

Oscillation mechanics of the respiratory system in never-smoking patients with silicosis: pathophysiological study and evaluation of diagnostic accuracy

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OBJECTIVES: Silicosis is a chronic and incurable occupational disease that can progress even after the cessation of exposure. Recent studies suggest that the forced oscillation technique may help to clarify the changes in lung mechanics resulting from silicosis as well as the detection of these changes. We investigated the effects of airway obstruction in silicosis on respiratory impedance and evaluated the diagnostic efficacy of the forced oscillation technique in these patients.

METHODS: Spirometry was used to classify the airway obstruction, which resulted in four subject categories: controls ($n = 21$), patients with a normal exam ($n = 12$), patients with mild obstruction ($n = 22$), and patients with moderate-to-severe obstruction ($n = 12$). Resistive data were interpreted using the zero-intercept resistance (R_0), the resistance at 4 Hz (R_{rs4}), and the mean resistance. We also analyzed the mean reactance (X_m) and the dynamic compliance. The total mechanical load was evaluated using the absolute value of the respiratory impedance (Z_{4Hz}). The diagnostic potential was evaluated by investigating the area under the receiver operating characteristic curve. ClinicalTrials.gov: NCT01725971.

RESULTS: We observed significant ($p < 0.0002$) increases in R_0 , R_{rs4} , R_m , and Z_{4Hz} and significant reductions in $C_{rs,dyn}$ ($p < 0.0002$) and X_m ($p < 0.0001$). R_0 , R_{rs4} , R_m , and Z_{4Hz} performed adequately in the diagnosis of mild obstruction (area under the curve > 0.80) and highly accurately in the detection of moderate-to-severe obstruction (area under the curve > 0.90).

CONCLUSIONS: The forced oscillation technique may contribute to the study of the pathophysiology of silicosis and may improve the treatment offered to these patients, thus representing an alternative and/or complementary tool for evaluating respiratory mechanics.

KEYWORDS: Silicosis; Respiratory Physiopathology; Forced Oscillations; Respiratory Impedance; Diagnostic; Respiratory Mechanics.

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INTRODUCTION

Silicosis refers to pulmonary fibrosis caused by inhalation of dust that contains crystalline silica (1,2). Silicosis is an occupational disease that is chronic and incurable; it starts in the peripheral airways and can progress even after the cessation of exposure (2). Although the incidence of silicosis

has decreased since the Second World War, the disease continues to be a major cause of occupational lung disease in exposed workers (3).

Currently, the diagnosis of silicosis is based on a patient's occupational history and radiological findings. However, many cases are detected several years after exposure. The advent of high-resolution computed tomography has enabled the earlier identification of radiological signs of silicosis (2). However, this method is expensive and less commonly available, and trained professionals are necessary to perform the examination (4). Several authors have observed that changes in airway resistance, as measured by plethysmography, significantly influence the prognosis of individuals who are exposed to dust (5), but these measurements are difficult to obtain for claustrophobic patients and demand high levels of subject cooperation (6,7).

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The carbon monoxide diffusion technique may also be used; however, this technique requires a high level of expertise and patient cooperation (8). Currently, spirometry, which is a test that also requires a high degree of patient cooperation, is commonly used to assess pulmonary function in individuals with silicosis. This test, which requires patients to perform forced expirations and inspirations, can generate changes in bronchial tone that modify airway patency and rendering the indices obtained hardly physiologic (9).

There is general agreement in the literature regarding the necessity of developing new, accurate, and non-invasive tests of lung function (10-12). One of the possible methods, namely, the forced oscillation technique (FOT), may overcome the aforementioned inconveniences and may be conducted during spontaneous breathing. It was recently noted that the FOT represents the current state-of-the-art technique in the assessment of lung function (13). Several authors have argued that the FOT has the potential to improve diagnosis and the tracking of treatments and that further studies are necessary in this area (7,13,14). Previous studies from our group suggest that this technique may contribute to the detection of respiratory changes in smokers (15,16) and in patients suffering from sarcoidosis (17) and rheumatoid arthritis (18). Therefore, the FOT may facilitate the diagnosis of patients with occupational diseases (8) and enable simple, routine evaluations in these patients. However, few studies that utilize the FOT have been conducted to analyze the changes in respiratory mechanics that are associated with silicosis (6,8,19,20,21).

Based on the above-mentioned considerations, the aims of the present study were 1) to use the FOT to analyze how respiratory mechanics are affected in patients with silicosis, 2) to evaluate the potential of the FOT for detecting mild and moderate-to-severe alterations in patients with silicosis, and 3) to identify the best FOT parameters for the diagnosis of respiratory changes in silicosis patients.

