Abstract. [Purpose] This study aimed to evaluate the impact of lung function and peripheral muscle function on the six-minute walking distance (6MWD) in systemic sclerosis (SS) patients and, thereby, to develop an explanatory model of functional exercise capacity for these individuals. [Methods] In a cross-sectional study, 31 SS patients underwent pulmonary function testing (including spirometry, diffusing capacity for carbon monoxide [DLCO], and respiratory muscle strength), isometric dynamometry with surface electromyography, and the 6MWD. [Results] There was a significant correlation between the 6MWD (% predicted, 6MWD%) and the following parameters: height ($r = 0.427$) and DLCO ($r = 0.404$). In contrast, no other independent variable showed a significant correlation with the 6MWD% ($r \leq 0.257$). The final prediction model for 6MWD% ($R^2 = 0.456$, SE of bias=12%) was $6\text{MWD}\%_{\text{Gibbons}} = -131.3 + 1.16 \times \text{height cm} + 0.33 \times \text{DLCO% predicted}$. [Conclusion] In SS patients, body height and pulmonary diffusion are the main determinants of the 6MWD. Our results justify further investigation of the performance of SS patients during exercise, which may increase the understanding of the pathophysiological mechanisms involved in the disease. The impact of these findings in SS patients may be useful for evaluating the effects of rehabilitation programs.

Key words: Scleroderma, Respiratory function tests, Exercise

INTRODUCTION

Systemic sclerosis (SS) is a connective tissue disease characterized by the activation of fibroblasts and abnormal accumulation of extracellular matrix, leading to severe multisystemic effects, many of which are debilitating. SS is a rare disease with an overall incidence ranging from 0.3–2.8 cases per 100,000 per year and an estimated prevalence of 10 cases per 100,000 people. The disease affects women in more than 80% of cases. The constant changes arising from chronic SS affect the whole body. The progression of SS is characterized by involvement of the respiratory, cardiovascular, muscular and osteoarticular systems, leading to a significant impact on patient functionality.

Pulmonary involvement is currently the leading cause of death in SS. The lungs are affected in 70–90% of SS patients, with interstitial lung disease and pulmonary arterial hypertension being the most frequent pulmonary complications. Excess collagen irreversibly damages lung structures, alveolar walls, and interstitial spaces, altering respiratory mechanics, pulmonary ventilation, and gas exchange, resulting in restrictive ventilatory dysfunction. As symptoms progress, dyspnea with mild exertion appears.

The prevalence of muscular involvement in SS varies between 7–81%, which reflects the high degree of heterogeneity in
the defining criteria used\textsuperscript{7, 8}. Some drugs may affect SS muscle disease, because muscle weakness develops in conjunction with therapeutic use of agents known to cause myopathy\textsuperscript{9}. Osteoarticular complications have also been described, occurring in up to 70% of patients with SS\textsuperscript{10}. The lesions are usually located near the joints, causing atrophy due to disuse, joint contractures, and muscle shortening\textsuperscript{11}. A reduced six-minute walking distance (6MWD) predicts an increased risk of morbidity and mortality in several patient populations\textsuperscript{12, 13}. In SS, the six-minute walk test (6MWT) has been used increasingly to monitor and track the disease\textsuperscript{14}. Due to the vasculopathies that occur in SS, blood flow to the lungs and heart becomes inadequate, which, in conjunction with musculoskeletal complications, limits exercise capacity\textsuperscript{15}. Despite the importance of the 6MWT in several clinical conditions, its value has often been questioned in SS patients, due to weak correlations with clinical parameters and the absence of objective assessments of the impact of peripheral dysfunction on the 6MWD\textsuperscript{16, 17}. The 6MWT is considered of great value for identifying possible risk factors in different diseases\textsuperscript{18, 19}. Although many factors can potentially influence exercise performance in patients with SS, few studies have addressed their role during physical activity in these individuals. We hypothesized that the various limitations occurring in SS cause different effects on 6MWT performance. Thus, our objective was to evaluate the impact of lung function and peripheral muscle function on exercise performance in patients with SS and thereby develop an explanatory model of functional exercise capacity for these individuals.

