at rest, 19 ± 5.3 bpm; mean 6MWD, 478 ± 82 m; mean SpO2 at rest was 98 ± 0.8%; mean fall in SpO2, 4 ± 6 points. When the study population was divided according to the 400-m walk distance cut-off value, the heart rate immediately before the test was significant lower in those participants who walked less than 400 m (p = 0.0043), just like the value of Borg scale (p = 0.0036); according to the presence of saturation ≥ 4, heart rate at the end of the test was significantly higher in those participants who were showing desaturation (p = 0.0170); MEP (p = 0.0282) and 6MWD (p = 0.0291) were significantly lower, and MIP showed a tendency towards being smaller (p = 0.0504). FVC < normal inferior limit was significantly associated with the group with desaturation (p = 0.0274).

Conclusion: Compared to 6MWD, desaturation was better suited to find the patients with the most compromised indexes in respiratory function tests.

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which, in their turn, have the same endothelial cells as tars-ticular tone and activate the immune and coagulation systems different autoantibodies, are the central pathological distur-blogical deregulation, which leads to the production of many habitants.1 A study involving Brazilian population observed (9-10:1), with its prevalence ranging from 14 to 50/100.000 in-studies, the disease most frequently affects young women.3 In pulmonary manifestations, we have, by frequen-cy, pleural involvement (pleural effusion, pleuritis). However, there may be vascular manifestations (pulmonary hypertension, alveolar hemorrhage), interstitial disease (interstitial pneumonitis with possible progression to pulmonary fibrosis), neurological involvement (phrenic neuropathy and diaphragmatic paralysis), among other problems.4,5

The activation of the endothelial cells and the immuno-logical deregulation, which leads to the production of many different autoantibodies, are the central pathological distur-bances of the disease.3

The endothelial cells produce substances that control vas-cular tone and activate the immune and coagulation systems which, in their turn, have the same endothelial cells as tar-getst of the inflammation generated by the immune processes and the coagulation cascade. Vascular injury is probably the primary site of lesion in lupus pathogenesis.1 The activation and damage of the endothelial cells of the immune system are capable of explaining the involvement of the renal, central nervous, cardiovascular and respiratory systems in patients with SLE.6

Apart from serositis, no other pulmonary or respiratory in-volvement appears in the list of diagnostic criteria proposed by the American College of Rheumatology (ACR).7 The diagno-sis of SLE is not simple and requires the fulfillment of a mini-mum number of criteria from a set developed by the ACR.8

Various respiratory manifestations of SLE can provoke acute respiratory symptoms such as pleural thickening, pleur-ral effusion and alveolar hemorrhage; however, some may be insidious and difficult to diagnose, such as interstitial lung disease or vascular disease, which are often silent for quite a long time.

Early diagnosis of respiratory involvement in patients with lupus is fundamental because it allows the therapeutic management established in the earliest stages of the disease, which can prevent the progression to a more dramatic functional impairment. Therefore, it is essential to actively search for symptoms and to perform tests – preferably little or minimally invasive – which indicate involvement in early disease. Thus, 6MWT is a submaximal exercise test that has already been validated in the evaluation of several lung diseases.9-13 This test is easy to be performed, low cost and has a good cor-relation with other more sophisticated tests such as the diffu-sion test for carbon monoxide (DLCO) or cardiorespiratory.11,14

This study aimed to evaluate a patient group with stable SLE, without overt respiratory compromise, by six-minute walk test (6MWT), a self-paced and submaximal exercise test, in order to investigate the possibility of an unnoticed respira-tory involvement.
Methods

This was a cross-sectional study that enrolled stable SLE patients, diagnosed according to the updated and revised American College of Rheumatology (ACR) criteria,7 who attended the SLE outpatient clinic of the Teaching Hospital of the University of Campinas, between November 2007 and August 2009.

