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FULL PAPER

Relationships between the pulmonary densitometry values obtained by CT and the forced oscillation technique parameters in patients with silicosis

^{1,2}A J LOPES, MD, PhD, ^{1,3}R MOGAMI, MD, PhD, ^{1,3}G B CAMILO, MD, MSc, ^{1,3}D C MACHADO, MD, MSc, ^{1,4,5}P L MELO, BME, PhD and ^{6,7}A R S CARVALHO, PT, PhD

¹Postgraduate Programme in Medical Sciences, State University of Rio de Janeiro, Rio de Janeiro, Brazil

²Laboratory of Pulmonary Function, University of the State of Rio de Janeiro, Rio de Janeiro, Brazil

³Department of Radiology, State University of Rio de Janeiro, Rio de Janeiro, Brazil

⁴Biomedical Instrumentation Laboratory, Institute of Biology and Faculty of Engineering, State University of Rio de Janeiro, Rio de Janeiro, Brazil

⁵Postgraduate Program in Clinical and Experimental Physiopathology (FISCLINEX), School of Medical Sciences, State University of Rio de Janeiro, Rio de Janeiro, Brazil

⁶Laboratory of Respiration Physiology, Carlos Chagas Filho Institute of Biophysics, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

⁷Laboratory of Pulmonary Engineering, Biomedical Engineering Program, Alberto Luis Coimbra Institute of Post-graduation and Research in Engineering, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

Address correspondence to: Dr Agnaldo José Lopes

E-mail: agnaldolopes.uerj@gmail.com

Objective: To evaluate the correlations between pulmonary densitometry values and forced oscillation technique (FOT) parameters in patients with silicosis.

Methods: This cross-sectional study comprised 36 non-smoker patients with silicosis and 20 matched control subjects who were submitted to FOT and multidetector CT (MDCT).

Results: Compared with the control subjects, the MDCT evaluation demonstrated that patients with silicosis exhibited greater total lung mass. These patients also had larger non-aerated and poorly aerated compartments, which included nodules and scarring. Compared with the control subjects, FOT evaluation demonstrated that patients with silicosis exhibited changes in both reactive and resistive properties of the respiratory system. In these patients, there was a greater heterogeneity of the respiratory system and increased work of breathing. Significant correlations between non-aerated

compartment size and FOT parameters that reflect the non-homogeneity of the respiratory system were observed. The dynamic compliance of the respiratory system was negatively correlated with non-aerated compartment size, while the impedance at 4 Hz was positively correlated with non-aerated compartment size.

Conclusion: Patients with silicosis have heavier lungs. In these patients, a larger non-aerated compartment is associated with a worsening of lung function. A more significant pulmonary involvement is associated with a loss of homogeneity and increased mechanical load of the respiratory system.

Advances in knowledge: The findings provided by both pulmonary densitometry and FOT may add valuable information to the subjective analysis of silicosis; however, more studies are necessary to evaluate the potential use of these methods for assessing disease progression.

Silicosis is a lung disease caused by inhaling crystalline silica, which induces a fibrogenic reaction in the tissue, and represents the most common pneumoconiosis.¹ Silicosis is a preventable but incurable disease that can be fatal owing to significant health impairment. The most common occupations at risk for silicosis are those involving tunnels, quarry and mine drilling, and foundry activities.² Simple silicosis is characterized by the presence of multiple nodules measuring 1–10 mm in diameter that are distributed predominantly in the superior and posterior segments of the upper lobes. Complicated silicosis, also called

progressive massive fibrosis (PMF), is characterized by the presence of large opacities with homogeneous consolidation areas that mainly affect the superior and middle segments of the lungs.^{3,4}

CT, especially high-resolution CT (HRCT), has been considered the best test for assessing environmental and occupational respiratory diseases.^{5–8} Lopes et al⁹ reported that in cases of silicosis, HRCT is superior to chest radiography in both the early detection of the disease as well as the identification of PMF. With technological advances and

the development of multidetector CT (MDCT),¹⁰ the chest can be scanned in one apnoea, and high-resolution thin sections can be quickly obtained. Volumetric acquisition has proven ideal for generating images reformatted into coronal, sagittal and oblique planes and in curved multiplanar reconstructions; it also assists in the evaluation of occupational diseases by depicting changes in a more anatomical manner.¹¹ In addition, image processing through lung volume quantification using MDCT (Q-MDCT) has the potential advantage of estimating regional volumes in different compartments that are already determined by classifications previously proposed in the literature.^{12–16}

The forced oscillation technique (FOT) is a simple method to investigate the mechanical properties of the respiratory system and represents the current state-of-the-art in the assessment of lung function.¹⁷ FOT characterizes the respiratory impedance and its two components: respiratory system resistance and reactance. These parameters are typically measured at various frequencies using small-amplitude pressure oscillations superimposed on the spontaneous breathing of the individual. FOT has a high potential to increase our understanding of the pathophysiology of respiratory diseases as well as to aid in the diagnosis of abnormalities resulting from these diseases.^{18–20} In silicosis, de Mesquita Júnior *et al*²¹ and Sá *et al*²² reported that the reduction of spirometric parameters promoted increased resistive properties, decreased reactive properties and decreased homogeneity of the respiratory system measured by FOT.