**SUBJECTS AND METHODS**

This study used a cross-sectional design, including 31 patients with SS, and was conducted between September 2013 and July 2014. These patients were regularly seen at the Federal Hospital of Bonsucesso and at the Federal Hospital of Lagoa in Rio de Janeiro, Brazil. The diagnosis of SS was confirmed following the recommendations of the American College of Rheumatology/European League against Rheumatism\textsuperscript{20}.

The inclusion criteria encompassed men and women with SS \( \geq \text{18 years of age}. \) The exclusion criteria were history of smoking or asthma, presence of neurological diseases, presence of orthopedic disorders or a history of orthopedic surgery, and presence of any physical disability that would render the individuals unable to perform the 6MWT. All patients signed an informed consent form, which was previously approved by the Research Ethics Committee of the Augusto Motta University Center under study number 300.826/2013.

All measurements were taken within two days. Pulmonary function tests, isometric dynamometry, and surface electromyography were performed on the first day, while the 6MWT was administered on the second day.

The pulmonary function testing consisted of spirometry, diffusing capacity for carbon monoxide (DLCO), and respiratory muscle strength tests\textsuperscript{21–23}. Spirometry was performed with the KoKo PFT spirometer (PDS Instrumentation, Inc., Louisville, CO, USA). DLCO and respiratory muscle strength tests were performed using the HDpt 3000 device (nSpire Health, Inc., Longmont, CO, USA). All assessments followed the protocol established by the American Thoracic Society/European Respiratory Society\textsuperscript{24}. The pulmonary function testing results were expressed as the percent of the predicted values\textsuperscript{25–27}.

Peripheral muscle strength was assessed by isometric dynamometry (model DIN-TRO, EMG System do Brasil LTDA, Brazil), and the endurance test was performed adding surface electromyography (EMG model 810C, EMG System do Brasil LTDA, Brazil). Maximal voluntary isometric contractions (MVIC) were performed at 90 degrees of knee flexion\textsuperscript{28}. The patient underwent three MVIC with a 2-minute interval between them, and the highest value was selected. The endurance test consisted of a sustained contraction for 60 seconds, using 30% of the MVIC values. The median frequency and root mean square slopes (MDF slope and RMS slope, respectively), corresponding to the EMG signal during isometric contraction over time, were used to represent the fatigue tolerance of the patients. The MDF slope is associated with the firing rates of motor units, while the RMS slope measures electrical activity during contraction\textsuperscript{29}.

The 6MWT was performed in a 30-m-long corridor\textsuperscript{30, 31}. The heart rate, peripheral oxygen saturation, and degree of dyspnea were measured before, in the third minute, and at the end of the test, following the American Thoracic Society recommendations\textsuperscript{13}. Heart rate was monitored with a Polar FT1 exercise tracker (Polar, Inc., Kempele, Finland). Oxygen saturation was measured by finger pulse oximetry using a Masimo Radical SET pulse oximeter (Masimo, Inc., Irvine, CA, USA). The degree of dyspnea was assessed by the modified Borg scale. The tests were repeated twice, and the highest value was recorded\textsuperscript{13, 32, 33}. The predicted values were calculated by equations of Gibbons et al.\textsuperscript{34} that were previously used in patients with SS\textsuperscript{11, 35}. The equations developed by Gibbons et al. provide a set of reference values for healthy individuals in a wide age range\textsuperscript{34}.

Several models were tested with variables commonly used as predictors of 6MWD (% predicted, 6MWD%). Anthropometric data variables (age, weight, height, and body mass index [BMI]) were entered into the model. Results from the assessment of pulmonary function (forced vital capacity [FVC], maximal inspiratory pressure [MIP], maximal expiratory pressure [MEP], and DLCO, all in %predicted values), peripheral muscular strength (MVIC), and fatigue (RMS slope and MDF slope), were also entered into the model. A forward stepwise method was applied, using the adjusted R\textsuperscript{2} value as a criterion for entry (p <0.05) and removal (p >0.10) of variables.

