

# The Role of Multidetector Computed Tomography and the Forced Oscillation Technique in Assessing Lung Damage in Adults With Cystic Fibrosis

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**BACKGROUND:** With increased survival rates and the consequent emergence of an adult population with cystic fibrosis (CF), developing novel tools for periodic evaluations of these patients has become a new challenge. Thus, we sought to determine the contribution of lung-volume quantification using multidetector computed tomography (CT) in adults with CF and to investigate the association between structural changes and functional abnormalities. **METHODS:** This was a cross-sectional study in which 21 adults with CF and 22 control subjects underwent lung-volume quantification using multidetector CT. Voxel densities were divided into 4 bands:  $-1,000$  to  $-900$  Hounsfield units (HU) (hyperaerated region),  $-900$  to  $-500$  HU (normally aerated region),  $-500$  to  $-100$  HU (poorly aerated region), and  $-100$  to  $100$  HU (non-aerated region). In addition, all participants performed pulmonary function tests including spirometry, body plethysmography, diffusion capacity for carbon monoxide, and the forced oscillation technique. **RESULTS:** Adults with CF had more non-aerated regions and poorly aerated regions with lung-volume quantification using multidetector CT than controls. Despite these abnormalities, total lung volume measured by lung-volume quantification using multidetector CT did not differ between subjects and controls. Total lung capacity (TLC) measured by body plethysmography correlated with both total lung volume ( $r_s = 0.71$ ,  $P < .001$ ) and total air volume ( $r_s = 0.71$ ,  $P < .001$ ) as measured with lung-volume quantification using multidetector CT. While the hyperaerated regions correlated with the functional markers of gas retention in the lungs (increased residual volume (RV) and RV/TLC ratio), the poorly aerated regions correlated with the resistive parameters measured by the forced oscillation technique (increased intercept resistance and mean resistance). We also observed a correlation between normally aerated regions and highest pulmonary diffusion values ( $r_s = 0.68$ ,  $P < .001$ ). **CONCLUSIONS:** In adults with CF, lung-volume quantification using multidetector CT can estimate the lung volumes of compartments with different densities and determine the aerated and non-aerated contents of the lungs; furthermore, lung-volume quantification using multidetector CT is clearly related to pulmonary function parameters. *Key words:* cystic fibrosis; diagnostic imaging; respiratory function tests; forced oscillation technique. [Respir Care 0;0(0):1-\*. © 0 Daedalus Enterprises]

## Introduction

Cystic fibrosis (CF) is an autosomal, recessive, multi-system, progressive hereditary disease caused by a muta-

tion in the gene responsible for the coding of the CF transmembrane regulator protein.<sup>1</sup> The disease affects 70,000 to 100,000 people worldwide, and its incidence varies among different regions of the world.<sup>2</sup> More than 50% of

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the population with CF is  $\geq 18$  years old, and there has been a significant increase in median survival from 27 years of age in 1986 to 40 years of age in 2013.<sup>1,2</sup>

Pulmonary involvement is the most influential factor on the morbidity and mortality of CF patients, accounting for 90% of deaths.<sup>3</sup> Thickening of bronchial secretions occurs in the respiratory system, which leads to progressive airway obstruction and involvement of local defense mechanisms that combat chronic infections. Moreover, mucoid impactions and chronic inflammation of the bronchial walls cause bronchiectasis and destruction of the lung parenchyma.<sup>1,2</sup> Sequential pulmonary function tests (PFTs), most commonly using spirometry, are routinely performed during the follow-up of CF patients to determine disease progression and therapeutic responses. Although more traditional PFTs are commonly used in the assessment of patients with CF, the functional changes shown by these tests can be preceded by structural changes detected on computed tomography (CT) scans.<sup>4</sup> Indeed, some studies have shown that spirometry is a suboptimal tool for monitoring early-stage CF lung disease and even later-stage CF characterized by clinically important respiratory involvement, which indicates the need to develop new PFTs for functional evaluation.<sup>5,6</sup>

In this context, the forced oscillation technique, a non-invasive and easy-to-perform method, has shown great potential for evaluating pulmonary involvement in CF by assessing both resistive and reactive properties of the respiratory system.<sup>7</sup> Recent studies by our research group successfully applied this method in the early diagnosis of respiratory abnormalities in workers exposed to asbestos<sup>8</sup> and in smokers,<sup>9</sup> as well as in the investigation of patho-

**QUICK LOOK****Current knowledge**

There is still no widely accepted standard imaging test to evaluate lung disease in adults with cystic fibrosis (CF). The quantification of lung volume using multidetector computed tomography (CT) was recently introduced to measure lung density. Moreover, the forced oscillation technique has shown great potential for analysis of pulmonary involvement in patients with CF.

