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Original article

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

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ABSTRACT

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

*Casuistic 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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## Avaliação do comprometimento respiratório em pacientes com lúpus eritematoso sistêmico com o teste de caminhada de seis minutos

*Palavras-chave:*
Lúpus eritematoso sistêmico (LES)
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Questionários

RESUMO

*Objetivo:* Avaliar pacientes com LES estável, sem comprometimento respiratório evidente, por meio do TC6M.

*Casuística e métodos:* Foram recrutados 45 pacientes com LES estável. Foi utilizado o protocolo ATS/ERS para TC6M, tendo sido escolhidos dois parâmetros com pontos de corte.

*Resultados:* Quarenta e dois dos pacientes eram mulheres. A média de idade foi 39 ± 11,4 anos; a duração média da doença, 121 ± 93,1 meses; valor médio de MRC 2 ± 0; CVF média 85,9 ± 34,2%; VEF1 médio 67,5 ± 21,6%; PIM média 82 ± 58,4%; PEM média 78 ± 37,3%; frequência cardíaca média em repouso 75 ± 12,8 bpm; frequência respiratória média em repouso 19 ± 5,3 bpm; Distância média no TC6M 478 ± 82 m; SpO2 média em repouso 98 ± 0,8%; queda média em SpO2 4 ± 6 pontos. Quando a população em estudo foi dividida de acordo com o valor de corte de 400 m de distância caminhada, a frequência cardíaca imediatamente antes do teste foi significativamente menor naqueles participantes que caminharam menos de 400 m (p = 0,0043), da mesma forma que o valor da escala de Borg (p = 0,0036). De acordo com a presença de saturação ≥ 4, a frequência cardíaca ao final do teste estava significativamente mais elevada naqueles participantes exibindo dessaturação (p = 0,0170); PEM (p = 0,0282) e TC6M (p = 0,0291) estavam significativamente menores e PIM revelou uma tendência para diminuir (p = 0,0504). CVF < limite inferior do normal foi achado significativamente associado com o grupo com dessaturação (p = 0,0274).

*Conclusão:* Comparado com TC6M, a dessaturação foi o indicador mais apropriado para localizar os pacientes com os índices mais comprometidos nos testes de função respiratória.



## Introduction

Systemic lupus erythematosus (SLE) is a progressive autoimmune disease of unknown etiology and a broad spectrum of clinical manifestations, that has a chronic course with periods of exacerbation and remission. According to American studies, the disease most frequently affects young women (9-10:1), with its prevalence ranging from 14 to 50/100.000 inhabitants.[1] A study involving Brazilian population observed a higher incidence in Caucasian patients[2] and also in young women.[3] In pulmonary manifestations, we have, by frequency, pleural involvement (pleural effusion, pleuritis). However, there may be vascular manifestations (pulmonary hypertension, alveolar hemorrhage), interstitial disease (interstitial pneumonia 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 immunological deregulation, which leads to the production of many different autoantibodies, are the central pathological disturbances of the disease.[5]

The endothelial cells produce substances that control vascular tone and activate the immune and coagulation systems which, in their turn, have the same endothelial cells as targets of the inflammation generated by the immune processes and the coagulation cascade. Vascular injury is probably the primary site of lesion in lupus pathogenesis.[5] 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 involvement appears in the list of diagnostic criteria proposed by the American College of Rheumatology (ACR).[7] The diagnosis of SLE is not simple and requires the fulfillment of a minimum 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, pleural 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 correlation with other more sophisticated tests such as the diffusion 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 respiratory 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 therapeuthic 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 ($SpO_2$) 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 $SpO_2$, 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 were measured and $SpO_2$ was determined with a Nonin® pulse oximeter (finger probe) (Nonin Medical, Inc; MN, USA). The walking course had 30 m of length. The patients walked on a level surface and were gently encouraged periodically. Assessment of dyspnea by the Borg index was performed at the beginning and at end of the test. $SpO_2$ was measured at rest and immediately after the end of the 6-minute period, and the patients were carefully observed to avoid dangerously exceeding their exercise limits.

For the purpose of data analysis, desaturation was defined as a decrease in $SpO_2$ of 4 points or more (Δsat = resting saturation – saturation immediately after the 6-minute period), in comparison with the initial values. Maximal distance was defined as the maximal achieved walking distance on room air 6MWT.