Despite the high potential of FOT in occupational disease, few studies in the literature have addressed this subject, and to the best of our knowledge, there are no studies associating FOT and CT results. Because Q-MDCT allows the evaluation of lung aeration distribution and the calculation of volume in different areas of the lung, we hypothesized that both Q-MDCT and FOT can be useful tools for the evaluation of patients with silicosis and that there is an association between pulmonary structure and function in these individuals. Therefore, this study aimed to evaluate the correlations between the pulmonary densitometry values obtained by CT and FOT parameters in patients with silicosis.

METHODS AND MATERIALS

Patients

This cross-sectional study included 58 patients with silicosis and was conducted between January 2008 and October 2010. The diagnosis of silicosis in workers with a history of silica dust exposure was established by the presence of a chest radiograph classified as category $\geq 1/0$ according to the International Labour Organization.²³ The exclusion criteria were as follows: history of smoking, radiological findings suggestive of pulmonary tuberculosis, and heart or neuromuscular diseases. The control group included 23 individuals aged more than 18 years (17 males), all non-smokers with no history of lung disease or exposure to silica, and normal chest CT. These control subjects were asked to perform FOT after undergoing chest CT scan in our service owing to the following reasons: staging of tumours ($n = 8$); evaluation of trauma ($n = 6$); investigation of contact with tuberculosis patients ($n = 5$); and evaluation of fever of unknown origin ($n = 4$).

All participants signed an informed consent form. The protocol was approved by the Research Ethics Committee of the State University of Rio de Janeiro, Rio de Janeiro, Brazil, under number 1117.

Body plethysmography

Measurements of total lung capacity (TLC) were conducted using the Collins Plus Pulmonary Function Testing Systems (Warren E Collins, Inc., Braintree, MA), following the standards set by the American Thoracic Society/European Respiratory Society. On a body plethysmograph, measurements were made with the subject panting shallowly at a rate of one to two breaths per second with an open glottis. The reported thoracic gas volume was averaged from three to five acceptable panting manoeuvres.²⁴

Forced oscillation technique

The FOT device was developed in the Biomedical Instrumentation Laboratory of the State University of Rio de Janeiro and has been previously described.²⁰ Briefly, the system applies a pseudorandom pressure signal of low amplitude containing all of the 2-Hz harmonics between 4 and 32 Hz to the respiratory system of the individual. The pressure at the inlet is measured using a Honeywell 176 PC transducer (Honeywell Microswitch, Boston, MA), and the airflow is measured using a pneumotachograph attached to a similar transducer. Pressure and flow signals are measured in 16-s periods, and the respiratory impedance is estimated by calculating the ratio between the Fourier transform of the applied pressures and the Fourier transform of the resulting flow, obtained for each frequency applied. During FOT measurements, the individuals remained seated and wore a nose clip; the patients supported their cheeks and chin with their hands while breathing calmly through a mouthpiece. A minimum coherence value of 0.9 was considered acceptable for the tests. Three measurements were made, and the median was calculated to obtain the final test result.^{19,20}

Classical FOT parameters were used in data interpretation.^{18,25–29}

The resonance frequency (Fr) is defined as the frequency at which the reactance equals zero and is associated with the homogeneity of the respiratory system.²⁵ The mean reactance (X_m) is a property usually related to respiratory system non-homogeneity and is calculated based on the entire studied frequency range (4–32 Hz). The dynamic compliance of the respiratory system (C_{dyn}) was estimated using the reactance (X_{rs}) at 4 Hz with the equation $C_{dyn} = -1/(\omega X_{rs})$.²⁶ The analysis of linear regression in the resistive component of the impedance in the frequency range between 4 and 16 Hz was used to determine the intercept resistance (R_0).³⁰ The mean of the resistance values in the range mentioned was used to estimate the mean resistance (R_m). The total energy loss through heat production in the respiratory system is described as intercept resistance, and mean resistance describes the energy loss related to the airways.¹⁹ The slope of the resistive component of the respiratory impedance (S) was also obtained and is associated with respiratory system homogeneity.^{19,20} Therefore, both reactive (Fr , X_m and C_{dyn}) and resistive (R_0 , R_m and S) properties of the respiratory system were evaluated. Moreover, the impedance at 4 Hz (Z_{rs4Hz}) was also estimated to evaluate the total mechanical load of the respiratory system.

Pulmonary densitometry

The CT images were acquired on a helical CT scanner with 64 channels (Brilliance 40; Philips Medical Systems, Cleveland, OH). The readout time was set to 4 s, with an X-ray tube current of 458 mA and voltage of 120 kVp. Each image acquisition consisted of a block with 2-mm-thick cross sections separated by 1 mm. The images were represented by a square matrix of 768 rows and 768 columns. In all subjects, the images were obtained during inspiration. Iodinated contrast agent was not used in any test.

The next step was segmentation of the lung parenchyma. Subsequently, images were exported according to the instructions of the DICOMDIR file in software (CT processing) written in MATLAB® (MathWorks®, Natick, MA) in the Laboratory of Respiration Physiology, Carlos Chagas Filho Institute of Biophysics, and Laboratory of Pulmonary Engineering, Biomedical Engineering Program, Alberto Luis Coimbra Institute of Post-graduation and Research in Engineering, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil, and the pulmonary densitometry could be performed at the end of the entire process.