**What this paper contributes to our knowledge**

Adults with CF presented greater non-aerated and poorly aerated regions in relation to the volume of the lungs, as evaluated by quantification of lung volume using multidetector CT. When evaluated via the forced oscillation technique, CF subjects showed changes in both resistive and reactive properties of the respiratory system. The total lung volume assessed by quantification of lung volume using multidetector CT was positively and strongly correlated with the thoracic gas volume measured by body plethysmography. Moreover, findings from quantification of lung volume using multidetector CT were significantly associated with the indices provided by spirometry, diffusion capacity for carbon monoxide, and the forced oscillation technique.

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physiological changes in subjects with sarcoidosis,<sup>10</sup> silicosis,<sup>11</sup> and COPD.<sup>12</sup> Similar clinical studies have also been performed by other researchers who have investigated the detection of initial obstructive airway disease in subjects with asthma,<sup>13</sup> changes in lung mechanics after bariatric surgery,<sup>14</sup> airway obstruction in sleep apnea,<sup>15</sup> and primary Sjögren's syndrome.<sup>16</sup>

Numerous studies have demonstrated the superiority of CT over chest radiography for the morphological evaluation of lung diseases, notably for the diagnosis and follow-up of chronic lung diseases such as CF.<sup>17,18</sup> Despite this great advantage of CT, there is still no widely accepted standard imaging test to evaluate lung disease in adults with CF.<sup>19</sup> Lung-volume quantification using multidetector CT was recently introduced with the aim of measuring lung density based on histogram analysis of the frequency distribution of lung attenuation values in Hounsfield units (HU).<sup>20-23</sup> The analysis of voxel density distribution represents an important tool for studying the aeration distribution in CT slices. Thus, lung-volume quantification using multidetector CT has great potential to expand existing knowledge of the pathophysiology of CF in adults, to increase the diagnostic yield, and to aid in the staging of pulmonary involvement.

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Due to the lifespan in CF has been increasing for several decades now emergence of an adult population with CF and the absence of studies evaluating the potential of lung-volume quantification using multidetector CT in conjunction with the forced oscillation technique in this group of subjects, evaluating the contribution of these techniques to CF is of particular interest. Thus, the objectives of our study were to determine the type and extent of lung-volume quantification using multidetector CT findings in adults with CF and to investigate the association between structural lesions assessed with lung-volume quantification using multidetector CT and lung function parameters, especially those measured by the forced oscillation technique.

### Methods

#### Subjects

We conducted this cross-sectional study between May 2016 and January 2017, with a convenience sample of 26 CF subjects recruited at the Piquet Carneiro Polyclinic at the State University of Rio de Janeiro, Brazil. Disease diagnosis was based on the presence of at least 2 of the following criteria: sweat chloride concentration  $> 60$  mmol/L, 2 clinical features consistent with CF, or genetic testing demonstrating 2 mutations associated with CF.<sup>24</sup> Patients of both genders age  $\geq 18$  y were included in the study. The following exclusion criteria were used: clinical instability (evidence of an exacerbation or receiving medical treatment for an exacerbation in the 2 weeks prior to admission to the clinic),<sup>25</sup> history of previous or current smoking, report of previous pleuropulmonary disease not related to CF, and inability to perform PFTs or chest CT. An exacerbation was defined as the presence of any 4 of the following manifestations: increased cough, increased sputum production, increased dyspnea, new or increased hemoptysis, fatigue, oral temperature  $> 38^{\circ}\text{C}$ , sinus pain, decreased FEV<sub>1</sub> by  $\geq 10\%$  from a previously recorded value, and radiographic changes indicative of infection.<sup>25,26</sup>

Through medical records and CT scans stored at our institution, we also included a control group of healthy volunteers who previously underwent chest CT for other reasons. Inclusion criteria for the control group were inspiratory/expiratory CT scans without any abnormalities and no history of smoking or chronic lung disease. Individuals in the control group were invited to perform the PFTs. In case of any abnormalities in PFTs (ie, any value below the lower limit of normal or above the upper limit of normal in relation to the predicted value), the subject was excluded from the study. This control group was paired in age and gender with the CF group.

The project was approved by the Research Ethics Committee of our institution under the number

CAAE-27352814.8.0000.5259 and complied with the provisions of the Declaration of Helsinki. All individuals signed a consent form. The project received financial support from the Brazilian Council for Scientific and Technological Development and the Rio de Janeiro State Research Supporting Foundation.

#### Pulmonary Function Testing

The PFTs performed were spirometry, body plethysmography, and diffusing capacity of the lung for carbon monoxide ( $D_{\text{LCO}}$ ). The exams were performed using an HDpft 3000 system (nSpire Health, Longmont, Colorado) according to the standards outlined by the American Thoracic Society/European Respiratory Society.<sup>27</sup> The equations used for predicted values were reported by Pereira et al<sup>28</sup> for spirometry, Neder et al<sup>29</sup> for body plethysmography, and Neder et al<sup>30</sup> for  $D_{\text{LCO}}$  measurements, and the results were expressed as a percentage of the predicted values. In addition, we also performed the forced oscillation technique using a device developed at the Biomedical Instrumentation Laboratory, which was used previously in several clinical studies.<sup>8,10-12,31,32</sup> The standardization of this method has been previously reported.<sup>33</sup> To avoid the effects of the deep inhalation maneuver on the airways, patients were initially evaluated by the forced oscillation technique upon inclusion in the study. Spirometry, body plethysmography, and  $D_{\text{LCO}}$  measurements were then sequentially performed.