The overall performance measures of the regression consisted of the R\textsuperscript{2} value adjusted for the number of variables retained in the proposed model, as well as the standard error of the difference (bias = measured − predicted). The specific performance
of the new prediction model was assessed by regression diagnosis and calibration analyses as described below\(^{36}\).

Regression diagnosis was performed using Pearson’s correlation coefficient between the dependent and independent variables and among the independent ones. Multicollinearity was assessed using the variance inflation factor (VIF); a VIF > 5 indicates that the associated regression coefficients are poorly estimated\(^{37}\). Analysis of residuals was also performed using empirical distributions of residuals\(^{38}\), and the one-sample Kolmogorov-Smirnov test was used with the Lilliefors correction to test the null hypothesis of normality of the distribution of residuals.

Calibration was verified by an assessment of the calibration plot (measured vs. predicted, along with regression lines showing slope and intercept) and the limits of agreement (LOA) plot. The bias was tested against 0 with the one sample Student’s t-test. The error was determined as the SD of the bias. The LOA plot\(^{39}\) was used to determine bias and agreement between the values predicted by the equations and those measured. LOA were defined as the upper and lower 95% CI and were determined by the mean differences ±1.96 SD.

A complete-case analysis was conducted because there were no missing data. Data were initially tabulated in Excel (Microsoft Corporation, USA), and statistical analysis was performed using SPSS 22 (IBM Corp., USA). Descriptive results are shown as the mean ± SD and frequency (%) for continuous and categorical variables, respectively. Predicted values were calculated using the simplified model using coefficients rounded to three digits of precision. Statistical significance was considered as p < 0.05 (two-tailed) for all analyses.

**RESULTS**

A total of 55 outpatients were initially selected for inclusion in the study. Thirty-one of these met the inclusion criteria, while 24 were excluded for the following reasons: history of smoking (n=9), refusal to participate in the study (n=4), physical disability impairing locomotion (n=4), oxygen desaturation at rest (n=3), asthma (n=2), and history of orthopedic surgery (n=2). Thus, the final study population included 29 women and 2 men, with a mean age of 47.5 ± 14.0 years. The mean duration of illness was 7.14 ± 5.60 years. Eighteen patients exhibited the diffuse form of the disease, and 13 exhibited the limited form. The mean distance covered was 461.9 ± 101.4 meters. Table 1 shows the demographic, clinical, pulmonary function, peripheral muscle performance, and functional capacity data of the studied sample.

The 6MWD\(^ %\) was significantly correlated with body height (r=0.427, p=0.017) and DLCO\(^ %\) predicted (r=0.404, p=0.024). No other independent variable showed a significant correlation with the 6MWD\(^ %\) (r≤0.257, p≥0.162; Table 2).

Significant associations among the independent variables included the paired analyses of the following: weight and BMI (r=0.908; p<0.001); RMS slope and MDF slope (r=−0.845; p<0.001); FVC\(^%\) predicted with DLCO\(^%\) predicted (r=0.652; p<0.001); age (r=0.402; p=0.025) and MEP\(^%\) predicted (r=0.357; p=0.049); and MEP\(^%\) predicted with MIP\(^%\) predicted (r=0.609; p<0.001) and DLCO\(^%\) predicted (r=0.396; p=0.027). Multicollinearity was not identified for any independent variable (height=1.063, DLCO\(^%\) predicted=1.063).

The adjusted R\(^ 2\) values obtained using the stepwise method began at 0.154, including height as the first variable. Entering the variable DLCO\(^%\) predicted significantly increased the adjusted R\(^ 2\) values to 0.456. The forward inclusion of all other independent variables did not significantly increase the adjusted R\(^ 2\) value. The final prediction model for 6MWD\(^ %\) (equation 1; adjusted R\(^ 2\)=0.456, SE of bias = 12%, p<0.001) was as follows (Table 3):

\[
1) \text{6MWD}^{\%} \text{ Gibbons} = -131.284 + 1.161 \times \text{height}_\text{cm} + 0.330 \times \text{DLCO}^{\%}\text{predicted} \]

There was an obvious relationship between the bias and the mean; the bias SD was 0.1 ± 11.3%. The histogram plot of the differences showed no apparent skew, and the assumption of normality of the distribution was not violated (p = 0.200). The 95% CI for the bias was [−4; 4] %, and the LOA and respective 95% CI for the lower and upper LOA were −22% [−29; −15] and 22% [15; 29], respectively.