All patients were evaluated in order to check if there was presence of any respiratory symptom. The patients were clinically stable — during the prior three months — using one or a combination of the following drugs: hydroxychloroquine, chloroquine, prednisone, azathioprine, and/or mycophenolate mofetil. None of them had recently changed their therapeutic regimen. Six months before the study, all patients were radiographically evaluated by a radiologist and, if it had been noticed the presence of pleural thickening or pleural abnormalities suggestive of interstitial involvement or increased cardiac area in some of these patients, they would not have been included in the study.

Patients would not be considered eligible for the 6MWT if they had a recent chest X-Ray showing any abnormality, hemoglobin concentration below normal values, complaints that could interfere with the walk, if the oxygen saturation (SpO2) levels in rest were under 90% on ambient air, or the pulse signal on a pulse oximeter was inadequate due to Raynaud’s phenomenon. Aiming to ensure an accurate assessment of SpO2, the respiratory therapist checked if the pulse oximeter showed an acceptable pulse signal and if the oximeter light was green and pulsing in synchrony with the heart rate before beginning all tests.

The study was approved by the Research Ethics Committee of the Faculty of Medical Sciences of the University of Campinas, and an informed consent was signed by each patient.

The protocol used for the 6MWT was designed to ensure an accurate assessment of the walking distance and the oxygen desaturation, as proposed by the American Thoracic Society.8 All patients were tested under standardized conditions by the same technician (ML). Baseline blood pressure and heart rate before beginning all tests.

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For the purpose of data analysis, desaturation was defined and used to separate the study population in groups: a fall in saturation (Δsat) ≥ 4% and walking distance < 400 m. Considering the cut-off value of 400 m of walking distance, no differences were found between the groups concerning age, disease duration, height, MIP, MEP, FVC, FEV1, FEV1/FVC, initial SpO2, Δsat, increase in heart rate, initial respiratory rate, increase in respiratory rate, and increase in the Borg scale value. In addition, no association was found for the groups regarding sex, MRC value and the finding of a FVC inferior to the low limit of normality. The MIP was 82 ± 58.4 and MEP was 78 ± 37.3 (% of predicted value).

The quantitative variables measured in these groups were submitted to the Anderson-Darling test to define their distribution. Variables with normal distribution were analyzed using the Student t test. Variables identified as not having a normal distribution were studied with the Wilcoxon test. The categorical data were compared using chi-square test or Fisher’s exact test when necessary. The statistical software used was SAS, version 8®. Differences were considered significant in the face of a p-value < 0.05.

Results

There were forty-five consecutive patients enrolled who agreed to participate in the study and fulfilled the inclusion criteria. There were 42 women with 39 ± 11.4 years, in total. None of the patients were smokers. The duration of the disease was 121 ± 93.1 months in the occasion. The characteristics of the patients and their functional measurements are detailed in Table 1.

For the purpose of data analysis, two main variables were defined and used to separate the study population in groups: a fall in saturation (Δsat) ≥ 4% and walking distance < 400 m. Considering the cut-off value of 400 m of walking distance, no differences were found between the groups concerning age, disease duration, height, MIP, MEP, FVC, FEV1, FEV1/FVC, initial SpO2, Δsat, increase in heart rate, initial respiratory rate, increase in respiratory rate, and increase in the Borg scale value. In addition, no association was found for the groups regarding sex, MRC value and the finding of a FVC inferior to the low limit of predicted value. The heart rate obtained immediately before the test was significantly smaller in those participants who walked less than 400 m (p = 0.004) when considering the
Borg scale value \((p = 0.004)\). The distance walked by the patients in the two groups was also significantly different \((p < 0.001)\): the value in the group \(\geq 400\) m was 505.3 \pm 53.7 m; and in the group \(< 400\) m was 350.8 \pm 70.4 m (Table 2).