#### CT Scan Protocol

CT scans were performed using a 64-channel Multislice Philips system (Brilliance 40, Philips Medical Systems, Cleveland, Ohio) capable of performing volumetric acquisitions with subsequent multiplanar reconstructions. Acquisition was always performed in the axial plane, with subjects in dorsal decubitus, using the following technical parameters: 120 kV, 458 mA (which varied according to the biotype of the subject), slice thickness of 2 mm, and pitch of 2 mm from the jugular notch to the xiphoid process during maximal inspiration and expiration. There was no inclination of the gantry. After image acquisition, a high-resolution reconstruction with a  $512 \times 512$  matrix was performed using a high-frequency algorithm, a window width of 1,200 HU, and a mean center level of  $-800$  HU. The CT scans were interpreted independently by 2 experienced radiologists, who were blinded to the clinical and functional data of the subjects evaluated; in addition, the CT scans of the control and CF groups were mixed for evaluation of the images. Disagreements were resolved by consensus.

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**Image Processing**

The first step of density and volumetry was the segmentation of the pulmonary parenchyma, which was performed using the OsiriX program (OsiriX 64-bits, Pixmeo Sarl, Geneva, Switzerland). This process consisted of the selection of the lung parenchyma and specific altered regions, such as areas of hyperinflation, excluding the chest wall, heart, and large vessels. After segmentation and export of the lung parenchyma images, the images were processed according to the instructions of the DICOMDir file in a CT-processing program written in MATLAB 2014a (MathWorks, Natick, Massachusetts) at the Laboratory of Pulmonary Engineering, Biomedical Engineering Program, Alberto Luiz Coimbra Institute of Post-Graduation and Research in Engineering, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil.

Analysis of the voxel density distribution is an important tool in studying the aeration distribution in a CT slice. The distribution histogram of the voxels was divided into compartments, which varied between  $-1,000$  and  $+100$  HU. The voxel densities were divided into 4 bands within the following ranges:  $-1,000$  to  $-900$  HU (hyperaerated region),  $-900$  to  $-500$  HU (normally aerated region),  $-500$  to  $-100$  HU (poorly aerated region), and  $-100$  to  $100$  HU (non-aerated region). These values were determined according to previously proposed classifications.<sup>11,21,34,35</sup> The total lung volume and the total air volume were calculated considering only the image contained within the region of interest. The total lung volume (ie, the sum of air plus tissue volume) was calculated as (size of the pixel)<sup>2</sup>  $\times$  slice thickness  $\times$  total number of pixels of the region of interest for the whole lung.<sup>21,34,35</sup>

**Statistical Analysis**

The sample size for this study was calculated using MedCalc 8.2 software (Medical Software, Mariakerke, Belgium). A minimum sample size of 21 cases was required to test the alternative hypothesis that the correlation coefficient (ie, correlation between the structural lesion assessed with lung-volume quantification using multidetector CT and the forced oscillation technique parameter) was  $> 0.40$  (or  $< -0.40$ ), assuming a type-1 error of 5% and a type-2 error of 20%.<sup>36</sup>

Non-parametric tests were applied because almost none of the variables presented a Gaussian distribution, as the normality hypothesis was rejected according to the Shapiro-Wilk test. Comparisons of the clinical variables, PFTs, and findings from the lung-volume quantification using multidetector CT between the experimental and control groups were evaluated using the Mann-Whitney test for numerical data and the chi-square test for categorical data. To evaluate the associations between the numerical vari-

ables of PFTs and lung-volume quantification using multidetector CT, the Spearman correlation coefficient ( $r_s$ ) was used. Multivariate forward stepwise regression analysis was performed to determine the dependent relationship of lung function parameters on lung-volume quantification using multidetector CT variables. Natural logarithmic transformation was applied to the variables dependent on lung-volume quantification using multidetector CT. The clinical potential of the lung-volume quantification using multidetector CT indices for the detection of pulmonary alterations in subjects with CF was evaluated by means of receiver operating characteristic curves. The criterion for determining significance was  $P = .05$ . Statistical analysis was performed using SAS 6.11 software (SAS Institute, Cary, North Carolina).

**Results**

Among the 26 patients who were evaluated for inclusion in the study, 5 were excluded (3 due to difficulty performing spirometry, and 2 due to clinical instability during the study). Thus, the CF group ( $n = 21$ ) consisted of 14 females and 7 males, with a median age of 24 y (interquartile range 19.5–29 y), and  $> 60\%$  of included subjects were chronically colonized by *Pseudomonas aeruginosa*. The control group ( $n = 22$ ) consisted of 15 females and 7 males, with a median age of 30.5 y (interquartile range 26–35.3 y). In the forced oscillation technique exam, the adults with CF presented higher values of intercept resistance, mean resistance, resonance frequency, and impedance module at 4 Hz, and lower values of mean reactance and dynamic compliance of the respiratory system compared with controls. Comparisons of clinical and pulmonary function data between the adult subjects with CF and the control subjects are shown in Table 1.