Total lung volume (TLV), total air volume (TAV) and total lung mass (TLM) were calculated only in images within the region of interest (lung parenchyma). The TLV (*i.e.* the sum of air plus tissue volume) was calculated as follows: $[(\text{size of the pixel})^2 \times \text{slice thickness} \times \text{total number of pixels of the region of interest for the whole lung}]$. The X-ray attenuation of each pixel, expressed in Hounsfield units (HU), was calculated by the density

(mass/volume ratio) of the tissue and shown as the CT number, that is, $\text{CT}/(-1000) = [\text{volume of gas}/(\text{volume of gas} + \text{volume of tissue})]$.^{12,14,31} This CT number is achieved, in any given pixel, by determining the percentage of radiation absorbed by that volume of the lung. Then, the weight of the lungs was calculated as follows: $[(1 - \text{CT}/(-1000)) \times (\text{size of the pixel})^2 \times \text{slice thickness} \times \text{total number of pixels of the region of interest for the whole lung}]$.^{12,14,32,33} The weight of the lungs was the sum of the weight of all selected pixels.^{12,14}

The study of the distribution of aeration was performed to evaluate the frequency distribution of voxels as a function of the density in HU, where the histogram of voxel distribution was divided in compartments between -1000 and +100 HU. The number of voxels in each compartment was analysed as a fraction of the number of voxels present within the region of interest. The images were analysed to calculate the percentages of hyperaerated (-1000 to -900 HU), normally aerated (-900 to -500 HU), poorly aerated (-500 to -100 HU) and non-aerated (-100 to +100 HU) compartments in TLV (Figure 1). The hyperaerated compartment includes emphysema while the non-aerated compartment includes nodules and scarring.^{12,14,34}

Data analysis

To check the homogeneity of the sample, Kolmogorov–Smirnov's test was used; if a meaningful number of variables did not have a normal distribution, then non-parametric tests were selected. The results are expressed as the median and inter-quartile range values or as frequencies (percentage). Numerical variables and categorical variables were compared using the

Figure 1. Three-dimensional (3D) images of the lungs reconstructed from the binary matrix of the region of interest in the anteroposterior view (top left). The 3D representation (posteroanterior view) of the lung parenchyma and each compartment reveals the hyperaerated compartment (red), the poorly aerated compartment (light grey), the non-aerated compartment (black) and the normally aerated compartment (blue).

Mann–Whitney *U* test and the Fisher's exact test, respectively. Spearman's rank correlation coefficient (*rs*) was calculated to investigate associations. Data analysis was performed using SAS® v. 6.11 software (SAS Institute Inc., Cary, NC). The statistical significance level was set at $p < 0.05$.

RESULTS

Of the 58 patients with silicosis initially recruited, 22 were excluded for the following reasons: history of smoking (15), imaging findings consistent with pulmonary tuberculosis (4), cardiac disease (2) and neuromuscular disease (1).

A total of 33 participants were male and three were female. The median age was 46.5 years (interquartile range, 38.5–57.0 years). Sandblasting and stone cutting were the professional activities most often cited (47.2% and 30.5%, respectively). According to the chest radiograph, 44.4% of participants were diagnosed with simple silicosis, whereas 55.6% were diagnosed with complicated silicosis. When compared with the control subjects, FOT revealed

that patients with silicosis exhibited higher values of intercept resistance, mean resistance, resonant frequency and impedance at 4 Hz. When compared with the control subjects, these patients showed lower values of resistance curve angular coefficient, mean reactance and dynamic compliance of the respiratory system. The general characteristics and pulmonary function parameters of the patients with silicosis and the control group are outlined in Table 1.

Q-MDCT revealed that patients with silicosis exhibited higher TLM values compared with the control subjects. These patients also exhibited larger non-aerated (including nodules and scarring) and poorly aerated compartments, as calculated in millilitre, % TLV, grams and %TLM. Table 2 presents a comparison of the CT findings between patients with silicosis and control subjects.

We compared the patients with simple and complicated silicosis. Patients with complicated silicosis had lower values of mean reactance $[-0.35 (-0.88 \text{ to } 0.05) \text{ vs } -0.13 (-0.46 \text{ to } 0.20) \text{ cmH}_2\text{O l}^{-1} \text{ s}^{-2}$; $p = 0.018$] and higher values of impedance at 4 Hz $[4.36 (3.68\text{--}6.43)$

Table 1. General characteristics and pulmonary function parameters of patients with silicosis and the control group

Variable	Patients with silicosis ($n = 36$)	Control group ($n = 23$)	<i>p</i> -value
Demographic data			
Age (years)	46.5 (38.5–57)	42.5 (32–54)	0.415
Male (%)	33 (91.7)	17 (73.9)	0.220
Clinical data			
Duration of silica exposure (years)	15 (10–20)	–	–
Time since withdrawal (years)	14 (10–18.5)	–	–
Professional activity			
Sandblasting	17 (47.2)	–	–
Stone cutting	11 (30.6)	–	–
Marble quarrying	3 (8.33)	–	–
Foundry work	2 (5.56)	–	–
Dental prosthesis design	1 (2.78)	–	–
Grinding	1 (2.78)	–	–
Rock quarrying	1 (2.78)	–	–
Body plethysmography			
Total lung capacity (l)	5.19 (3.99–5.84)	5.01 (3.61–5.72)	0.882
Forced oscillation technique			
R_0 ($\text{cmH}_2\text{O l}^{-1} \text{ s}^{-1}$)	3.47 (2.55–4.42)	2.60 (2.04–3.41)	0.012
R_m ($\text{cmH}_2\text{O l}^{-1} \text{ s}^{-1}$)	3.32 (2.50–4.07)	2.41 (1.95–2.95)	0.017
S ($\text{cmH}_2\text{O l}^{-1} \text{ s}^{-2}$)	$-28.7 (-66.0 \text{ to } 2.93)$	$-20.2 (-41.0 \text{ to } 6.15)$	0.033
F_r (Hz)	20.2 (15.1–24.4)	10.3 (8.95–16.1)	0.021
X_m ($\text{cmH}_2\text{O l}^{-1} \text{ s}^{-2}$)	$-0.31 (-0.85 \text{ to } 0.10)$	0.43 (0.28–0.85)	0.005
C_{dyn} [$\text{l (cmH}_2\text{O)}^{-1}$]	0.014 (0.009–0.018)	0.019 (0.014–0.027)	0.015
Z_{rs4Hz} ($\text{cmH}_2\text{O l}^{-1} \text{ s}^{-1}$)	4.28 (3.22–6.09)	3.30 (2.54–4.32)	0.008