Spirometric maneuvers were performed as recommended by Brazilian guidelines,[15] and the curves for forced vital capacity (FVC) and slow vital capacity (VC) were performed using a flow spirometer (microQuark model; COSMED Srl, Rome, Italy). The measured values were compared with those predicted for age, sex and height for each patient, and the inferior limit of the normal value for FVC was used to diagnose the reduction in FVC.[16]

British MRC (Medical Research Council) questionnaire modified and translated to Portuguese was used to assess the degree of shortness of breath (0=o shortness of breath, except with strenuous exercise; 1=troubled by shortness of breath when hurrying or walking up a slight hill; 2=walks slower than people of the same age due to shortness of breath; need to stop for catch their breath when walking at their own pace; 3=stops to breath after walking for approximately 100 m or after a few minutes; 4=show themselves with an excessive shortness of breath; breathless when dressing or undressing).[17]

The static maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) were determined using a digital manuvacuometer (*MVD30*-Globalmed). The maneuvers were performed as recommended in ATS/ERS statement about respiratory muscle testing[18], and the normal values were expressed as percentage of expected values predicted for Brazilians.[19]

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.

The 6MWD was 478 ± 82 m and the $SpO_2$ at rest was 98 ± 0.8%. The fall in $SpO_2$ at the end of the 6MWT was 4 ± 6 points.

The spirometric evaluation showed FVC of 85.9 ± 34.2 (% of predicted value) and 21 patients with FVC below the limit of normality. The MIP was 82 ± 58.4 and MEP was 78 ± 37.3 (% of predicted value).

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, $FEV_1$, $FEV_1$/FVC, initial $SpO_2$, 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

**Table 1 – Study population characteristics and functional measurements (n = 45)**

| Variables | Mean±SD | Median (Min–Max) |
|---|---|---|
| Age (years) | 39±11.4 | 39 (17-70) |
| Height (cm) | 161±7.5 | 162 (145-179) |
| Duration of disease (months) | 121±93.1 | 96 (12-373) |
| MRC questionnaire | 2±0.5 | 2 (0-4) |
| FVC (% of predicted value) | 85.9±34.2 | 81(31.6-247.7) |
| FEV1 (% of predicted value) | 67.5±21.6 | 62.3 (30.4-113) |
| MIP (% of predicted value) | 82±58.4 | 73(13-316) |
| MEP (% of predicted value) | 78±37.3 | 75 (30-163) |
| Heart rate (bpm) | 75±12.8 | 70 (57-99) |
| Respiratory rate (cpm) | 19±5.3 | 18 (12-32) |
| SpO2 (%) | 98±0.8 | 98 (94-99) |
| 6MWD (m) | 478±82 | 500 (180-600) |
| Δ SpO2(%) | 4±6 | 1 (0-22) |

Mean ± SD, mean ± standard deviation; Median (Min-Max), Median (minimum and maximum); MRC, Medical Research Council; FVC, Forced Capacity Value; FEV1, Forced Expired Volume in one second; MIP, Maximal Inspiratory Pressure; MEP, Maximal Expiratory Pressure; 6MWD, Six minute walk distance; cpm, cycles per minute; bpm, beat per minute.

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 ≥ 400 m was 505.3 ± 53.7 m; and in the group < 400 m was 350.8 ± 70.4 m (Table 2).

When the population studied was divided in two groups, according to the presence of desaturation ≥ 4 by the end of the 6MWT, no differences were found between the groups concerning age, disease duration, height, $FEV_1$/FVC, initial $SpO_2$, 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 ± 94.6 m and in the group without desaturation was 497 ± 68.5 m. The ΔSat was also significantly different in the two groups: the value in the group with desaturation was 11.6 ± 4.6 points; and in the one without desaturation, the fall was of 0.5 ± 0.9 points. The finding of a FVC below the limit of the normal expected value was significantly associated with the group with desaturation (p = 0.027) (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 $SpO_2$ 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.[20] 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).[9]

Subjects in this study with ΔSat ≥ 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 $FEV_1$/FVC ratio).

Conversely, those who walked less than 400 m showed no significant differences regarding initial saturation or ΔSat ≥ 4%. In addition, there were no significant differences between the groups with 6MWD < 400 m and MWD ≥ 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 (6MWD), symptoms and $SpO_2$ 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 ± 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)**