In CT scans, all adults with CF showed signs characteristic of lung disease in at least 1 lobe. The alterations found in CT scans included air trapping and mosaic attenuation (81%); bronchiectasis, thickening of the bronchial walls, and mucous plugs (76.2%); consolidations/collapse (61.9%); sacculations/abscess (47.6%); ground glass opacities (38.1%); septal thickening (33.3%); and bubbles/emphysema (19%). With both inspiratory and expiratory lung-volume quantification using multidetector CT, CF subjects presented greater non-aerated area based on either the absolute number of non-aerated regions or total percentage of the non-aerated area. Inspiratory lung-volume quantification using multidetector CT also demonstrated that CF subjects presented greater poorly aerated area based on either the absolute number of non-aerated regions or total percentage of the non-aerated area. Comparisons of inspiratory and expiratory lung-volume quantification using multi-

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Table 1. General Characteristics and Pulmonary Function Parameters of Patients With Cystic Fibrosis and Control Group

Variable	Cystic Fibrosis Group, <i>n</i> = 21	Control Group, <i>n</i> = 22	<i>P</i>
Demographic data			
Age, years, <i>n</i> (%)	24 (19.5–29)	30.5 (26–35.3)	.09
Female sex, <i>n</i> (%)	14 (66.7)	15 (68.2)	.91
Weight, median (IQR) kg	53 (46.6–76)	69.8 (61.5–82.8)	.005
Height, median (IQR) cm	164 (155–171)	168 (162–173)	.35
Body mass index, median (IQR) kg/m <sup>2</sup>	20.5 (17.7–26.3)	25.3 (22.6–31.7)	.008
Pulmonary microbiology, <i>n</i> (%)			
Chronic <i>Staphylococcus aureus</i> colonization	15 (71.4)	NA	NA
Chronic <i>Pseudomonas aeruginosa</i> colonization	13 (61.9)	NA	NA
Chronic MRSA colonisation	2 (9.5)	NA	NA
Chronic <i>Burkholderia cepacia</i> complex colonization	1 (4.8)	NA	NA
No colonization	3 (14.3)	NA	NA
Spirometry, median (IQR)			
FVC, % predicted	83 (64–87.5)	101.5 (95.8–106.3)	< .001
FEV <sub>1</sub> , % predicted	68 (47.5–82)	103 (94.3–106.3)	< .001
FEV <sub>1</sub> /FVC, %	82 (67–94)	98 (96–104)	< .001
FEF <sub>25–75%</sub> , % predicted	42 (16–69)	99 (86–117.5)	< .001
Body plethysmograph, median (IQR)			
TLC, % predicted	93 (83.5–106)	92 (87–98)	.81
RV, % predicted	139 (90–168)	74 (56–91)	< .001
RV/TLC, %	39.7 (32.6–45.8)	21 (17.9–27.8)	< .001
Diffusing capacity, median (IQR)			
D <sub>LCO</sub> , % predicted	82 (73–96)	105.5 (95–112)	.001
Forced oscillation technique, median (IQR)			
R0, cm H <sub>2</sub> O/L/s	3.67 (2.82–4.57)	2.80 (2.35–3.65)	.036
Rm, cm H <sub>2</sub> O/L/s	3.35 (2.75–3.98)	2.67 (2.39–3.21)	.02
S, cm H <sub>2</sub> O/L/s <sup>2</sup>	–26.9 (–49.5 to –6.1)	–10.4 (–29.9 to –5.3)	.53
Fr, Hz	14.2 (10.4–21.1)	9.7 (8.5–11.2)	.003
Xm, cm H <sub>2</sub> O/L/s <sup>2</sup>	0.08 (–0.30–0.69)	0.68 (0.22–1.24)	.01
Cdyn, L/cm H <sub>2</sub> O	13.5 (10.7–16.7)	19.2 (15.2–24.1)	.004
Zrs4Hz, cm H <sub>2</sub> O/L/s	4.58 (3.62–6.01)	3.36 (2.97–4.45)	.007

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

NA = not applicable

MRSA = methicillin-resistant *Staphylococcus aureus*

FEF<sub>25–75%</sub> = forced expiratory flow during the middle half of the FVC maneuver

TLC = total lung capacity

RV = residual volume

D<sub>LCO</sub> = diffusion capacity for carbon monoxide

R0 = intercept resistance

Rm = mean resistance

S = resistance curve angular coefficient

Fr = resonance frequency

Xm = mean reactance

Cdyn = dynamic compliance of the respiratory system

Zrs4Hz = impedance module at 4 Hz

detector CT data between the CF subjects and the control subjects are shown in Table 2.