**DISCUSSION**

The 6MWT is a simple submaximal test that does not require expensive equipment and is highly reproducible; furthermore, it reflects quality of life and the ability to perform activities of daily living, and has been used to evaluate various patient populations\(^{13}\). In the present study, the mean 6MWD value was close to those observed by Deuschle et al.\(^{40}\), Garin et al.\(^{41}\), and Schoindre et al.\(^{17}\), who also evaluated SS patients. However, these authors only measured the absolute value of the 6MWD and did not consider predictive equations, rendering it difficult to accurately compare the results\(^{17, 40, 41}\). The non-use of reference equations is important because the demographic data independently affect the 6MWD in healthy adults, requiring additional interpretation of test results when these confounding factors are not used\(^{31}\).

In our study, the DLCO was the only pulmonary function test parameter that was included in the explanatory model for the 6MWD. Corroborating our findings, the DLCO (% predicted) was also an explanatory variable for the 6MWD in Deuschle et al.\(^{40}\) and Garin et al.\(^{41}\). Interestingly, a declining DLCO in patients with SS is the single most significant marker of poor outcome\(^{42}\). In SS, Peters-Golden et al.\(^{43}\) showed a 5 year cumulative survival rate of only 9% in patients with DLCO ≤40%, compared with 75% when the DLCO was >40%. The distance for pulmonary diffusion includes the entire route from the
alveolar gas to the hemoglobin in the red blood cell. In SS, a decreased DLCO may represent both a structural change in the alveolar-capillary membrane as well as a change in the capillary blood volume because both interstitial fibrosis and pulmonary hypertension are common complications of this disease\textsuperscript{44}. It should be mentioned that FVC and DLCO are the lung function parameters currently most often used in monitoring patients with SS\textsuperscript{6}.

### Table 1. Demographic data, lung function, peripheral muscle performance, and functional capacity of patients with systemic sclerosis

| Variable                     | Value       |
|------------------------------|-------------|
| **Demographic data**         |             |
| Age (years)                  | 47.5 ± 14.0 |
| Weight (kg)                  | 60.6 ± 13.2 |
| Height (cm)                  | 156.9 ± 7.48|
| BMI (kg/m\(^2\))             | 24.6 ± 5.24 |
| **Clinical data**            |             |
| Raynaud’s phenomenon         | 30 (96.8)   |
| Arthralgia                   | 21 (67.7)   |
| Interstitial lung disease    | 15 (48.4)   |
| Gastrointestinal disease     | 10 (32.2)   |
| Cardiovascular disease       | 8 (25.8)    |
| **Previous or current treatment** |         |
| Glucocorticoids              | 17 (54.8)   |
| Chloroquine                  | 11 (35.5)   |
| Methotrexate                 | 8 (25.8)    |
| Cyclophosphamide             | 7 (22.6)    |
| Calcium-channel blockers     | 7 (22.6)    |
| Bosentan                     | 5 (16.1)    |
| Epoprostenol                 | 4 (12.9)    |
| **Lung function**            |             |
| FVC (% predict)              | 75.1 ± 19.6 |
| DLCO (% predict)             | 63.0 ± 24.6 |
| MIP (% predict)              | 56.0 ± 17.7 |
| MEP (% predict)              | 43.0 ± 14.2 |
| **Peripheral muscle performance** |         |
| MVIC (kg)                    | 26.8 ± 8.81 |
| RMS slope                    | 0.87 ± 0.37 |
| MDF slope                    | –0.20 ± 8.21|
| 6MWD (% predict)             | 71.4 ± 15.3 |

Results are presented as the mean ± SD. BMI: body mass index; FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; 6MWD: 6-minute walking distance; MVIC: maximal voluntary isometric contraction.