| | 6MWD | | | | | Δ Sat | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | ≥ 400 m (n=37) | | < 400 m (n= 8) | | p value | With desaturation (fall in SpO2 ≥ 4%) (n=16) | | Without desaturation (n=29) | | p value |
| | Mean ± SD | Median (Min-Max) | Mean ± SD | Median (Min-Max) | | Mean ± SD | Median (Min-Max) | Mean ± SD | Median (Min-Max) | |
| Age (years) | 37.7±10.9 | 39 (17-62) | 43.1±13.3 | 40.5(26-70) | 0.307 | 38.9±9.2 | 38.5(17-51) | 38.5±12.6 | 39(18-70) | 0.914 |
| Duration of disease (months) | 118.7±98.5 | 84 (12-373) | 129±67.2 | 126(24-240) | 0.502 | 117±95.8 | 90(12-312) | 122.5±93.2 | 120(12-373) | 0.830 |
| Height (cm) | 160.7±8.0 | 160 (145-179) | 163.4±4.1 | 163(157-169) | 0.185 | 158.9±5.5 | 160(150-169) | 162.4±8.2 | 163(145-179) | 0.091 |
| MIP * | 83.5±61.6 | 73 (29-316) | 73.5±42.8 | 65(13-137) | 0.835 | 61±33 | 53.5(13-137) | 93.1±66.3 | 84(30-316) | 0.050 |
| MEP * | 78.9±37.1 | 75 (31-163) | 76.3±40.4 | 71(30-123) | 0.867 | 63.9±35.4 | 56.5(30-150) | 86.5±36.4 | 81(32-163) | 0.028 |
| FVC * | 85.7±35.9 | 80.4 (31.6-247.7) | 87±26.4 | 89.7(53-127.3) | 0.523 | 70.1±27.9 | 68.2(31.6-127.6) | 94.7±34.5 | 93(53.4-247.7) | 0.015 |
| FEV1* | 68.5±22.8 | 67.1 (30.4-113) | 62.6±13.9 | 58.5(47.5-83.6) | 0.352 | 57.5±18 | 55.8(30.4-91.3) | 73±21.7 | 74.7(39.8-113) | 0.015 |
| FEV1/FVC | 0.7±0.2 | 0.7 (0.39-0.99) | 0.7±0.2 | 0.6(0.42-0.89) | 0.355 | 0.7±0.1 | 0.7(0.49-0.94) | 0.7±0.2 | 0.7(0.39-0.99) | 0.231 |
| Heart rate (bpm) | 76.8±12.9 | 73 (57-99) | 64±4.9 | 64(57-70) | 0.004 | 76±15.8 | 69.5(57-99) | 73.7±11.1 | 70(57-96) | 0.952 |
| Δ HR (bpm) | 24.3±13.7 | 19 (4-60) | 23.9±12.8 | 18(12-49) | 0.917 | 29.4±12.2 | 28(15-51) | 21.3±13.3 | 17(4-60) | 0.017 |
| Respiratory rate (cpm) | 19.2±5.2 | 18 (12-32) | 19±6.0 | 18(12-32) | 0.856 | 21.4±6.3 | 20(12-32) | 17.9±4.2 | 18(12-28) | 0.080 |
| Δ RR (cpm) | 9±4.8 | 8 (0-20) | 8.1±4.2 | 8(4-16) | 0.610 | 10.6±5.1 | 10(3-20) | 7.9±4.2 | 8(0-16) | 0.080 |
| Initial $SpO_2$ % | 98.1±0.8 | 98 (94-99) | 97.9±0.8 | 98(96-99) | 0.369 | 97.8±1.2 | 98(94-99) | 98.2±0.5 | 98(97-99) | 0.139 |
| Δ $SpO_2$ (in % points) | 3.7±5.4 | 1 (0-16) | 8±7.8 | 8(0-22) | 0.127 | 11.6±4.6 | 12(4-22) | 0.5±0.9 | 0(0-3) | 0.000 |
| Initial Borg | 8.5±1.7 | 8 (6-13) | 6.8±1.0 | 6.5(6-9) | 0.003 | 7.8±1.4 | 8(6-10) | 8.4±1.9 | 8(6-13) | 0.396 |
| Δ Borg | 4.3±2.7 | 4 (0-10) | 5.5±3.2 | 5.5(1-10) | 0.330 | 5.4±3.1 | 5.5(1-10) | 4±2.4 | 4(0-9) | 0.132 |
| 6MWD (m) | 505.3±53.7 | 510 (401-600) | 350.8±70.4 | 367.5(180-397) | 0.000 | 443.1±94.6 | 450(180-600) | 497±68.5 | 512(360-600) | 0.029 |

Mean ± SD, mean ± standard deviation; Median (Min-Max), Median (minimum and maximum); 6MWD, 6 minutes walked distance; Δ Sat, Final $SpO_2$ – 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 $p < 0.05$.

[a]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 $SpO_2$ 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 $FEV_1$ and normal $FEV_1$/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 ($\Delta sat \geq 4\%$) 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 prompt 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 authors[28] 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.[13]

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 $SpO_2$ 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.[21] 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 $O_2$ pressure ($PaO_2$) by more than 1kPa and/or hemoglobin $O_2$ saturation ($SaO_2$) 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.[30] Exercise-induced hypoxemia is explained by the interplay of many different factors. Alveolar $PO_2$ must be maintained at a high level, so ventilation becomes a critical issue. A widening of the $P_AO_2$-$PaO_2$ 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 $O_2$ 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.[31] 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.[5] The 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-

rial 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.[35] In addition to that, the finding of desaturation justifies the indication of a more thorough cardiorespiratory evaluation using echocardiogram, CT scans, measurements of diffusion capacity and total lung capacity.

## Conflicts of interest

The authors declare no conflicts of interest.

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