We next evaluated the correlations between the findings from lung-volume quantification using multidetector CT and the PFT parameters (Tables 3 and 4). For inspiratory lung-volume quantification using multidetector CT, strong correlations were observed between total lung volume and total lung capacity (TLC) ( $r_s = 0.71$ ,  $P < .001$ ), between total air volume and TLC ( $r_s = 0.71$ ,  $P < .001$ ), between total lung volume and D<sub>LCO</sub> ( $r_s = 0.69$ ,  $P < .001$ ), and

between total air volume and D<sub>LCO</sub> ( $r_s = 0.69$ ,  $P < .001$ ). The poorly aerated region was significantly correlated with residual volume (RV;  $r_s = 0.42$ ,  $P = .005$ ), RV/TLC ( $r_s = 0.35$ ,  $P = .02$ ), and forced expiratory flow during the middle half of the FVC (FEF<sub>27–75%</sub>) ( $r_s = -0.45$ ,  $P = .003$ ). For expiratory lung-volume quantification using multidetector CT, the poorly aerated region was significantly correlated with the following forced oscillation technique parameters: intercept resistance ( $r_s = -0.41$ ,  $P = .02$ ) and mean resistance ( $r_s = -0.44$ ,  $P = .02$ ). The hyperaerated

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Table 2. Variables of Inspiratory and Expiratory Computed Tomography According to the Group

Variable	Inspiratory Computed Tomography			Expiratory Computed Tomography		
	Cystic Fibrosis Group, <i>n</i> = 21	Control Group, <i>n</i> = 22	<i>P</i>	Cystic Fibrosis Group, <i>n</i> = 21	Control Group, <i>n</i> = 22	<i>P</i>
TLV, mL	4112 (3389–5144)	4242 (3669–5338)	.45	2961 (2150–3472)	2182 (1528–3044)	.11
TAV, mL	3469 (2693–4264)	3622 (3055–4453)	.44	1997 (1543–2485)	1446 (940–2314)	.16
Non, mL	34.7 (12.7–97.4)	13.8 (9.5–19.8)	.02	39.6 (27.4–114)	11.5 (8.5–25)	.001
Non, % TLV	0.88 (0.29–1.69)	0.31 (0.22–0.52)	.008	1.94 (1.14–3.47)	0.63 (0.38–1.21)	.002
Poor, mL	139 (102–258)	89.9 (73–116)	.002	230 (171–330)	279 (112–297)	.63
Poor, % TLV	3.42 (2.61–5.25)	2.11 (1.53–2.66)	.001	8.15 (6.25–11.9)	12.8 (3.79–18)	.38
Norm, mL	2920 (2542–3306)	3156 (2797–3554)	.30	2362 (1879–2890)	1858 (1218–2616)	.18
Norm, % TLV	71.6 (61.6–79.7)	74.2 (67.3–79.8)	.58	83.4 (77.1–86)	83.9 (80.3–85.2)	.87
Hyper, mL	966 (652–1519)	1027 (556–1396)	.94	158 (55–267)	34 (14–302)	.19
Hyper, % TLV	22.8 (15.4–35.6)	23 (15.8–31)	.94	5.03 (2.35–8.44)	1.58 (0.98–9.98)	.29

Data are given as median (interquartile range).

TLV = total lung volume

TAV = total air volume

Non = non-aerated region

Poor = poorly aerated region

Norm = normally aerated region

Hyper = hyperaerated region

Table 3. Spearman's Correlation Coefficients Between the Inspiratory Lung-Volume Quantification by Multidetector Computed Tomography Values and the Pulmonary Function Parameters

Variable	FVC, L	FEV <sub>1</sub> /FVC, %	FEF <sub>25–75%</sub> , L/s	TLC, L	RV, L	RV/TLC, %	D <sub>LCO</sub> , mL/min/mm Hg	R0, cm H <sub>2</sub> O/L/s	Rm, cm H <sub>2</sub> O/L/s
TLV, mL	<b>0.61*</b>	−0.09	0.10	<b>0.71*</b>	0.22	−0.13	<b>0.69*</b>	−0.24	−0.25
TAV, mL	<b>0.62*</b>	−0.07	0.13	<b>0.71*</b>	0.20	−0.14	<b>0.69*</b>	−0.21	−0.21
Non, mL	−0.01	−0.11	−0.24	0.14	0.24	0.02	0.17	−0.07	−0.07
Non, % TLV	−0.17	−0.10	−0.30	−0.02	0.22	0.22	0.02	−0.03	−0.02
Poor, mL	−0.16	<b>−0.31</b>	<b>−0.45</b>	0.11	<b>0.42</b>	<b>0.35</b>	−0.02	−0.01	0.01
Poor, % TLV	<b>−0.39</b>	−0.20	<b>−0.45</b>	−0.20	0.28	<b>0.37</b>	−0.27	0.02	0.04
Norm, mL	<b>0.57*</b>	−0.03	0.18	<b>0.62*</b>	0.05	−0.26	<b>0.68*</b>	<b>−0.43</b>	<b>−0.46</b>
Norm, % TLV	−0.20	0.17	0.14	−0.28	−0.29	−0.17	−0.14	−0.17	−0.16
Hyper, mL	<b>0.40</b>	−0.15	−0.02	<b>0.51*</b>	<b>0.31</b>	0.10	<b>0.36*</b>	0.10	0.06
Hyper, % TLV	0.27	−0.13	−0.05	0.30	0.22	0.10	0.17	0.17	0.16

The values in bold refer to significant differences. \* *P* < .001.