■ MATERIALS AND METHODS

The present work is a transverse study that was developed at the Biomedical Instrumentation Laboratory and Pulmonary Function Laboratory at the Universidade do Estado do Rio de Janeiro (UERJ). The study was approved by the Ethics Committee of the Pedro Ernesto University Hospital (HUPE). Informed consent was obtained from all of the volunteers before inclusion in the study, which was registered at ClinicalTrials.gov (identifier: NCT01725971).

Subjects

A total of 67 subjects were analyzed. The control group (CG) included 21 subjects with normal spirometric data and without a history of smoking or pulmonary disease.

Smoking has been established as a potentially important confounding factor in the study of the pathophysiology of respiratory diseases. To eliminate this factor, 46 silicosis patients who had never smoked were analyzed. These patients were selected after an initial interview of 470 patients, 424 of whom were excluded due to their smoking history. The diagnosis of silicosis was established based on a history of substantial exposure to silica dusts and compatible radiological features, together with the exclusion of other competing diagnoses.

All of the subjects had a body mass index (BMI) of less than 29.9 kg/m². Spirometry was used to classify the airway obstruction into one of three categories (19,23): normal upon spirometric examination (NE, n = 12), mild obstruction (MO, n = 22), or moderate-to-severe obstruction (MSO = 12).

Spirometry

Measurements of forced expiratory volume in the first second (FEV₁), forced vital capacity (FVC), FEV₁/FVC, and forced expiratory flow (FEF) between 25 and 75% of FVC (FEF/FVC) were obtained for all of the patients according to the Brazilian Consensus on Spirometry (22). These parameters are presented as raw data and as a percentile of the predicted values, which were obtained from Knudson et al. (23) and Pereira et al. (24). The forced expiratory maneuvers were repeated until three sequential measurements were obtained. The indices were obtained from the best curve, which was associated with the highest value of FEV₁ plus FVC. Quality control measures for the spirometry were provided by the ATS criteria, with software used to detect non-acceptable maneuvers.

Forced Oscillation Technique

The FOT has previously been described in detail (25) and meets the international standards (26). The equipment was a standard multifrequency FOT test system that operated within the most commonly used frequency range (26,27). Briefly, a pseudorandom sinusoidal signal, which had a 2-cmH₂O peak-to-peak amplitude and contained all the harmonics of 2 Hz between 4 and 32 Hz, was applied by a loudspeaker. The pressure input was measured using a Honeywell 176 PC pressure transducer (Microswitch, Boston, MA, USA). The airflow was measured with a screen pneumotachometer coupled to a similar transducer with a matched frequency response. The signals were digitized at a rate of 1024 Hz for periods of 16 s by a personal computer, and a fast Fourier transform was computed using blocks of 4096 points with 50% overlap. To perform the FOT analysis, the subject remained in a sitting position, maintaining the head in a normal position and breathing at functional reserve capacity through a mouthpiece. During the measurements, the subject wore a nose clip and firmly supported his/her cheeks and mouth floor using both hands. A minimal coherence function of 0.9 was considered to be adequate (15-18,28). Three measurements were obtained, and the result was expressed as the mean of these three measurements.

Classical FOT parameters were used for data interpretation (26-33). A linear regression analysis over the frequency range of 4 to 16 Hz was performed to interpret the resistance results (29). The intercept resistance (R₀) was extrapolated from this analysis. This parameter is associated with the total respiratory resistance, including the Newtonian airway and tissue resistance plus the delayed airway resistance resulting from gas redistribution, and is generally employed as an index of airway obstruction (29). The mean resistance (R_m) is primarily sensitive to the airway caliber (30) and reflects the state of the central airways. The resistance at 4 Hz (R_{rs4}) was also evaluated. The slope of the linear regression (S) is related either to the intrapulmonary gas redistribution, which originates from mechanical non-homogeneities, or to the central airway compliance (29,31). Slopes that are more negative reflect more abnormal patterns of ventilation distribution.



The reactive properties were described by the following three parameters: the resonance frequency (f_r), which is defined as the frequency at which X_{rs} equals zero; the mean reactance (X_m), which is a property usually related to respiratory system non-homogeneity (32) and that is calculated based on the entire studied frequency range (4 to 32 Hz); and the dynamic compliance ($C_{rs,dyn}$). $C_{rs,dyn}$ includes the compliances of the lung and bronchial walls, the chest wall/abdominal compartment, the upper airways (associated with the soft tissues of the mouth, cheeks, and pharynx), and thoracic gas compression (30). $C_{rs,dyn}$ was estimated using X_{rs} at 4 Hz ($C_{rs,dyn} = -1/(2\pi f X_{rs})$) (33). The total mechanical load of the respiratory system, including the resistive and elastic effects (27,30), was estimated using the absolute value of respiratory impedance at 4 Hz (Z_{4Hz}). This parameter is associated with the necessary work to promote the movement of air within the respiratory system.