### Table 2. Correlation analysis of the six-minute walking distance as predicted by Gibbons et al. (2001) and independent variables used in the model

| Independent variables | Pearson’s correlation coefficient (dependent: 6MWD) (% predicted) |
|-----------------------|---------------------------------------------------------------|
| Height (cm)           | 0.427*                                                        |
| DLCO (% predict)      | 0.404*                                                        |
| MVIC (kg)             | 0.257 (p=0.162)                                              |
| MEP (% predict)       | 0.255 (p=0.167)                                              |
| FVC (% predict)       | 0.243 (p=0.187)                                              |
| MIP (% predict)       | 0.207 (p=0.265)                                              |
| Weight (kg)           | 0.165 (p=0.375)                                              |
| RMS slope (V/s)       | –0.151 (p=0.451)                                             |
| MDF slope (V/s)       | 0.094 (p=0.640)                                              |
| Age (years)           | –0.018 (p=0.925)                                             |
| BMI (kg/m\(^2\))     | 0.003 (p=0.998)                                              |

6MWD: 6-minute walking distance; DLCO: diffusing capacity for carbon monoxide; MVIC: maximal voluntary isometric contraction; MEP: maximal expiratory pressure; FVC: forced vital capacity; MIP: maximal inspiratory pressure; RMS slope: median frequency slope; MDF slope: root mean square slope; BMI: body mass index. *p<0.05

### Table 3. Multivariate regression analysis for prediction of six-minute walking distance in patients with systemic sclerosis

| Model       | Coefficient [95% CI] | Std. Error | t       |
|-------------|----------------------|------------|---------|
| Intercept   | –131.284 [–230.687; –31.882] | 48.527 | –2.705* |
| Height (cm) | 1.161 [0.549; 1.772] | 0.299 | 3.887** |
| DLCO (% predict) | 0.330 [0.150; 0.510] | 0.088 | 3.755** |

DLCO: diffusing capacity for carbon monoxide. *p<0.05; **p<0.01
In our study, height was also included in the explanatory model for 6MWD. This finding is not surprising, because the 6MWD is directly related to height in multiple predictive equations\(^{25, 45}\). Intuitively, a greater height is associated with a larger step, which most likely results in a greater distance covered by taller individuals\(^{13}\). Compared with healthy individuals, it is possible that the frequency of steps interferes further in the 6MWD of patients with SS, because osteoarticular involvement is observed in 46–97% of patients with SS\(^{11, 46}\).

Muscle weakness is a common occurrence in patients with SS\(^{8}\). In the present study, however, we did not observe any relationship between peripheral muscle function (strength or endurance) and 6MWD. Since severe pulmonary involvement with reduced DLCO is a common finding in patients with SS, we speculate that the limitation on exercise tolerance by deteriorating gas exchange imposes an additional limitation to that caused by peripheral muscle dysfunction. Thus, these patients could complete the 6MWT with an important change in gas exchange, but still with reasonable performance of the lower limbs muscles. We believe the cardiopulmonary exercise testing (CPET) could better demonstrate the limitation caused by peripheral muscle dysfunction, since the 6MWT is a submaximal test. In fact, an association between peak oxygen uptake measured by CPET and peripheral muscle dysfunction has been demonstrated by some authors\(^{47}\).

The strength of the present study is that it provides an explanatory model for functional exercise capacity in patients with SS based on predictive 6MWD equations, after eliminating various confounding factors. Furthermore, we considered the influence of the peripheral muscle strength measured objectively in this model. The need for a study using the impact of this measurement on the interpretation of the 6MWT had previously been stated by several authors\(^{43, 44}\). However, this study has specific limitations that should be considered. First, gender was not considered in the correlation analysis because the disease affects women in almost 90% of cases\(^{48}\); in fact, in the present study there were 29 women and only two men. Moreover, most of the variables were analyzed with respect to the predicted percentage; this allowed the standardization of absolute values for gender, including the value of DLCO that came into the final prediction model. Second, we did not investigate pulmonary vasculopathy or left ventricular dysfunction that may have influenced the patient’s performance on the 6MWT\(^{14, 15}\).

In conclusion, the results show that, in patients with SS, body height and pulmonary diffusion are the main determinants of the 6MWD. We believe it is important to validate this predictive model in another scleroderma population. Moreover, we believe that our results justify further investigation of the performance of patients with SS during exercise.

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