TLV = total lung volume

TAV = total air volume

Non = non-aerated region

Poor = poorly aerated region

Norm = normally aerated region

Hyper = hyperaerated region

FEF<sub>25–75%</sub> = forced expiratory flow during the middle half of the FVC maneuver

TLC = total lung capacity

RV = residual volume

D<sub>LCO</sub> = diffusion capacity for carbon monoxide

R0 = intercept resistance

Rm = mean resistance

region was significantly correlated with RV ( $r_s = 0.59$ ,  $P < .001$ ), RV/TLC ( $r_s = 0.45$ ,  $P = .02$ ), and FEF<sub>27–75%</sub> ( $r_s = -0.49$ ,  $P = .007$ ).

We also constructed models to explain the dependent relationship between lung-volume quantification using multidetector CT variables and lung function parameters.

The models with the greatest clinical relevance and statistical significance are shown in Table 5. We also found that poorly aerated regions more accurately detected the initial lung disease in CF than non-aerated regions. The receiver operating characteristic curves, areas under the curves, and 95% CIs for the most accurate parameters observed in

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Table 4. Spearman's Correlation Coefficients Between Expiratory Lung-Volume Quantification by Multidetector Computed Tomography Values and the Pulmonary Function Parameters

Variable	FVC, L	FEV <sub>1</sub> /FVC, %	FEF <sub>25-75%</sub> , L/s	TLC, L	RV, L	RV/TLC, %	D <sub>LCO</sub> , mL/min/mm Hg	R0, cm H <sub>2</sub> O/L/s	Rm, cm H <sub>2</sub> O/L/s
TLV, mL	0.13	-0.26	<b>0.39</b>	<b>0.45</b>	<b>0.56</b>	0.34	<b>0.38</b>	0.05	0.05
TAV, mL	0.13	-0.26	<b>0.39</b>	<b>0.44</b>	<b>0.57</b>	0.36	0.34	0.07	0.08
Non, mL	-0.17	-0.22	<b>-0.47</b>	0.07	<b>0.39</b>	0.33	-0.01	0.04	0.04
Non, % TLV	-0.24	-0.14	<b>-0.40</b>	-0.08	0.27	0.27	-0.15	0.07	0.07
Poor, mL	0.23	0.01	-0.01	0.15	0.01	-0.14	0.18	<b>-0.41</b>	<b>-0.44</b>
Poor, % TLV	0.11	0.16	0.28	-0.14	-0.35	-0.35	-0.07	<b>-0.44</b>	<b>-0.47</b>
Norm, mL	0.19	-0.17	-0.27	<b>0.44</b>	<b>0.47</b>	0.24	<b>0.44</b>	-0.01	-0.01
Norm, % TLV	0.01	0.11	0.21	0.03	-0.05	-0.06	0.14	0.21	0.22
Hyper, mL	-0.01	-0.35	<b>-0.49</b>	0.35	<b>0.59*</b>	<b>0.45</b>	0.14	0.23	0.24
Hyper, % TLV	-0.07	<b>-0.36</b>	<b>-0.50</b>	0.31	<b>0.57</b>	<b>0.47</b>	0.06	0.30	0.30

The values in bold refer to significant differences. \*  $P < .001$ .

TLV = total lung volume

TAV = total air volume

Non = non-aerated region

Poor = poorly aerated region

Norm = normally aerated region

Hyper = hyperaerated region

FEF<sub>25-75%</sub> = forced expiratory flow during the middle half of the FVC maneuver

TLC = total lung capacity

RV = residual volume

D<sub>LCO</sub> = diffusion capacity for carbon monoxide

R0 = intercept resistance

Rm = mean resistance

Table 5. Relationship Between the Variables for Lung-Volume Quantification by Multidetector Computed Tomography and the Lung Function Parameters

Outcome Variable	Independent Variables	Regression Coefficient ( $\beta$ ), 95% CI	$P$
Inspiratory Q-MDCT			
Poor, mL	RV, L	0.34 (0.14–0.54)	.002
Norm, mL	D <sub>LCO</sub> , mL/min/mm Hg	0.01 (0.01–0.02)	.005
	TLC, L	0.06 (0.01–0.11)	.01
Expiratory Q-MDCT			
Poor, mL	Rm, cm H <sub>2</sub> O/L/s	-0.29 (-0.48 to -0.09)	.005
Norm, mL	TLC, L	0.27 (0.14–0.39)	< .001
	FVC, L	-0.37 (-0.58 to -0.16)	.001
	D <sub>LCO</sub> , mL/min/mm Hg	0.03 (0.01–0.06)	.01

Poor = poorly aerated region

Norm = normally aerated region

RV = residual volume

D<sub>LCO</sub> = diffusing capacity of the lung for carbon monoxide

TLC = total lung capacity

Rm = mean resistance

FVC = forced vital capacity

inspiratory lung-volume quantification using multidetector CT are shown in Figure 1.