Data processing, data presentation, and statistical analysis

The results are presented as the mean \pm SD. A commercial software package (STATISTICA for Windows, release 5.0) was used to compare the differences between the groups. A one-way ANOVA with Tukey's test was performed to analyze the normally distributed data; conversely, a non-parametric analysis (Kruskal-Wallis) with a Mann-Whitney test was performed for the non-normally distributed data. The results with $p < 0.05$ were considered to be statistically significant. Correlations between the spirometry and FOT indices were determined using Pearson's correlation coefficient.

The clinical potential of the FOT indices for the early detection of respiratory alterations due to silicosis was evaluated using receiver operation characteristic (ROC) analyses, which were performed using Med Calc 8.2 (MedCalc Software, Mariakerke, Belgium).

RESULTS

Table 1 lists the subjects' biometric and spirometric characteristics. No significant differences were found between the groups with respect to the biometric characteristics. The spirometric parameters exhibited significant reductions with increases in airway obstruction.

The mean courses of R_{rs} and X_{rs} as a function of frequency in the normal patients and the patients with

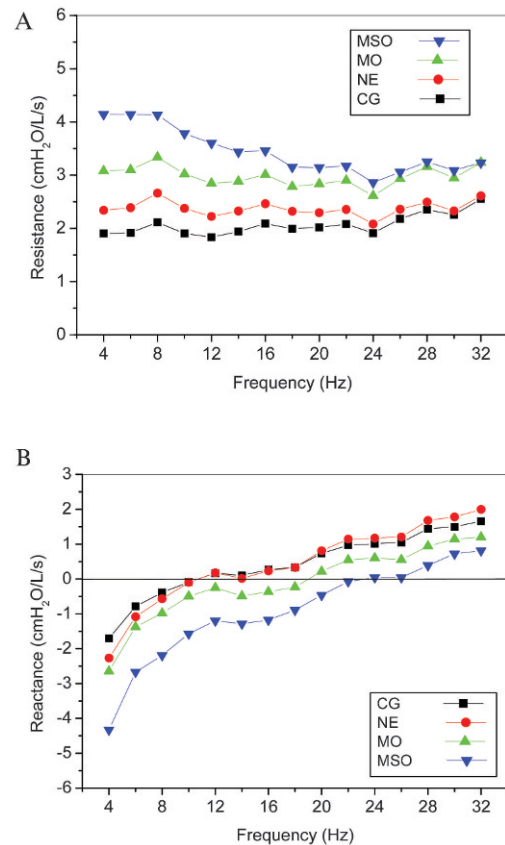


Figure 1 - Mean course of R_{rs} (A) and X_{rs} (B) as a function of frequency in the normal subjects and in the patients with silicosis. CG: control group; NE: normal upon spirometric examination; MO: mild obstruction; MSO: moderate-to-severe obstruction.

silicosis are presented in Figure 1. Parameters derived from R_{rs} are described in Figure 2, and significant increases in R_{rs4} (ANOVA, $p < 0.0002$), R_0 ($p < 0.0001$), and R_m ($p < 0.0001$), as well as decreases in S ($p < 0.0004$), were associated with the worsening of airway obstruction.

Regarding the parameters derived from X_{rs} , we observed that X_m (Figure 3A) became more negative and that $C_{rs,dyn}$ (Figure 3B) decreased with airway obstruction ($p < 0.0001$ and $p < 0.0002$, respectively).

Table 1 - Biometric and spirometric characteristics of the studied individuals.