When the population studied was divided in two groups, according to the presence of desaturation \(\geq 4\) by the end of the 6MWT, no differences were found between the groups concerning age, disease duration, height, FEV1/FVC, initial SpO2, initial heart rate, initial respiratory rate, increase in respiratory rate, initial value and increase in Borg scale. The heart rate at the end of the test was significantly higher in those participants who showed desaturation \((p = 0.017)\). MEP was significantly lower in the group with desaturation \((p = 0.028)\) and MIP as well, but it did not reach significance \((p = 0.050)\). The distance walked by the patients in the two groups was also significantly different \((p = 0.029)\): the value in the group with desaturation was 443.1 \pm 94.6 m and in the group without desaturation was 497 \pm 68.5 m. The ΔSat was also significantly different \((p = 0.029)\): the value in the group \(\geq 400\) m was 505.3 \pm 53.7 m; and in the group \(< 400\) m was 350.8 \pm 70.4 m (Table 2).

### Discussion

One finding that seems quite relevant in this study is that, within a population of SLE patients without relevant respiratory symptoms, the 6MWT can give useful information about respiratory compromise, especially if there is a reduction in SpO2 by the end of the test. It was considered a reduction equal to or greater than 4 points as significant, based on the findings by Prefaut et al., who validated this cut-off value in a study of exercise-induced hypoxemia during maximal exercise tests in athletes.\(^2\) This 4% fall was defined as accounted for potential inaccuracy of oximetry plus the effects of metabolic acidosis on the hemoglobin saturation curve (a right shift).\(^3\)

Subjects in this study with ΔSat \(\geq 4\) showed a significant reduction in walking distance \(443\) m versus \(497\) m, \(p = 0.029)\), although both values were way above the accepted inferior limit for 6MWD. Furthermore, these patients, when compared to those who did not desaturate had a higher heart rate at the end of the 6MWT \((p = 0.017)\), lower MEP \((p=0.028)\), lower MIP \((p = 0.050)\) and a spirometry restrictive defect (FVC below the lower limit of predicted value, \(p = 0.027\), with a normal FEV1/FVC ratio).

Conversely, those who walked less than \(400\) m showed no significant differences regarding initial saturation or ΔSat \(\geq 4\). In addition, there were no significant differences between the groups with 6MWD \(< 400\) m and MWD \(\geq 400\) m in spirometric values, heart rate, static pressures or severity of dyspnea, either.

These findings suggest the hypothesis that desaturation during the 6MWT may be a useful tool to evaluate SLE patients without respiratory symptoms – perhaps more sensitive than the 6MWD.

The 6MWT is a standardized submaximal test of exercise capacity that is self-paced, simple, reproducible and inexpensive. The measured variables are distance walked in 6 minutes \(6\)MWD), symptoms and SpO2 at rest and at the end of the test.\(^8\) Because of its safety profile, physician attendance is not required, but a health professional, such as physiotherapist or a nurse, with clinical experience should supervise the patient during the test.

Age, sex, height, weight and ethnicity are important determinants of an individual’s 6MWD. In general, men walk further than women; and the distance walked declines with increasing age.\(^21\) Equations are available to predict expected normal values of 6MWD, with some variation in the expected distances.\(^21,22\) A walking distance of less than \(350\) m has predictive value of increased mortality in a number of cardiopulmonary disorders, such as COPD, interstitial lung disease, pulmonary arterial hypertension, cystic fibrosis, congestive heart failure.\(^10,11,14,22-24\)

Although the 6MWD is a sensitive measurement of walking ability for patients with moderate to severe disease, it is likely that its sensitivity in patients with better preserved exercise tolerance may not be so good. A ceiling effect was reported in patients with pulmonary arterial hypertension whose 6MWD is greater than \(450\) m, and this observation may be true for patients with other conditions.\(^25\)

From the studies mentioned above, it can be seen that the cut-off value for the walking distance is not well established; apparently, it is between \(350\) m and \(450\) m.

In this study, only 8 patients walked less than \(400\) m, with median value of \(367.5\) m and mean value of \(350.8 \pm 70\) m.