C_{dyn} , dynamic compliance of the respiratory system; F_r , resonant frequency; R_0 , intercept resistance; R_m , mean resistance; S , resistance curve angular coefficient; X_m , mean reactance; Z_{rs4Hz} , impedance at 4 Hz.

Data are given as median (interquartile range) or number (%).

Bold values indicate significant differences.

Table 2. Values of pulmonary densitometry obtained by CT according to the group

Variable	Patients with silicosis	Control group	<i>p</i> -value
TLV (ml)	4416 (3696–5289)	4198 (3677–5165)	0.552
Total air volume (ml)	3406 (2653–4234)	3587 (3154–4551)	0.548
TLM (g)	996 (882–1130)	654 (572–683)	0.008
Non (ml)	148 (83.1–205)	11.8 (7.40–15.2)	0.0001
Poor (ml)	259 (199–337)	76 (61.5–88)	0.0001
Norm (ml)	2920 (2501–3313)	2744 (2594–3290)	0.065
Hyper (ml)	1078 (705–1841)	1142 (938–1879)	0.100
Non (%TLV)	2.95 (1.69–5.37)	0.23 (0.18–0.30)	0.0001
Poor (%TLV)	5.37 (3.92–8.96)	1.67 (1.42–2.10)	0.005
Norm (%TLV)	64.9 (60.2–68.4)	69.7 (58.3–79.5)	0.060
Hyper (%TLV)	25.2 (20.3–33.5)	29.5 (20.8–41.0)	0.054
Non (g)	148 (82.6–208)	11.5 (7.10–14.2)	0.0001
Poor (g)	174 (129–221)	53.8 (40.5–58.1)	0.002
Norm (g)	607 (512–663)	523 (458–670)	0.084
Hyper (g)	64.7 (41.7–105.7)	80.3 (64.7–131.4)	0.156
Non (%TLM)	14.2 (9.0–20.5)	1.52 (1.22–2.10)	0.0001
Poor (%TLM)	17.2 (13.9–21.3)	7.20 (6.31–8.37)	0.003
Norm (%TLM)	61.8 (53.2–67.5)	78.4 (70.1–83.6)	0.075
Hyper (%TLM)	6.78 (4.42–9.84)	14.2 (8.13–19.5)	0.033

Hyper, hyperaerated compartment; non, non-aerated compartment; norm, normally aerated compartment; poor, poorly aerated compartment; TLM, total lung mass; TLV, total lung volume.

Data are given as median (interquartile range).

Bold values indicate significant differences.

vs 3.88 (2.85–5.24); $p = 0.021$]. Regarding lung densitometry, patients with complicated silicosis had higher values of non-aerated compartments [182 (100.0–256.3) vs 98.2 (60.5–134.6) ml; $p = 0.008$; 182.5 (102.3–246.0) vs 92.0 (75.4–172.9) g; $p = 0.013$] and hyperaerated compartments [1302 (925–2025) vs 994 (547–1520) ml; $p = 0.024$].

We also evaluated the correlations between the pulmonary densitometry findings and the pulmonary function parameters of the patients with silicosis (Table 3, Figures 2 and 3). In these patients, the highest values of TLV and TAV were associated with the highest values of TLC, mean reactance and dynamic compliance of the respiratory system. TLC was also positively correlated with hyperaerated compartment size calculated in millilitres ($rs = 0.749$; $p < 0.001$), %TLV ($rs = 0.626$; $p < 0.001$), grams ($rs = 0.763$; $p < 0.001$) and %TLM ($rs = 0.618$; $p < 0.001$). Resonant frequency was positively correlated with non-aerated compartment size calculated in millilitres ($rs = 0.486$; $p < 0.005$), %TLV ($rs = 0.529$; $p < 0.001$), grams ($rs = 0.488$; $p < 0.005$) and %TLM ($rs = 0.540$; $p < 0.001$). Mean reactance was negatively correlated with non-aerated compartment size calculated in millilitres ($rs = -0.517$; $p < 0.005$), %TLV ($rs = -0.582$; $p < 0.001$), grams ($rs = -0.520$; $p < 0.005$) and %TLM ($rs = -0.576$; $p < 0.001$). Dynamic compliance of the respiratory system was negatively correlated with non-aerated compartment size

calculated in millilitres ($rs = -0.481$; $p < 0.005$), %TLV ($rs = -0.548$; $p < 0.001$), grams ($rs = -0.484$; $p < 0.005$) and %TLM ($rs = -0.552$; $p < 0.001$). Finally, impedance at 4 Hz was positively correlated with non-aerated compartment size calculated in %TLV ($rs = 0.435$; $p < 0.001$) and %TLM ($rs = 0.437$; $p < 0.001$).