	CG (n = 21) (group 1)	NE (n = 12) (group 2)	MO (n = 22) (group 3)	MSO (n = 12) (group 4)	Between-groups ANOVA
Male/Female	20/1	12/0	21/1	11/1	-
Age (years)	46.7 \pm 15.1	47.9 \pm 13.5	49.4 \pm 9.8	57.6 \pm 15.0	ns
Weight (kg)	69.5 \pm 11.5	69.6 \pm 12.2	69.3 \pm 9.4	65.3 \pm 13.1	ns
Height (m)	168.5 \pm 7.2	169.4 \pm 4.6	167.1 \pm 9.1	165.2 \pm 8.9	ns
BMI (kg/m ²)	24.4 \pm 3.2	24.2 \pm 3.6	24.8 \pm 2.9	23.7 \pm 4.0	ns
FVC (L)	4.2 \pm 0.6	4.21 \pm 0.7	4.1 \pm 1.0	3.1 \pm 0.8	$p < 0.001/1,2,3-4$
FVC (%)	107.8 \pm 18.6	102.9 \pm 17.4	108.5 \pm 15.3	88.7 \pm 17.1	$p < 0.01/1,2,3-4$
FEV ₁ (L)	3.6 \pm 0.6	3.4 \pm 0.5	2.8 \pm 0.6	1.6 \pm 0.5	$p < 0.001/1,2,3-4$
FEV ₁ (%)	111.2 \pm 17.7	101.3 \pm 15.8	92.9 \pm 14.1	57.7 \pm 15.3	$p < 0.001/1,2,3-4$
FEV ₁ /FVC	84.8 \pm 5.6	80.8 \pm 5.0	70.4 \pm 4.5	51.9 \pm 8.9	$p < 0.001/1,2-3-4$
FEF _{25-75%} (L)	4.3 \pm 1.2	3.3 \pm 0.6	2.0 \pm 0.3	0.8 \pm 0.4	$p < 0.001/1-2-3-4$
FEF _{25-75%} (%)	122.3 \pm 30.1	91.8 \pm 17.9	59.7 \pm 14.5	26.9 \pm 10	$p < 0.01/1-2-3-4$
FEF/FVC	101.7 \pm 29.8	79.2 \pm 18.1	52.4 \pm 15.7	26.6 \pm 9.7	$p < 0.001/1-2-3-4$

n: number of subjects; ns: non-significant ($p > 0.05$); %pred: percentage of the predicted values; comparisons of the three groups/comparisons between adjacent groups: the dashes indicate a significant difference.

