



ORIGINAL ARTICLE

## Ventilation distribution and small airway function in patients with systemic sclerosis

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### KEYWORDS

Systemic sclerosis;  
Respiratory function tests;  
Nitrogen single-breath washout test

### Abstract

**Background:** Despite the importance of traditional pulmonary function tests (PFTs) in managing systemic sclerosis (SSc), many patients with pulmonary disease diagnosed by computed tomography (CT) present with normal PFTs.

**Objective:** To evaluate the efficacy of the nitrogen single-breath washout (N<sub>2</sub>SBW) test in diagnosing SSc and to correlate N<sub>2</sub>SBW parameters with the PFT indexes used in the follow-up of these patients, clinical data, and CT findings.

**Methods:** Cross-sectional study in which 52 consecutive SSc patients were subjected to spirometry, body plethysmography, analysis of the diffusing capacity for carbon monoxide (DLCO), analysis of respiratory muscle strength, N<sub>2</sub>SBW testing, and CT analysis.

**Results:** Twenty-eight patients had a forced vital capacity (FVC) that was <70% of the predicted value. In the N<sub>2</sub>SBW test, 44 patients had a phase III slope (Phase III slope<sub>N<sub>2</sub>SBW</sub>) that was >120% of the predicted value, while 15 patients had a closing volume/vital capacity (CV/VC) that was >120% of the predicted value. A significant difference in Phase III slope<sub>N<sub>2</sub>SBW</sub> was observed when the patients with predominant traction bronchiectasis and honeycombing were compared to the patients with other CT patterns ( $p < 0.0001$ ). The Phase III slope<sub>N<sub>2</sub>SBW</sub> was correlated with FVC ( $r_s = -0.845$ ,  $p < 0.0001$ ) and DLCO ( $r_s = -0.600$ ,  $p < 0.0001$ ), and the CV/VC was correlated with FVC ( $r_s = -0.460$ ,  $p = 0.0006$ ) and residual volume/total lung capacity ( $r_s = 0.328$ ,  $p = 0.017$ ).

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**Conclusion:** Ventilation heterogeneity is a frequent finding in SSc patients that is associated with restrictive damage, changes in pulmonary diffusion, and CT patterns. In addition, approximately one-third of the patients presented with findings that were compatible with small airway disease.

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## Introduction

Systemic sclerosis (SSc) is a chronic inflammatory disease of the connective tissue that is characterised by cutaneous and visceral fibrosis, self-immunity, and vascular destruction.<sup>1,2</sup> Almost 90% of SSc patients present with some form of lung injury over the evolution of the illness, and interstitial lung diseases associated with the SSc (ILD-SSc) and pulmonary arterial hypertension (PAH) are the most frequent manifestations.<sup>2,3</sup> Among the investigation methods for ILD-SSc, lung biopsy is rarely performed. Therefore, computed tomography (CT) is currently considered the method of choice.<sup>4</sup> Because the frequent use of ionising radiation is a matter of growing concern, CT is rarely used in the follow-up of these patients. Indeed, the severity of the pulmonary involvement of SSc is more frequently quantified using pulmonary function tests (PFTs) in clinical practice.<sup>5,6</sup>

Among the PFTs used in the diagnosis and follow-up of SSc patients, the most widespread are spirometry and diffusing capacity for carbon monoxide (DLCO).<sup>7</sup> Despite the importance of traditional PFTs in the management of pulmonary involvement associated with SSc, a significant proportion of patients present with normal PFT results, even in the presence of ILD-SSc diagnosed by imaging methods.<sup>8</sup> With the evolution of technical equipment in recent years, growing interest has developed in the use of the nitrogen single-breath washout ( $N_2$ SBW) test to assess ventilation homogeneity and the role of small airways in several clinical conditions.<sup>9,10</sup> The  $N_2$ SBW test is used for the early diagnosis and stratification of patients and to assess the severity of several lung diseases.<sup>9,11–13</sup> In asthma patients, poor disease control is correlated with both an increase in the closing volume (CV) and the phase III slope of the  $N_2$ SBW (Phase III slope $_{N_2SBW}$ ).<sup>13</sup> In COPD patients, Lopes and Mafor<sup>9</sup> observed that Phase III slope $_{N_2SBW}$  was the only predictor, regardless of the degree of dyspnoea and functional capacity for exercise. Mikamo et al.<sup>12</sup> described significant correlations between the Phase III slope $_{N_2SBW}$  and the measurements of mechanical ventilation and emphysema score evaluated by CT. However, to the best of our knowledge, no studies have previously assessed the use of the  $N_2$ SBW test in SSc patients.

In addition to causing poor ventilation distribution, lung interstitium involvement can potentially lead to structural changes in small airways, resulting in a loss of air flow that can reflect in increased ventilatory demand.<sup>14</sup> We hypothesised that the structural disarray caused by the excessive secretion of collagen in the respiratory systems of SSc patients may be reflected in the  $N_2$ SBW test. Thus, the present study sought to assess the usefulness of the  $N_2$ SBW test in SSc patients and to correlate the parameters measured by the  $N_2$ SBW test with the PFT indexes classically

used in the follow-up of these patients, degree of dyspnoea, and CT findings.

## Methods

### Patients

This was a cross-sectional study conducted between December 2015 and July 2016 in which 66 consecutive SSc patients were evaluated. These patients were recruited from the Piquet Carneiro Polyclinic of the State University of Rio de Janeiro, Rio de Janeiro, Brazil. Patients  $\geq 18$  years of age of both genders who met the criteria for SSc diagnosis<sup>15</sup> were included in the study. The following exclusion criteria were used: patients with a previous history of smoking or those who were current smokers; individuals with asthma; evidence of overlap with other connective tissue diseases, except Sjogren's syndrome; reports of infection within the previous four weeks; and inability to perform PFTs. The protocol was approved by the Research Ethics Committee of the Pedro Ernesto University Hospital of the State University of Rio de Janeiro, Rio de Janeiro, Brazil under the number CAAE- 50752615.9.0000.5259. All of the patients signed informed consent forms.

### Measurements

Dyspnoea was assessed by means of the modified Medical Research Council (mMRC) scale.<sup>16</sup>

Spirometry, body plethysmography, measurement of DLCO, and measurement of respiratory muscle strength were conducted with Collins Plus Pulmonary Function Testing Systems equipment (Warren E. Collins, Inc., Braintree, MA, USA) using the standardisation of the consensus statement.<sup>17</sup> The Brazilian reference values were used,<sup>18–21</sup> and the results are expressed as % predicted.

The  $N_2$ SBW test was performed using the HDpft 3000 instrument (nSpire Health, Inc., Longmont, CO, USA). Briefly, individuals exhaled until the residual volume (RV) was reached and then inhaled 100%  $O_2$  until the total lung capacity was reached (TLC). Then, they slowly exhaled at a flow rate of approximately 0.3–0.5 L/s until the RV was reached. The two indexes derived from the procedure are reported as % predicted<sup>22,23</sup> and include the Phase III slope $_{N_2SBW}$ , which is the change in the concentration of  $N_2$  between 25% and 75% of the exhaled volume, and the closing volume/vital capacity (CV/VC), which is the portion of the VC that is exhaled after the airway begins to close. The  $N_2$ SBW test was performed according to the recommendations of the consensus statement.<sup>11</sup>

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