In patients with simple silicosis, the larger non-aerated compartment size (which is basically composed of nodules) in %TLV was associated with lower values of mean reactance (-0.429 ; $p < 0.01$) and dynamic compliance of the respiratory system (-0.405 ; $p < 0.05$). Moreover, the higher non-aerated compartment weight in %TLM was associated with lower value of mean reactance (-0.411 ; $p < 0.05$).

DISCUSSION

The main findings of this study were as follows: (1) patients with silicosis exhibited changes in both reactive and resistive properties of the respiratory system; (2) these patients had heavier lungs with larger non-aerated and poorly aerated compartments in the lung parenchyma; (3) the larger non-aerated compartment size was associated with a non-homogeneity and reduced compliance of the respiratory system as measured by FOT; (4) both the larger hyperaerated compartment size and the higher hyperaerated compartment weight were associated with higher values of TLC;

Table 3. Spearman's correlation coefficients between the pulmonary densitometry values and the pulmonary function parameters of the patients with silicosis

Variable	Total lung capacity	R0	Rm	S	Fr	Xm	Cdyn	Zrs4Hz
TLV (ml)	0.806 ^a	-0.251	-0.227	0.035	-0.323	0.432 ^b	0.444 ^b	-0.366
Total air volume (ml)	0.829 ^a	-0.267	-0.236	0.078	-0.370	0.480 ^c	0.481 ^c	-0.392
TLM (g)	0.287	-0.066	-0.063	-0.116	-0.011	0.046	0.103	-0.109
Non (ml)	-0.236	0.228	0.115	-0.323	0.486 ^c	-0.517 ^c	-0.481 ^c	0.368
Poor (ml)	-0.151	0.003	-0.015	-0.113	0.119	-0.161	-0.127	0.046
Norm (ml)	0.601 ^a	-0.233	-0.148	0.088	-0.369	0.475 ^c	0.492 ^c	-0.372
Hyper (ml)	0.749 ^a	-0.221	-0.228	0.088	-0.318	0.383	0.370	-0.312
Non (% TLV)	-0.383	0.256	0.132	-0.315	0.529 ^a	-0.582 ^a	-0.548 ^a	0.435 ^b
Poor (% TLV)	-0.529 ^a	0.083	0.080	-0.053	0.222	-0.306	-0.282	0.182
Norm (% TLV)	-0.506 ^c	0.110	0.154	0.002	0.096	-0.063	-0.068	0.098
Hyper (% TLV)	0.626 ^a	-0.148	-0.179	0.059	-0.249	0.265	0.248	-0.207
Non (g)	-0.236	0.231	0.114	-0.328	0.488 ^c	-0.520 ^c	-0.484 ^c	0.372
Poor (g)	-0.153	0.013	-0.015	-0.136	0.149	-0.191	-0.151	0.066
Norm (g)	0.334	-0.141	-0.064	0.039	-0.236	0.299	0.329	-0.253
Hyper (g)	0.763 ^a	-0.233	-0.236	0.083	-0.332	0.407 ^d	0.391	-0.327
Non (%TLM)	-0.285	0.256	0.110	-0.349	0.540 ^a	-0.576 ^a	-0.552 ^a	0.437 ^b
Poor (%TLM)	-0.394	0.049	0.017	-0.084	0.179	-0.263	-0.253	0.145
Norm (%TLM)	0.153	-0.124	-0.016	0.245	-0.384	0.421 ^d	0.405 ^d	-0.272
Hyper (%TLM)	0.618 ^a	-0.201	-0.199	0.132	-0.336	0.385	0.355	-0.284

Cdyn, dynamic compliance of the respiratory system; Fr, resonant frequency; hyper, hyperaerated compartment; non, non-aerated compartment; norm, normally aerated compartment; poor, poorly aerated compartment; R0, intercept resistance; Rm, mean resistance; S, resistance curve angular coefficient; TLM, total lung mass; TLV, total lung volume; Xm, mean reactance; Zrs4Hz, impedance at 4 Hz.

Significant differences:

^a $p < 0.001$.

^b $p < 0.01$.

^c $p < 0.005$.

^d $p < 0.05$.

and (5) compared with simple silicosis, patients with complicated silicosis showed a greater heterogeneity of the respiratory system and larger sizes of non-aerated and hyperaerated compartments.

FOT provides a simple and detailed approach to investigate the mechanical properties of the respiratory system. The method is simple and requires only passive co-operation from the patient, with no forced expiratory manoeuvres.^{18–20} However, like any other measurement of lung function, FOT is influenced by several factors that can complicate pathophysiological understanding of the disease. Thus, this study was carefully performed to eliminate the effects of tobacco on the interpretation of the findings from both FOT and pulmonary densitometry.

In agreement with other studies,^{21,22} patients with silicosis showed changes in both reactive and resistive properties of the respiratory system. Silicosis is characterized by airway impairment owing to its distortion and compression by the silicotic nodules and the involvement of the lung parenchyma owing to the conglomerate masses and scar-related emphysema.^{35,36} These anatomopathological changes are in agreement with the findings revealed by FOT in the present study. Interestingly, patients with complicated silicosis

showed a greater non-homogeneity of the respiratory system and increased work of breathing. This suggests that FOT may be a useful tool for demonstrating disease severity.