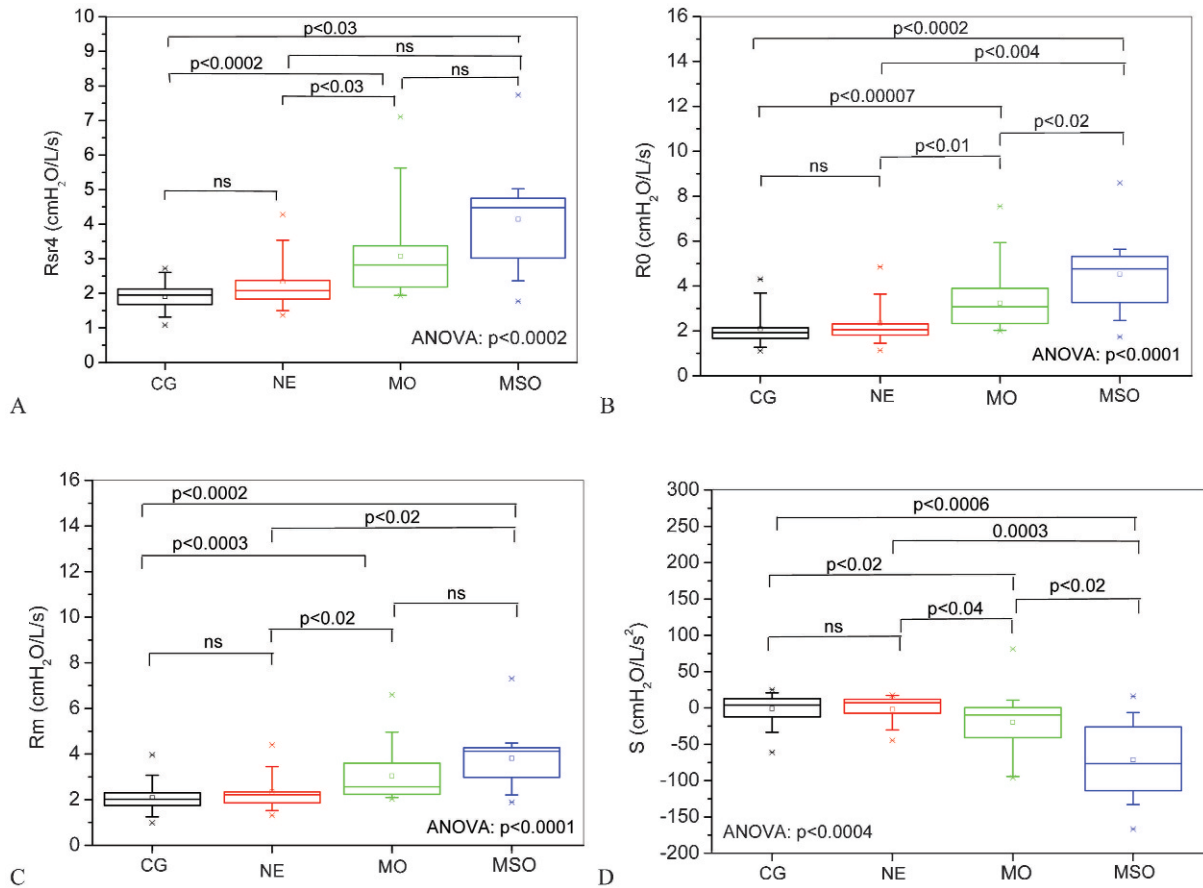


Figure 2 - Resistive parameters at 4 Hz (R_{rs4} ; A), total resistance (R_0 ; B), mean resistance (R_m ; C), and resistance slope (S ; D) in the normal subjects and in the patients with silicosis. The bottom and top of the box plot represent the 25th and 75th percentile values, respectively, while the circle represents the mean value, and the bar across the box represents the 50th percentile value. The whiskers outside the box represent the 10th to 90th percentile values.

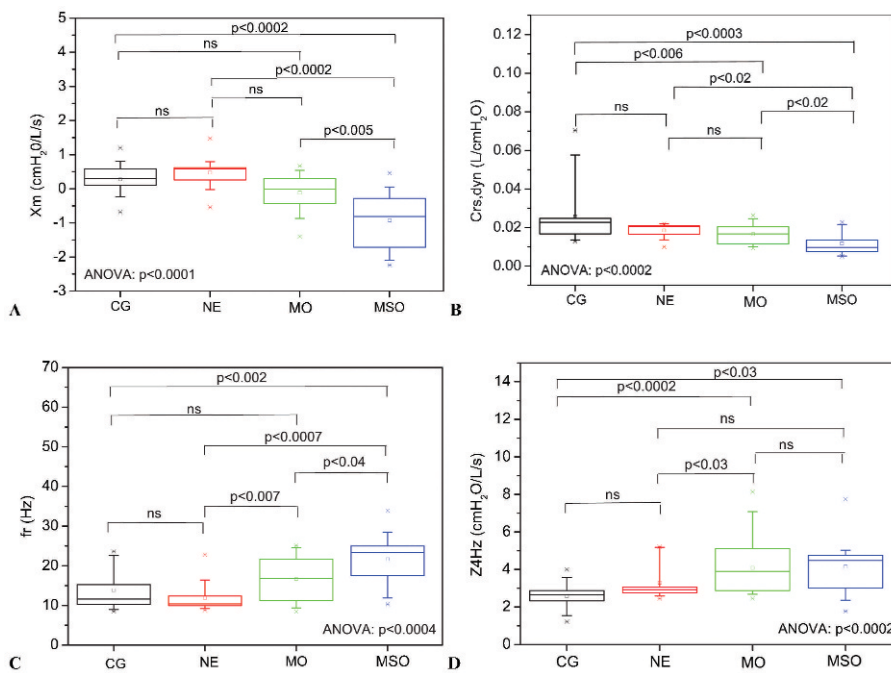


Figure 3 - Comparative analysis of the reactive parameters in the normal subjects and in the patients with silicosis. Mean values (X_m ; A), dynamic compliance of the respiratory system ($C_{dyn,rs}$; B), resonant frequency (f_r ; C), and impedance modulus at 4 Hz (Z_{4Hz} ; D).



Table 2 - Correlations between the forced oscillation technique parameters and spirometric indices.

	FVC (L)	FVC (%)	FEV ₁ (L)	FEV ₁ (%)	FEV ₁ /FVC	FEF _{25-75%} (L)	FEF _{25-75%} (%)	FEF/FVC
Resistance								
Rsr4	-0.25*	ns	-0.49***	-0.44**	-0.57***	-0.51***	-0.53***	-0.48***
R0	-0.28*	ns	-0.51***	-0.48**	-0.57***	-0.53***	-0.54***	-0.48***
Rm	-0.24*	ns	-0.45**	-0.41**	-0.49***	-0.49***	-0.51***	-0.45**
S	0.31**	ns	0.56***	0.54***	0.64***	0.51***	0.51***	0.45***
Reactance								
Xm	0.47***	ns	0.70***	0.56***	0.70***	0.63***	0.56***	0.53***
fr	-0.55***	-0.24*	-0.67***	-0.45***	-0.52**	-0.56***	ns	ns
Crs,dyn	0.50*	0.24*	0.40**	0.47***	0.61***	0.46**	0.55***	0.44**
Z4Hz	ns	ns	-0.41**	-0.38**	-0.49***	-0.44**	-0.45**	-0.42**

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.0001$; ns: non-significant ($p > 0.05$); %: percentage of the predicted values. The moderate correlations are displayed in blue.

