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Lung structure and function relation in systemic sclerosis: Application of lung densitometry

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ABSTRACT

Introduction: Interstitial lung disease occurs frequently in patients with systemic sclerosis (SSc). Quantitative computed tomography (CT) densitometry using the percentile density method may provide a sensitive assessment of lung structure for monitoring parenchymal damage. Therefore, we aimed to evaluate the optimal percentile density score in SSc by quantitative CT densitometry, against pulmonary function.

Material and methods: We investigated 41 SSc patients by chest CT scan, spirometry and gas transfer tests. Lung volumes and the *n*th percentile density (between 1 and 99%) of the entire lungs were calculated from CT histograms. The *n*th percentile density is defined as the threshold value of densities expressed in Hounsfield units. A prerequisite for an optimal percentage was its correlation with baseline DLCO %predicted. Two patients showed distinct changes in lung function 2 years after baseline. We obtained CT scans from these patients and performed progression analysis.

Results: Regression analysis for the relation between DLCO %predicted and the *n*th percentile density was optimal at 85% (Perc85). There was significant agreement between Perc85 and DLCO %predicted ($R = -0.49$, $P = 0.001$) and FVC %predicted ($R = -0.64$, $P < 0.001$). Two patients showed a marked change in Perc85 over a 2 year period, but the localization of change differed clearly.

Conclusions: We identified Perc85 as optimal lung density parameter, which correlated significantly with DLCO and FVC, confirming a lung parenchymal structure–function relation in SSc. This provides support for future studies to determine whether structural changes do precede lung function decline.

1. Introduction

Clinical risk assessment of organ manifestations in systemic sclerosis (SSc) has revealed that interstitial lung disease (ILD) is present in 53% of cases with diffuse cutaneous SSc (dcSSC) and in 35% of cases with limited cutaneous SSc (lcSSc) [1]. For evaluating the response to treatment of ILD, pulmonary function tests (PFTs) such as the diffusion capacity for carbon monoxide (DLCO) and forced vital capacity (FVC) are key outcome measures. However, these measures are affected by pulmonary vascular changes and chest wall skin stiffening, respectively [1]. Therefore, more specific measures of lung parenchymal involvement of ILD may provide additional structural information.

Currently, chest high-resolution computed tomography (HRCT) is considered the most accurate noninvasive imaging method for ILD assessment. Both severity and extent of ILD are usually estimated by semi-quantitative scoring of a limited number of cross-sectional slices through the lungs [2,3]. However, visual scoring has limited reproducibility, because of its subjective nature, and is time-consuming, thereby constraining the number of slices that can be assessed. HRCT data provide a means to quantitatively analyze the structure of the whole lung, since inflammation, ground glass opacities and fibrosis can be quantified by lung densitometry. Therefore, objective quantitative techniques by CT densitometry

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may provide a more sensitive measurement, similar to what has been proven in assessing progression of pulmonary emphysema by the percentile density method [4]. Since these quantitative techniques are automated, it is feasible to quantify the entire lungs instead of only a limited number of slices, with a smaller chance of missing pathological changes.

Previously, Camiciotolli et al. [5] reported that lung density histogram parameters are more reproducible than visual assessment of HRCT and are more closely related to functional, exercise and quality-of-life impairment in SSc. In their evaluation of each patient, they calculated the average global density of the lung and included kurtosis and skewness of the density histogram of the whole lung. However, this analysis did not provide a single overall score for the structure of the lungs and, more importantly, lung density values were not corrected for lung volume. In a recent report, the same investigators clearly demonstrated the need for volume correction of density parameters [6]. By a so-called sponge model [7], in which the lungs are considered mass preserving (i.e. the total lung mass is constant during breathing), density values can be corrected in a relatively simple calculation. Volume-corrected lung density parameters calculated by specific software may be useful outcome measures in evaluating the progression of ILD and the response to treatment. Therefore, the aim of this study was to identify the optimal volume correction and percentage threshold for the percentile density method in SSc.