Q-MDCT accurately reflects regional air and non-air content and is related to lung disease, which has led many investigators to use this method to assess the density of lung compartments in different clinical conditions.^{10,37,38} When compared with control subjects, the patients with silicosis exhibited larger non-aerated and poorly aerated compartments and heavier lungs. Because more than half of the patients had PMF, we assume that the large fibrotic masses characteristic of this condition might explain, at least in part, the results of the present study. Moreover, patients with complicated silicosis showed higher values of non-aerated and hyperaerated compartments when the two subgroups of the disease were compared. In agreement with our findings, de Castro *et al*¹¹ also reported that the large opacities occupy a considerable percentage of lung volume in patients with silicosis.

There was no good correlation between the imaging and functional findings, although the correlation between HRCT and lung function is better than that observed with

Figure 2. (a) Relationship between the total air volume (TAV) and the total lung capacity (TLC; $r_s = 0.806$; $p < 0.001$). (b) Relationship between the hyperaerated compartment (hyper) and the TLC ($r_s = 0.749$; $p < 0.001$).

radiography.^{9,39} However, significant correlations were observed between non-aerated compartment size measured in millilitres, %TLV, grams and %TLM and FOT parameters, which reflect the non-homogeneity of the respiratory system; there was a positive correlation with resonant frequency and negative correlation with mean reactance (these two parameters represent reactive properties and are inversely related).^{19,20} We believe that in silicosis, the non-homogeneity of the respiratory system is largely owing to the conglomeration of fibrous masses that cause a significant distortion of the pulmonary parenchyma owing to retraction. Thus, the extensive replacement of the pulmonary parenchyma by fibrous tissue in patients with silicosis can contribute to changes in elasticity, which in turn can cause an imbalance in the respiratory system's time constants and increase the heterogeneity of the system.²²

In this study, a reduced dynamic compliance of the respiratory system was associated with larger size and higher weight of non-aerated compartment. Dynamic compliance of the respiratory

system includes the compliances of the lung and bronchial walls, the chest wall and thoracic gas compression.¹⁹ In silicosis, the silica particles stimulate macrophages and the proliferation of fibroblasts, causing a significant inflammatory process in the lung interstitium; the final result is an uncontrolled increase of fibroblast proliferation and collagen production, resulting in interstitial fibrosis.^{40,41} Because tissue resistance is inversely related to lung compliance,⁴² the fibrotic changes occurring in the pulmonary interstitium of patients with silicosis can directly impact the pulmonary mechanics.

We also observed that an increased Zrs4Hz was associated with larger size and higher weight of non-aerated compartment. Zrs4Hz is related with the necessary work to promote the movement of air in the respiratory system and may therefore be associated with fatigue and shortness of breath, which are common symptoms in patients with silicosis.^{22,43,44} We suggest that Zrs4Hz can be used as a severity marker for silicosis. Thus, Zrs4Hz might be of clinical importance in the clinical scenario.

Figure 3. (a) Relationship between the non-aerated compartment size, measured by the percentage of total lung volume (non %TLV), and the mean reactance (X_m ; $r_s = -0.582$; $p < 0.001$). (b) Relationship between the non-aerated compartment size, measured by the percentage of TLV (non %TLV), and the dynamic compliance of the respiratory system (C_{dyn} ; $r_s = -0.548$; $p < 0.001$).

It is worth mentioning the significant correlation between the hyperaerated compartment size and TLC observed in the present study. The hyperaerated compartment size reflects the overfilling of the acini with gas,¹⁴ with a density that may represent areas of emphysema.⁴⁵ Interestingly, Lopes *et al*⁹ observed emphysema in $>60\%$ of silicosis cases in a sample comprising only non-smoking individuals. Those authors attributed such lesions to the presence of PMF or the silica dust itself. Therefore, the observed correlation is consistent with the pathophysiology of the disease.

The strength of this study is the demonstration that the findings provided by both pulmonary densitometry and FOT are highly linked to the pathophysiology of silicosis. We consider the small sample size to be the main limitation of our study.

We also consider that quantification by expiratory MDCT would be interesting for improving the understanding of the morphofunctional correlations. The exclusion of smokers can also be considered as a limitation of the study because it restricts the use of our results. However, as mentioned above, we consider that the effects of smoking on the interpretation of the findings from both FOT and pulmonary densitometry could negatively impact the assessment of the morphofunctional correlations.

CONCLUSIONS

The present study demonstrates that patients with silicosis have heavier lungs and larger non-aerated and poorly aerated compartments (which include nodules and scarring) as evidenced by pulmonary densitometry. Changes in both reactive and resistive

properties and loss of homogeneity of the respiratory system are demonstrated by FOT in these patients. Moreover, there is a relationship between pulmonary structure and functional findings that is consistent with the pathophysiology of the disease. In these patients, a larger non-aerated compartment is associated with a worsening of lung function. A more significant pulmonary involvement is associated with a loss of homogeneity and increased mechanical load of the respiratory system. Thus,

we think the pulmonary densitometry and FOT may add valuable information to the subjective analysis of silicosis; however, more studies are necessary to evaluate the potential use of these methods for assessing disease progression.