For the groups separated by the walking distance, the only statistically significant differences were initial heart rate (slower for those who walked less) and degree of dyspnea in Borg scale (smaller for those who walked less). There were no significant differences for these variables at the end of the 6MWT. It is hard to have an explanation for these findings, perhaps because of the small number of patients in one of the groups.
Table 2 – Comparison of functional variables and 6MWT parameters between the groups separated by distance and desaturation (n = 45)

<table>
<thead>
<tr>
<th></th>
<th>≥ 400 m (n=37)</th>
<th>&lt; 400 m (n=8)</th>
<th>p value</th>
<th>Δ Sat (n=16)</th>
<th>Without desaturation (n=29)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Median (Min-Max)</td>
<td>Mean ± SD</td>
<td>Median (Min-Max)</td>
<td>Mean ± SD</td>
<td>Median (Min-Max)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>37.7±10.9</td>
<td>39 (17-62)</td>
<td>43.1±13.3</td>
<td>40.5(26-70)</td>
<td>38.9±9.2</td>
<td>38.5(17-51)</td>
</tr>
<tr>
<td>Duration of disease (months)</td>
<td>118.7±98.5</td>
<td>84 (12-373)</td>
<td>129±67.2</td>
<td>126(24-240)</td>
<td>117±95.8</td>
<td>90(12-312)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160.7±8.0</td>
<td>160 (145-179)</td>
<td>163.4±4.1</td>
<td>163(157-169)</td>
<td>158.9±5.5</td>
<td>160(150-169)</td>
</tr>
<tr>
<td>MIP *</td>
<td>83.5±61.6</td>
<td>73 (29-316)</td>
<td>73.5±42.8</td>
<td>65(13-137)</td>
<td>61±33</td>
<td>53.5(13-137)</td>
</tr>
<tr>
<td>MEP *</td>
<td>78.9±37.1</td>
<td>75 (31-163)</td>
<td>76.3±40.4</td>
<td>71(30-123)</td>
<td>63.9±35.4</td>
<td>56.5(30-150)</td>
</tr>
<tr>
<td>FVC *</td>
<td>85.7±35.9</td>
<td>80.4 (31.6-247.7)</td>
<td>87±26.4</td>
<td>89.7(53-127.3)</td>
<td>70.1±27.9</td>
<td>68.2(31.6-127.6)</td>
</tr>
<tr>
<td>FEVI *</td>
<td>68.5±22.8</td>
<td>67.1 (30.4-113)</td>
<td>62.6±13.9</td>
<td>58.5(7.5-83.6)</td>
<td>57.5±18</td>
<td>55.8(30.4-91.3)</td>
</tr>
<tr>
<td>FEVI/FVC</td>
<td>0.7±0.2</td>
<td>0.7 (0.39-0.99)</td>
<td>0.7±0.2</td>
<td>0.6(0.42-0.89)</td>
<td>0.7±0.1</td>
<td>0.7(0.49-0.94)</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>76.8±12.9</td>
<td>73 (57-99)</td>
<td>64±4.9</td>
<td>64(57-70)</td>
<td>76±15.8</td>
<td>69.5(57-99)</td>
</tr>
<tr>
<td>Δ HR (bpm)</td>
<td>24.3±13.7</td>
<td>19 (4-60)</td>
<td>23.9±12.8</td>
<td>18(12-49)</td>
<td>29.4±12.2</td>
<td>28(5-51)</td>
</tr>
<tr>
<td>Respiratory rate (cpm)</td>
<td>19.2±5.2</td>
<td>18 (12-32)</td>
<td>19±6.0</td>
<td>18(12-32)</td>
<td>21±4.6</td>
<td>20(12-32)</td>
</tr>
<tr>
<td>Δ RR (cpm)</td>
<td>9±4.8</td>
<td>8 (0-20)</td>
<td>8±1.2</td>
<td>8(4-14)</td>
<td>10.6±5.1</td>
<td>10(3-20)</td>
</tr>
<tr>
<td>Initial SpO2 %</td>
<td>98.1±0.8</td>
<td>98 (94-99)</td>
<td>97.9±0.8</td>
<td>98(6-99)</td>
<td>97.8±1.2</td>
<td>98(94-99)</td>
</tr>
<tr>
<td>Δ SpO2 (in % points)</td>
<td>3.7±5.4</td>
<td>1 (0-16)</td>
<td>8±7.8</td>
<td>80 (22)</td>
<td>11.6±4.6</td>
<td>12(4-22)</td>
</tr>
<tr>
<td>Initial Borg</td>
<td>8.5±1.7</td>
<td>8 (6-13)</td>
<td>8±6.0</td>
<td>6(5-9)</td>
<td>8±1.4</td>
<td>8(6-10)</td>
</tr>
<tr>
<td>Δ Borg</td>
<td>4.3±2.7</td>
<td>4 (0-10)</td>
<td>5±2.2</td>
<td>5(1-10)</td>
<td>5.4±3.1</td>
<td>5.5(1-10)</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>505.3±35.7</td>
<td>510 (401-600)</td>
<td>350.8±70.4</td>
<td>367.5(180-397)</td>
<td>350±70.4</td>
<td>350(180-397)</td>
</tr>
</tbody>
</table>