### Discussion

The main findings of our study were that adults with CF presented larger non-aerated and poorly aerated regions in relation to the volume of the lungs evaluated with lung-

volume quantification using multidetector CT than control subjects. When evaluated with the forced oscillation technique, CF subjects showed changes in both resistive properties (intercept resistance and mean resistance) and reactive properties (resonance frequency, mean reactance, and dynamic compliance) of the respiratory system. The total lung volume assessed with lung-volume quantification using multidetector CT was positively and strongly corre-

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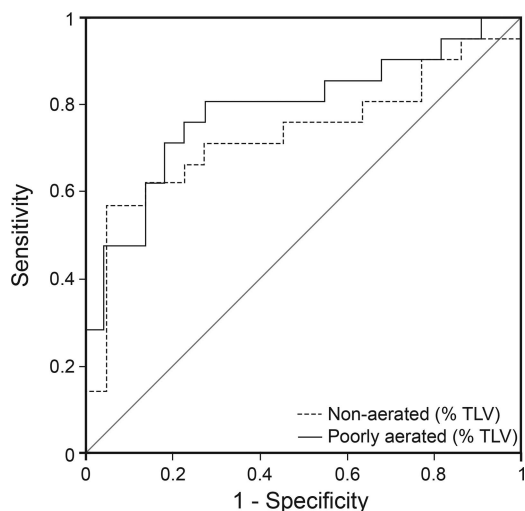


Fig. 1. Receiver operating characteristic curves, area under the curves (AUC), and 95% CI in inspiratory lung volume quantification using multidetector computed tomography for the non-aerated region (AUC = 0.74,  $P = .008$ , 95% CI 0.58–0.89) and the poorly aerated region (AUC = 0.79,  $P = .001$ , 95% CI 0.65–0.93). TLV = total lung volume.

lated with thoracic gas volume measured with body plethysmography. Moreover, findings with lung-volume quantification using multidetector CT were significantly associated with the indices provided by spirometry,  $D_{LCO}$ , and the forced oscillation technique.

Our findings show that in adults with CF, lung-volume quantification using multidetector CT was able to estimate compartment volumes with different densities and to determine the aerated and non-aerated contents of the lungs, providing information on the volume of the organ and its compartments. However, in line with the study by Wielpütz et al,<sup>22</sup> the total lung volume of CF subjects remained unchanged for both inspiratory and expiratory lung-volume quantification using multidetector CT compared with the total lung volume of control subjects. This finding indicates that, despite the imbalance between the volume of non-aerated, poorly aerated, normally aerated, and hyperaerated regions, the total lung volume was close to values observed in healthy lungs, which is translated anatomopathologically by the presence of areas with increased density (mucoïd impactions, consolidations, and collapses) in the lungs of adults with CF, along with areas of diminished density (air trapping, bubbles, and emphysema).<sup>37,38</sup> In addition, we observed that the adult CF subjects had larger non-aerated and poorly aerated regions with both inspiratory and expiratory lung-volume quantification using multidetector CT. These regions exhibited a higher density than the parenchyma with normal aeration, which suggests the presence of areas of consolidation, collapse, and fibrosis in CF.<sup>7-19</sup> Considering clinical practice, lung-volume quantification using multidetector CT may con-

tribute to the early identification of lung disease. In fact, we have found that the presence of poorly aerated regions on inspiratory lung-volume quantification using multidetector CT has good accuracy for diagnosing pulmonary disease in CF. This becomes even more relevant in light of the growing number of individuals being diagnosed with atypical forms and the increased life expectancy provided by new treatments (including CF transmembrane conductance regulator modulators).<sup>39</sup>

In this paper, we showed that total lung volume and total air volume assessed with inspiratory lung-volume quantification using multidetector CT were positively and strongly correlated with TLC as measured by body plethysmography. Although these parameters are acquired using different diagnostic methods, the physiological and conceptual similarities between the volumetric variables make it possible for both lung-volume quantification using multidetector CT and body plethysmography to be used as important tools in the follow-up of adults with CF. Increased patient survival in recent decades has emphasized the need for periodic evaluations of adults with CF; therefore, the relationships between lung function and imaging parameters further support the routine performance of PFTs in this population to reduce concern about the frequent use of ionizing radiation. It is worth noting that both overall lung-volume quantification using multidetector CT measurements (total lung volume and total air volume) and the total thoracic gas volume assessed by PFTs (TLC) did not differ significantly between the subjects and the controls, which reinforces our hypothesis that regions of higher density are counterbalanced by lower-density regions in adults with CF.