2. Material and methods

2.1. Patients

We investigated 41 patients with SSc who were referred consecutively to our tertiary outpatient targeted multidisciplinary healthcare program. As part of this program, all patients underwent, among other tests, PFTs and an HRCT scan of the thorax; they were instructed to take their usual medication before scanning. Included patients were classified as lcSSc or dcSSc according to LeRoy et al. [8]. The local Medical Ethical Committee approved the protocol. Written informed consent was obtained from each patient prior to enrolment. In two individual patients PFTs (both FVC and DLCO) significantly changed during clinical follow-up. To analyze this we performed additional CT scans.

2.2. Pulmonary function testing

All SSc patients had lung volume, spirometry and gas transfer studies. These PFTs included inspiratory vital capacity, total lung capacity, FVC, forced expiratory volume in 1 s and single-breath DLCO. Results are expressed as a percentage of the predicted value [9,10].

2.3. Computed tomography

All patients were scanned during full inspiration without contrast enhancement by the same CT scanner (Aquilion 64, Toshiba Medical Systems, Otawara, Japan), calibrated according to the manufacturer's guidelines. The standardized protocol comprised the following: tube voltage = 120 kVp; tube current = 140 mA without modulation; rotation time = 0.4 s; collimation = 64 × 0.5 mm; helical beam pitch = 0.8. Axial slices were reconstructed for visual ILD scoring with 0.5 mm slices with 0.4 mm increment and lung kernel (FC30), and for densitometry with 5 mm thick slices with an increment of 2.5 mm and smooth kernel (FC03).

2.4. Image analysis

Images were processed by Pulmo-CMS software (version 2.1, Medis medical imaging systems BV, Leiden, the Netherlands) [11]. The CT scans were first recalibrated on the basis of densities measured in extrathoracic air and blood in the descending aorta [12]. After automated lung contour detection with user correction options was complete, lung volumes and the *n*th percentile density of the entire lungs were calculated. The *n*th percentile density is defined as the threshold value of densities expressed in Hounsfield units (HU), below which *n*% of all lung voxels in the CT images are distributed (as schematically illustrated in Fig. 1). In order to optimize the percentile method, we calculated all percentile densities by using percentages between 5% and 95% (Perc5–Perc95) with increments of 5%.

Subclinical parenchymal lung disease was previously defined as high attenuation areas (%HAAs) within the lung fields having a CT attenuation value between −600 and −260 HU [13]. For comparison, we therefore performed a similar analysis in our data set of lung densities. Finally, an experienced chest radiologist (LK) scored all CT scans visually according to the Kazerooni scoring system [3].

2.5. Statistical analysis

Optimization of the percentile density method was based on the correlation between *n*th percentile density and DLCO, which should be as high as possible. This was investigated by regression analysis, with DLCO as the dependent variable and one of the *n*th percentile densities as the independent variable. Lung volume was entered as a covariate to correct for different lung sizes. The partial correlation coefficient was then plotted against the percentage *n*. The statistical analysis was performed by using SPSS version 20.0.2, with a programmability extension for python scripting. The relation between the percentile and the correlation coefficient was automatically plotted by using Matplotlib [14].

Using the optimal percentage for the percentile density method, we investigated the cross-sectional correlations with the remaining lung function parameters. In addition, we studied the correlation of %HAA with the cross-sectional DLCO %predicted and FVC %predicted.

2.6. Progression map analysis

We noticed distinct changes in the FVC %predicted and DLCO %predicted during clinical follow-up of our patient population. Therefore we obtained CT scans from these patients and performed a recently published progression analysis between baseline and follow-up CT scans [15]. Local changes in lung density were computed by progression analysis [15]. Corresponding locations in the CT scans between baseline and follow-up were obtained by non-rigid intensity-based image registration using elastix [16]. After we corrected for lung volume differences with the sponge model, local changes in lung density were calculated and displayed [15].

3. Results

The clinical characteristics of the 41 SSc patients (lcSSc: $n = 15$) in this prospective cross-sectional study are shown in Table 1.

3.1. Determination of the optimal percentage

From the regression analysis (with CT-derived lung volume as a covariate), we found that the relation between the gas transfer