Mean ± SD, mean ± standard deviation; Median (Min-Max), Median (minimum and maximum); 6MWD, 6 minutes walked distance; Δ Sat, Final SpO2 – Initial SpO2; MIP, Maximal inspiratory pressure; MEP, Maximal expiratory pressure; FVC, Forced Capacity Value; FEV1, Forced Expired Volume in one second; HR, Heart rate; Δ HR, Final HR – Initial HR; cpm, cycles per minute; Δ RR, final RR – Initial RR; Δ Borg, Final Borg – Initial Borg.

Differences were considered significant with a p < 0.05.

*Values expressed as % of predicted value.
The relation between walking distance and mortality is not seen in patients suffering from untreated pulmonary arterial hypertension, in whom desaturation during the 6MWT was a better predictor of mortality than walking distance: for every percent decrease in SpO2 there was a 26% increase in the risk of death.12

The desaturation during 6MWT has demonstrated its value as an index of severity of disease and prognostic factor. Lama et al. showed that, in patients with interstitial pulmonary fibrosis without resting hypoxemia, desaturation up to 88% at any point during the 6MWT was associated to an increased hazard of death; however, no associations between 6MWD and survival were observed.26

In this study, FVC values below the lower limit of normality, simultaneously reduced FEV1, and normal FEV1/FVC indexes, indicating the presence of a restrictive defect, were significantly more frequent among patients who showed desaturation. In addition, patients with desaturation had significantly lower MEPs and showed a trend towards significantly lower MIPs. The 6MWD was not able to detect the patients who had reductions in FVC, and not even the ones with reduced expiratory pressures. In this study, desaturation was associated with lower 6MWD, although the mean walking distance in the group that showed desaturation was much greater than 350 m.

In our patients, an association between the presence of desaturation (Asat ≥ 4%) with the values of MIP (p = 0.050) and MEP (p = 0.028) was observed, suggesting that some impairment of respiratory muscles, not only the diaphragm, was present.

The presence of unexplained dyspnea, especially in the supine position, small lung volumes on chest radiographs, dysfunction and elevation of the diaphragm and pulmonary function tests displaying patterns of restrictive disease in the absence of parenchymal involvement prompted the diagnosis of shrinking lung syndrome.

Some authors found that the ability of the diaphragm to generate pressure is impaired in patients with the shrinking lung syndrome;27 however, other authors28 were unable to show a reduced diaphragmatic strength in a cohort of 12 patients.

In a comparison to the 6MWD, desaturation revealed itself as better suited to find patients with the most impaired indexes in respiratory function tests. A previous published study, carried out by our group, showed that desaturation during a 6MWT provides additional information regarding severity of disease in patients with scleroderma presenting pulmonary manifestations.11

Inter-test variation is high in cases of oxygen desaturation. This fact implies that therapeutic decisions should not be based on a single measurement of exertional desaturation recorded on a 6MWT. This inter-test variation is expressed by the finding of different values of SpO2 at the end of various tests performed by the same patient.