Higher resonance frequencies were found to be associated with increased airway obstruction (Figure 3C; $p < 0.0004$). A similar behavior was found for Z4Hz (Figure 3D; $p < 0.0002$).

The correlations between the FOT and spirometric parameters are presented in Table 2. Rrs4, R0, and Rm had significant inverse correlations with the spirometric parameters (except for FVC), whereas S was directly correlated with almost all of the spirometric parameters, excluding FVC. Xm, Crs,dyn, and Z4Hz were directly correlated with all of the spirometric parameters, excluding FVC. The resonance frequency was inversely associated with the spirometric indices and did not present a significant correlation with FEF/FVC.

The parameters obtained from the ROC analysis, including the sensitivity (Se), specificity (Sp), area under the curve (AUC), and cut-off points, are described in Table 3. Rrs4, R0, Rm, and Z4Hz presented the highest AUC values (0.933, 0.905, 0.905, and 0.933, respectively).

DISCUSSION

The main findings of the present study are the following: 1) in the initial phases of airway obstruction in silicosis (NE and mild) there is a predominance of the obstructive component; 2) in contrast to earlier stages, in the late stages of airway obstruction increase (moderate-to-severe) a clear mixed pattern is developed; and 3) four of the studied FOT parameters showed great potential to enable easier detection of the abnormal respiratory effects of silicosis.

Table 3 - Values of the AUC, sensitivity, and specificity for the optimal cut-off points for the forced oscillation technique indices describing their performance in the detection of patients with mild and moderate-to-severe obstruction.

	AUC	Se (%)	Sp (%)	Cut-off
Rrs4 (cmH ₂ O/L/s)	0.885/0.933	72.7/83.3	90.5/100.0	2.19/2.72
R0 (cmH ₂ O/L/s)	0.847/0.905	81.8/83.3	81.8/90.5	2.22/2.86
Rm (cmH ₂ O/L/s)	0.829/0.905	90.9/83.3	71.4/90.5	2.19/2.73
S (cmH ₂ O/L/s ²)	0.719/0.865	68.2/75.0	66.7/90.5	3.85/25.91
Xm (cmH ₂ O/L/s)	0.716/0.897	63.6/75.0	76.2/95.2	0.07/0.28
fr (Hz)	0.662/0.841	68.2/83.3	61.9/76.2	13.54/15.25
Crs,dyn (L/cmH ₂ O)	0.747/0.889	72.7/75.0	71.4/95.2	0.018/0.013
Z4Hz (cmH ₂ O/L/s)	0.885/0.933	72.7/83.3	90.5/100.0	4.80/7.41

Values from the group with mild obstruction/values from the group with moderate-to-severe obstruction.

The forced oscillation parameters did not demonstrate systematic changes that were strictly related to spirometry (Table 2). The linear correlation coefficients between all of the spirometric and FOT parameters were evaluated, and, similar to previous studies (34-36), these coefficients were low, ranging between -0.57 and 0.70. This result indicates that the FOT and spirometry data are complementary, each providing unique data, thereby confirming the ability of FOT to provide additional information on the mechanical characteristics of the respiratory system.

Pathophysiology

The FOT exams allowed us to obtain additional information from parameters that are easily associated with mechanical and structural properties of the respiratory system, including respiratory (R0) and airway (R4Hz, Rm) resistance, elastance (Crs,dyn), homogeneity (S, Xm, fr), and work of breathing (Z4Hz) (26-33). Based on these parameters, FOT may provide insight into both the obstructive and restrictive components of silicosis, thereby improving our understanding of the lung mechanics and how they change during this disease. However, this understanding may be impaired by the inclusion of data from smoking patients, which is an important confounding factor. We expended considerable effort to perform this pathophysiological study in a sample of never-smoking patients, thus eliminating this important confounding factor and precisely describing the effects of silicosis. The results of the present study demonstrated that the initial phases of airway obstruction in silicosis (NE and mild obstruction) cause a decrease in respiratory system homogeneity, which is primarily associated with changes in the resistive properties of the respiratory system (Figure 2C). This disease stage was also characterized by a decrease in Crs,dyn (Figure 3B) and an increase in the respiratory work (Figure 3D). These results provide evidence that, although the obstructive component predominates during this stage of the disease, changes in the elastic properties also exist, which suggests that a mixed pattern of disease develops.

The subsequent increase in airway obstruction (mild to moderate) is characterized by a significant rise in respiratory resistances (Figures 2A, B, C) and a decrease in the homogeneity associated with imbalances in the resistive (Figure 1D) and elastic (Figure 3A) airway properties. A further decrease in Crs,dyn (Figure 3B) and increased values of respiratory work (Figure 3D) are also characteristics of this more advanced disease state. These findings provide clear evidence that a mixed disease pattern develops during the latter stages of silicosis. Below, we discuss in detail the



pathophysiological changes that can be described by the FOT.