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REFERENCES

- Wagner GR. Asbestosis and silicosis. *Lancet* 1997; **349**: 1311–15.
- Lopes AJ, Costa W, Thomaz Mafort T, de Sá Ferreira A, Silveira de Menezes SL, Silva Guimarães F. Silicosis in sandblasters of shipyard versus silicosis in stone carvers in Brazil: a comparison of imaging findings, lung function variables and cardiopulmonary exercise testing parameters. [In English, Portuguese.] *Rev Port Pneumol* 2012; **18**: 260–6. doi: [10.1016/j.rppneu.2012.04.006](https://doi.org/10.1016/j.rppneu.2012.04.006)
- Fernández Álvarez R, Martínez González C, Quero Martínez A, Blanco Pérez JJ, Carazo Fernández L, Prieto Fernández A. Guidelines for the diagnosis and monitoring of silicosis. [In English, Spanish.] *Arch Bronconeumol* 2015; **51**: 86–93. doi: [10.1016/j.arbres.2014.07.010](https://doi.org/10.1016/j.arbres.2014.07.010)
- Ferreira AS, Moreira VB, Ricardo HM, Coutinho R, Gabetto JM, Marchiori E. Progressive massive fibrosis in silica-exposed workers. High-resolution computed tomography findings. [In English, Portuguese.] *J Bras Pneumol* 2006; **32**: 523–8.
- Cox CW, Rose CS, Lynch DA. State of the art: imaging of occupational lung disease. *Radiology* 2014; **270**: 681–96. doi: [10.1148/radiol.13121415](https://doi.org/10.1148/radiol.13121415)
- Padley S, Gleeson F, Flower CD. Review article: current indications for high resolution computed tomography scanning of the lungs. *Br J Radiol* 1995; **68**: 105–9.
- Hering KG, Tuengerthal S, Kraus T. Standardized CT/HRCT-classification of the German Federal Republic for work and environmental related thoracic diseases. [In German.] *Radiologe* 2004; **44**: 500–11.
- Suganuma N, Kusaka Y, Hering KG, Vehmas T, Kraus T, Arakawa H, et al. Reliability of the proposed international classification of high-resolution computed tomography for occupational and environmental respiratory diseases. *J Occup Health* 2009; **51**: 210–22.
- Lopes AJ, Mogami R, Capone D, Tassarollo B, de Melo PL, Jansen JM. High-resolution computed tomography in silicosis: correlation with chest radiography and pulmonary function tests. [In English, Portuguese.] *J Bras Pneumol* 2008; **34**: 264–72.
- Molinari F, Amato M, Stefanetti M, Parapatt G, Macagnino A, Serricchio G, et al. Density-based MDCT quantification of lobar lung volumes: a study of inter- and intraobserver reproducibility. [In English, Italian.] *Radiol Med* 2010; **115**: 516–25. doi: [10.1007/s11547-010-0536-x](https://doi.org/10.1007/s11547-010-0536-x)
- de Castro MC, Ferreira AS, Irion KL, Hochegger B, Lopes AJ, Velarde GC, et al. CT quantification of large opacities and emphysema in silicosis: correlations among clinical, functional, and radiological parameters. *Lung* 2014; **192**: 543–51. doi: [10.1007/s00408-014-9590-9](https://doi.org/10.1007/s00408-014-9590-9)
- Carvalho AR, Spieth PM, Pelosi P, Beda A, Lopes AJ, Neykova B, et al. Pressure support ventilation and biphasic positive airway pressure improve oxygenation by redistribution of pulmonary blood flow. *Anesth Analg* 2009; **109**: 856–65. doi: [10.1213/ane.0b013e3181aff245](https://doi.org/10.1213/ane.0b013e3181aff245)
- Matsuoka S, Kurihara Y, Yagihashi K, Hoshino M, Watanabe N, Nakajima Y. Quantitative assessment of air trapping in chronic obstructive pulmonary disease using inspiratory and expiratory volumetric MDCT. *AJR Am J Roentgenol* 2008; **190**: 762–9. doi: [10.2214/AJR.07.2820](https://doi.org/10.2214/AJR.07.2820)
- Gattinoni L, Caironi P, Pelosi P, Goodman LR. What has computed tomography taught us about the acute respiratory distress syndrome? *Am J Respir Crit Care Med* 2001; **164**: 1701–11.
- Madani A, Keyzer C, Gevenois PA. Quantitative computed tomography assessment of lung structure and function in pulmonary emphysema. *Eur Respir J* 2001; **18**: 720–30.
- Stern EJ, Frank MS. CT of the lung in patients with pulmonary emphysema: diagnosis, quantification, and correlation with pathologic and physiologic findings. *AJR Am J Roentgenol* 1994; **162**: 791–8.
- Kaczka DW, Dellacá RL. Oscillation mechanics of the respiratory system: applications to lung disease. *Crit Rev Biomed Eng* 2011; **39**: 337–59.
- Oostveen E, MacLeod D, Lorino H, Farré R, Hantos Z, Desager K, et al; ERS Task Force on Respiratory Impedance Measurements. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. *Eur Respir J* 2003; **22**: 1026–41.
- MacLeod D, Birch M. Respiratory input impedance measurement: forced oscillation methods. *Med Biol Eng Comput* 2001; **39**: 505–16.
- de Melo PL, Werneck MM, Gianella-Neto A. Analysis of the ventilatory mechanics by forced oscillations technique: main concepts and clinical applications. *J Bras Pneumol* 2000; **26**: 194–206.
- de Mesquita Júnior JA, Lopes AJ, Jansen JM, de Melo PL. Using the forced oscillation technique to evaluate respiratory resistance in individuals with silicosis. [In English, Portuguese.] *J Bras Pneumol* 2006; **32**: 213–20.
- Sá PM, Lopes AJ, Jansen JM, Melo PL. Oscillation mechanics of the respiratory system in never-smoking patients with silicosis: pathophysiological study and evaluation of diagnostic accuracy. *Clinics (Sao Paulo)* 2013; **68**: 644–51. doi: [10.6061/clinics/2013\(05\)11](https://doi.org/10.6061/clinics/2013(05)11)
- Guidelines for the use of ILO international classification of radiographs of pneumoconiosis. Revised edition. Occupational safety and health series no. 22.* Geneva, Switzerland: International Labor Organization; 1980.
- Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, et al. Standardisation of the measurement of lung volumes. *Eur Respir J* 2005; **26**: 511–22.
- Ying Y, Peslin R, Duvivier C, Gallina C, Felicio da Silva J. Respiratory input and transfer mechanical impedances in patients with chronic obstructive pulmonary disease. *Eur Respir J* 1990; **3**: 1186–92.
- Nagels J, Ländsér FJ, van der Linden L, Clément J, van de Woestijne KP. Mechanical properties of lungs and chest wall during spontaneous breathing. *J Appl Physiol Respir Environ Exerc Physiol* 1980; **49**: 408–16.
- Peslin R, Marchal F, Duvivier C, Ying Y, Gallina C. Evaluation of a modified head generator for respiratory impedance measurements. *Eur Respir Rev* 1991; **1**: 140–5.