Some studies have shown that emphysema is a clinically relevant phenotype and contributes to the severity of lung disease in adults with CF.<sup>22,40,41</sup> In our study, we observed significant correlations of hyperaerated regions (mainly in expiratory lung-volume quantification using multidetector CT exams) with increases in RV and RV/TLC, which are functional markers of airway obstruction and gas retention in the lungs.<sup>23</sup> Because lung voxels are attributed to emphysema at densities  $\geq -950$  HU,<sup>22,42</sup> the hyperaerated region defined in our study primarily corresponded to emphysematous lesions. This finding reinforces the idea that the presence and extent of emphysema in lung-volume quantification using multidetector CT may serve as a marker of the severity of lung dysfunction in adults with CF.<sup>22</sup>

The forced oscillation technique allows respiratory mechanics to be evaluated in a complementary manner to traditional PFTs and has been increasingly incorporated in the functional evaluation of chronic respiratory diseases.<sup>43</sup> Another important advantage is that the forced oscillation technique requires only passive cooperation and does not entail any forced expiratory maneuvers. In fact, 3 of the



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recruited patients had difficulty performing spirometry and were excluded from the study. In our investigation, adults with CF showed lower mean reactance values than controls. Because mean reactance reflects the inhomogeneity of the respiratory system, we believe that the irregular distribution of preferential involvement in the upper lobes and changes in the small airways may explain, at least in part, the decline of mean reactance in adults with CF.<sup>7,44</sup> In addition, we observed higher impedance module at 4 Hz values in adults with CF than in controls. The impedance module at 4 Hz is related to the total mechanical load of the respiratory system, describing the effect resulting from respiratory system resistance, compliance, and inertia.<sup>45</sup> This parameter expresses the final result of the interactions of all pathophysiological changes involved in the respiratory mechanics of subjects with CF, including reduced airway caliber by mucoid impactions, decreased elastic properties with reduction in the dynamic compliance of the respiratory system, and inhomogeneity of the respiratory system.<sup>7,44</sup>

In inspiratory lung-volume quantification using multidetector CT, as expected, we observed negative correlations between the normally aerated regions and the forced oscillation technique resistive parameters (intercept resistance and mean resistance), which is in agreement with the notion that resistance is lower in well-ventilated areas. In expiratory lung-volume quantification using multidetector CT, we observed negative correlations between the poorly aerated regions and the forced oscillation technique resistive parameters. This is not surprising, as the poorly aerated regions represent areas with fibrosis conglomerates that cause radial traction on the caliber of the airways due to greater elastic recoil, which allows greater opening of the airways to any lung volume, in turn causing supranormal flow and reduced resistive parameters. Similar to the forced oscillation technique variables, we found significant correlations between  $FEF_{27-75\%}$  and variables in lung-volume quantification using multidetector CT (especially during the expiratory phase), which supports the idea that these parameters characterize the small airways.<sup>7</sup> Notably, we found associations between lung-volume quantification using multidetector CT and  $D_{LCO}$ , with the highest values of pulmonary diffusion observed in the normally aerated regions during inspiratory lung-volume quantification using multidetector CT. These associations can be justified by the fact that  $D_{LCO}$  directly depends on the surface area available for gas exchange, according to Fick's law, which calculates the rate of gas diffusion through the alveolar-capillary membrane. In fact, in adults with CF,  $D_{LCO}$  has been considered as one of the parameters that best portrays lung involvement in CT scans.<sup>46</sup>

Our study included some limitations, as can be found in any study. First, we evaluated a relatively small number of

adults with CF; however, it is worth emphasizing that, in addition to the fact that CF is a rare condition, an adult population with CF has only emerged in recent decades in light of increased survival rates due to improvements in the therapeutic arsenal and respiratory physiotherapy.<sup>1</sup> Second, the patient and control groups were not statistically paired for body mass index because weight matching was hampered by the fact that CF commonly causes a state of malnutrition due to pancreatic impairment and malabsorption syndrome<sup>47</sup>; however, weight does not influence the parameters of the PFTs because it is not a factor in the reference equations that model pulmonary function.<sup>12</sup> Finally, quantitative analysis of the airways through lung-volume quantification using multidetector CT could have been important in the correlation studies, especially in relation to the parameters provided by the forced oscillation technique.<sup>23,37</sup> Despite these limitations, we believe that both lung-volume quantification using multidetector CT and the forced oscillation technique can help in the early diagnosis and more aggressive management of lung disease in CF. Thus, future studies can be dedicated to evaluating the longitudinal impact of these new tools in the management of CF patients.

### Conclusion

Our study shows that there were larger non-aerated and poorly aerated regions in adults with CF. Despite these abnormalities, total lung volume measured with lung-volume quantification using multidetector CT remained unchanged and was associated with the total thoracic gas volume measured by body plethysmography. In these subjects, the hyperaerated regions were associated with the functional markers of gas retention in the lungs. Furthermore, the decrease in normally aerated regions was associated with increase of the resistive parameters revealed by the forced oscillation technique and reduced pulmonary diffusion. Taken together, lung-volume quantification using multidetector CT is able to estimate the lung volumes of compartments with different densities in adults with CF, in addition to being clearly associated with pulmonary function abnormalities.

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