Silica is a mineral oxide dust that exists as a crystal structure of silicon dioxide (SiO_2). Once silica particles reach the alveoli, they are ingested by alveolar macrophages. Silica causes toxicity by directly stimulating the inflammatory process and the proliferation of fibroblasts (3). This process may partly explain the increase in R_{rs4} together with the worsening of airway obstruction, as depicted in Figure 2A. In agreement with the present study, Yang et al. (21) observed higher levels of R_{rs} , measured at 3 Hz, in coal miners compared with healthy subjects.

Similar to R_{rs4} , R_0 (Figure 2B) increased with increasing obstructive disturbances, which is a finding that confirms the results of previous studies (8). Pham et al. (8) analyzed coal miners and obtained results similar to ours, with higher levels of R_0 in symptomatic workers compared with asymptomatic workers.

In agreement with the results obtained regarding obstructive diseases (28,36) and subjects with silicosis (6,8,19), R_m increased with airway obstruction (Figure 1C). This increase describes the typical pathophysiology of silicosis, which includes inflammation, tissue damage, fibrosis, and lung remodeling. R_m presented reasonable but significant correlation with the spirometric parameters related to the more peripheral airways (Table 2). As respiratory alterations begin at these points of the bronchial tree, we speculate that R_m may be useful in the early identification of silicosis.

The slope of the resistive component reflects the homogeneity of the respiratory system. In the present study, S was significantly more negative in the silicosis subjects with worse airway obstruction (Figure 1D). Similar results are described in the literature (6,8,21). The extensive replacement of the pulmonary parenchyma by fibrous tissue and the thickened alveolar septum in patients with silicosis may contribute to local changes in elasticity. This shift, in turn, may cause an imbalance in the time constants of the respiratory system and contribute to the increase in system heterogeneity (3).

The significant modification of the X_m values with airway obstruction (Figure 3A) was consistent with a previous pilot study (20) and previous studies of obstructive diseases (26,28,36). X_m is generally associated with respiratory heterogeneity. In silicosis, heterogeneity may result from a combination of reduced respiratory system compliance and higher peripheral resistance. Inflammation and airway wall remodeling may also be involved in this process (3,21). In contrast with the present study, Faria et al. (17) found significant changes in X_m when comparing a control group with subjects with sarcoidosis and normal spirometry values. These discrepant findings may be explained by differences in the pathophysiology of silicosis and sarcoidosis.

$C_{rs,dyn}$ reflects the combined effects of the pulmonary and chest wall tissue, as well as the compliance of the airways (27-29). The values of $C_{rs,dyn}$ diminished significantly with airway obstruction (Figure 3B). In agreement with our results, Pham et al. (8) obtained lower $C_{rs,dyn}$ values in symptomatic individuals with pneumoconiosis. Using the esophageal balloon technique, Van Noord et al. (37) observed a reduction in the pulmonary static compliance in patients with interstitial lung disease and a predicted TLC of <50%. In the same study, the authors

found decreased lung volumes in conjunction with increased resistances (R_{rs}) and decreased reactances (X_{rs}), and this trend was more obvious at low frequencies. Because tissue resistance is inversely related to lung compliance (37), these results are consistent with the findings of our study, namely the increase in R_0 and a decrease in $C_{rs,dyn}$.

The description of the pathophysiology of silicosis using $C_{rs,dyn}$ suggests that the FOT may be an alternative method to the use of esophageal balloons for evaluating these individuals. Thus, because the measurement is noninvasive, $C_{rs,dyn}$ may be useful as a functional parameter in monitoring silicosis.

In the present study, we observed higher values of f_r in individuals with silicosis compared with the control group. These results were more pronounced with increased airway obstruction (Figure 3C). Similar results have been described in obstructive diseases (28,36). In contrast with our findings, Faria et al. (17) found no significant difference for f_r in sarcoidosis. It is possible that f_r , which expresses the inertial and elastic properties of the respiratory system and acts as an indicator of the homogeneity of this system (37), is not the most suitable parameter for identifying obstructive changes associated with this disease. Pleuropulmonary involvement in silicosis (3) produces changes in elasticity and dynamic compliance that contribute to a loss of ventilation homogeneity (19). These factors may explain our findings.

We observed a progressive increase in Z_{4Hz} with airway obstruction (Figure 3D). The changes in the resistive and elastic properties of the respiratory system resulting from the pathophysiology of silicosis may explain the significant increase in this parameter. Similar results have been described in the literature regarding sarcoidosis (17). This parameter is related to the total mechanical load of the respiratory system (27,30) and may therefore be associated with fatigue and shortness of breath, which are common symptoms in patients with silicosis (1-3).