28. Rotger M, Peslin R, Farré R, Duvivier C. Influence of amplitude, phase and frequency content of pseudorandom pressure input on impedance data and their variability. *Eur Respir Rev* 1991; **1**: 178–82.
29. Miranda IA, Dias Faria AC, Lopes AJ, Jansen JM, Lopes de Melo P. On the respiratory mechanics measured by forced oscillation technique in patients with systemic sclerosis. *PLoS One* 2013; **8**: e61657. doi: [10.1371/journal.pone.0061657](https://doi.org/10.1371/journal.pone.0061657)
30. Lorino AM, Zerah F, Mariette A, Harf A, Lorino H. Respiratory resistive impedance in obstructive patients: linear regression analysis vs viscoelastic modelling. *Eur Respir J* 1997; **10**: 150–5.
31. Hounsfield GN. Computerized transverse axial scanning (tomography). 1. Description of system. *Br J Radiol* 1973; **46**: 1016–22.
32. Gattinoni L, Pesenti A, Bombino M, Baglioni S, Rivolta M, Rossi F, et al. Relationships between lung computed tomographic density, gas exchange, and PEEP in acute respiratory failure. *Anesthesiology* 1988; **69**: 824–32.
33. Protti A, Iapichino GE, Milesi M, Melis V, Pugini P, Comini B, et al. Validation of computed tomography for measuring lung weight. *Intensive Care Med Exp* 2014; **2**: 31.
34. Irion KL, Hochhegger B, Marchiori E, Porto Nda S, Baldisserotto Sde V, Santana PR. Chest X-ray and computed tomography in the evaluation of pulmonary emphysema. [In Portuguese.] *J Bras Pneumol* 2007; **33**: 720–32.
35. Diseases associated with exposure to silica and non fibrous silicate minerals. Silicosis and Silicate Disease Committee. *Arch Pathol Lab Med* 1988; **112**: 673–720.
36. Adverse effects of crystalline silica exposure. American Thoracic Society Committee of the Scientific Assembly on Environmental and Occupational Health. *Am J Respir Crit Care Med* 1997; **155**: 761–8.
37. Gabe LM, Baker KM, van Beek EJ, Hunninghake GW, Reinhardt JM, Hoffman EA. Effect of segmental bronchoalveolar lavage on quantitative computed tomography of the lung. *Acad Radiol* 2011; **18**: 876–84. doi: [10.1016/j.acra.2011.03.006](https://doi.org/10.1016/j.acra.2011.03.006)
38. Hoffman EA, Simon BA, McLennan G. State of the art. A structural and functional assessment of the lung via multidetector-row computed tomography: phenotyping chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2006; **3**: 519–32.
39. Talini D, Paggiaro PL, Falaschi F, Battolla L, Carrara M, Petrozzino M, et al. Chest radiography and high resolution computed tomography in the evaluation of workers exposed to silica dust: relation with functional findings. *Occup Environ Med* 1995; **52**: 262–7.
40. Terra Filho M, Santos Ude P. Silicosis. [In Portuguese.] *J Bras Pneumol* 2006; **32**(Suppl. 2): S41–7.
41. Castranova V. From coal mine dust to quartz: mechanisms of pulmonary pathogenicity. *Inhal Toxicol* 2000; **12**(Suppl. 3): 7–14.
42. van Noord JA, Clément J, Cauberghe M, Mertens I, van de Woestijne KP, Demedts M. Total respiratory resistance and reactance in patients with diffuse interstitial lung disease. *Eur Respir J* 1989; **2**: 846–52.
43. Leung CC, Yu IT, Chen W. Silicosis. *Lancet* 2012; **379**: 2008–18. doi: [10.1016/S0140-6736\(12\)60235-9](https://doi.org/10.1016/S0140-6736(12)60235-9)
44. Sirajuddin A, Kanne JP. Occupational lung disease. *J Thorac Imaging* 2009; **24**: 310–20. doi: [10.1097/RTI.0b013e3181c1a9b3](https://doi.org/10.1097/RTI.0b013e3181c1a9b3)
45. Gevenois PA, Scillia P, de Maertelaer V, Michils A, De Vuyst P, Yernault JC. The effects of age, sex, lung size, and hyperinflation on CT lung densitometry. *AJR Am J Roentgenol* 1996; **167**: 1169–73.