In the study by Eaton et al., the value of hemoglobin desaturation upon pulse oximetry was found to be non-reproducible, with unacceptable measurement variation. However, instead of using the hemoglobin desaturation as a categorical variable, they computed the values of desaturation in two 6MWTs.29 We believe that the important information here is the occurrence of desaturation per se, a fact that is not observed in normal subjects.31 We surely expect the value of desaturation to vary because of different homeostatic situations at different moments in individuals with pulmonary diseases and in whom gas exchange abnormalities are probably present.

Except for the involvement of the pleura, the most common pulmonary manifestation of SLE, all other pulmonary manifestations are infrequent, and many of them may cause decrease oxygenation during exercise, by different pathogenic mechanisms. Those less common respiratory disorders in patients with SLE include: interstitial lung disease, acute lupus pneumonitis, diffuse alveolar hemorrhage, pulmonary arterial hypertension, thromboembolic disease, acute reversible hypoxemia and shrinking lung syndrome. It is worth reminding that the prevalence of respiratory symptoms and signs in patients with SLE vary depending on several factors, most importantly the methods used for diagnosing respiratory tract compromise.

In athletes, the exercise-induced arterial hypoxemia is defined as a reduction in the arterial O2 pressure (PaO2) by more than 1kPa and/or hemoglobin O2 saturation (SaO2) below 95%, both determined by blood gas analysis. Desaturation is consistently found during maximal rowing ergometer and is most pronounced at the end of an exercise bout.20 Exercise-induced hypoxemia is explained by the interplay of many different factors. Alveolar PO2 must be maintained at a high level, so ventilation becomes a critical issue. A widening of the P(Alveolar)-PO2 difference frequently occurs, indicating that diffusion limitation or a ventilation-perfusion mismatch or shunt may be influencing the transport of oxygen from the alveoli to the pulmonary capillaries. Cardiac output increases greatly, leading to a fast transit time of red cells in the lungs and further limiting O2 uptake. It is well known that a post-exercise reduction in pulmonary diffusion capacity really occurs, and this suggests damage to the alveolar-capillary membrane.32 All these factors have been proposed to be involved in exercise-induced hypoxemia, but the six-minute walk test is a submaximal exercise. Disease states may facilitate the occurrence of desaturation by all these mechanisms.

Vascular injury with endothelial cell activation and damage play a central role in the pathogenesis of SLE.3 Vascular endothelial growth factor (VEGF) is the main mediator of angiogenesis, and increased levels of VEGF were found in serum from patients with rheumatoid arthritis, dermatomyositis/polymyositis, sclerodermapolymyositis, scleroderma complicated by interstitial lung disease,32 and SLE.33 The mitogen is connected to vascular hypertrophy, inflammation, tissue remodeling, extracellular matrix synthesis and fibrosis.34 Increased levels of endothelin-1, a potent vasoconstrictor, were observed in many collagen-vascular diseases including SLE.

The combination of inflammatory vascular lesion, slightly elevated arterial pulmonary pressures and initial fibrotic interstitial disease impaired function of diaphragm with exercise stress, although submaximal, may explain the occurrence of desaturation during the 6MWT in SLE patients.

Only the follow-up of these patients will be able to clarify the relevance of this desaturation during 6MWT; however, given the available data from studies that used other diseases, such as idiopathic pulmonary fibrosis and pulmonary arte-
rrial hypertension, associated with a poor prognosis, a close monitoring of the patients with SLE who presented desaturation during the 6MWT is advisable. A recently published study assesses the association between quality of life and distance walked during the 6MWT in Brazilian premenopausal patients with SLE and compared with a healthy control group. The authors of this study concluded that patients with SLE walked a shorter distance during the 6MWT, which was associated with poorer quality of life. In addition to that, the finding of desaturation justifies the indication of a more thorough cardiopulmonary evaluation using echocardiogram, CT scans, measurements of diffusion capacity and total lung capacity.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

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