Diagnostic accuracy in patients with mild and moderate-to-severe obstruction

An $AUC \geq 0.80$ is generally considered to be adequate for clinical use (38,39). In the comparison between the control group and patients with mild obstruction (Table 3), R_{rs4} , R_0 , R_m , and Z_{4Hz} all had an $AUC \geq 0.80$, making them suitable for clinical use. As expected, we observed higher AUCs in the analysis that compared the control group with patients exhibiting moderate-to-severe obstruction (3). S , X_m , f_r , and $C_{dyn,rs}$ presented sufficient accuracy for clinical use ($AUC > 0.80$), while R_{rs4} , R_0 , R_m , and Z_{4Hz} presented high diagnostic accuracy ($AUC > 0.90$). These results confirm the preliminary findings from our group (20), namely that R_0 and R_m presented high accuracy ($AUC = 0.90$) in the analysis comparing the control and MO groups. In close agreement with these findings, Pham et al. (8) determined that R_0 and R_m are the more accurate parameters for identifying individuals with obstructive coal miner's pneumoconiosis.

The FOT is a useful measure in research and potentially in routine clinical medicine because the associated exams are conducted during normal tidal breathing. Therefore, the FOT is easy to conduct and can provide information that is applicable to resting conditions. Other pulmonary function tests require maximum-effort maneuvers that are not



encountered during daily activities (40); thus, extrapolation to patient symptoms may be difficult. Another important characteristic of the FOT is that it provides information about the mechanical properties of the respiratory system that is complementary to that provided by traditional lung function tests (7,13,26). However, the routine clinical use of the FOT has yet to gain full acceptance. Although interest in the approach is growing and the technique shows considerable promise (6-9,13-21,25-37,41), realizing this promise remains a work in progress.

Limitations of the study

Similar to other functional assessment techniques, the limitations of the FOT and its consequences must be recognized. First, an important source of errors is related to the process of spontaneous breathing in patients, which introduces random and systematic errors. These errors are reduced by using excitation frequencies that are at least 10 times higher than those present during the spontaneous ventilation process and by using appropriate acceptance criteria (13,25,26,30). In the present study, these errors were minimized by using a minimal coherence function (γ^2) value of 0.9, which is usually considered to be adequate (30).

Second, the measurement of respiratory impedance may be influenced by the shunt effect of the upper airway walls (26,27). This effect becomes progressively stronger as the resistance of the pulmonary airways increases because fewer of the imposed flow oscillations are able to move beyond the upper airway shunt and make their way into the lungs. In practice, this drawback is minimized by asking the patient to firmly support his/her cheeks and mouth floor (26,27).

Although this study focused on the effect of airway obstruction on the resistive and reactive properties of the respiratory system, inclusion of the diffusion capacity and lung volumes in the analysis would have been beneficial. These factors may contribute to a more detailed study of the pathophysiology of silicosis and should be addressed in future research.

One of the primary objectives of the present work was to increase our understanding of the pathophysiological changes that are observed when patients with silicosis are examined using the most common, current pulmonary function method. This aim explains why spirometry was used as the gold standard. Another interesting possibility for future work is the comparison of the accuracies of the FOT and spirometry using computer tomography (CT) as a reference technique. In a previous study (19), we evaluated the associations between the CT and pulmonary function findings that were obtained by the FOT and spirometry. However, the present study did not employ CT as a gold standard. We are planning to perform this analysis in the next step of this research.

FOT analysis contributed further insights into how the respiratory system is affected by silicosis. The initial phases of airway obstruction in silicosis were observed to be mainly characterized by the increase in the respiratory system's resistive parameters. More advanced phases of airway obstruction are characterized by a significant reduction in the respiratory system's dynamic compliance, which is consistent with a mixed disease pattern. Rrs4, R0, Rm, and Z4Hz were shown to be useful for accurately and non-invasively identifying mild and mild-to-moderate modifications of the respiratory mechanics of patients with silicosis.

These results indicate that the FOT may contribute to the study of the pathophysiology of silicosis and to an improvement of the treatment that is offered to these patients. Therefore, this technique may represent an alternative and/or complementary tool for evaluating respiratory mechanics via forced expiration.

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AUTHOR CONTRIBUTIONS

Sá PM conducted the measurements for this study, analyzed the data, and drafted the manuscript. Lopes AJ provided data and subject identification. Jansen JM mentored Sá PM and participated in data analysis process. Melo PL mentored Sá PM, organized the study and helped to draft the manuscript. All the authors have read and approved the manuscript.

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