Increased Expiratory Computed Tomography Density Reveals Possible Abnormalities in Radiologically Preserved Lung Parenchyma in Idiopathic Pulmonary Fibrosis

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Objectives: Idiopathic pulmonary fibrosis (IPF) is a progressive lethal chronic lung disease with unclear pathogenesis. Radiological hallmark is the pattern of usual interstitial pneumonia accentuated in peripheral and basal areas with otherwise preserved lung structure. One hypothesis is that alveolar collapse and consequent induration lead to fibrotic transformation of lung tissue. The aim of the study was to investigate normal-appearing tissue during expiration for signs of collapsibility and differences from other diseases or controls.

Materials and Methods: We retrospectively assessed a total of 43 patients (15 IPFs, 13 chronic obstructive pulmonary diseases, and 15 controls) with nonenhanced computed tomography (CT) in inspiration and expiration, performed for routine clinical workup. Densitometry of visually unaffected lung tissue was conducted in all lung lobes with a region of interest of 15-mm in diameter on soft tissue kernel reconstruction (slice thickness, 1 mm) during inspiration and expiration.

Results: One-factor analysis of variance analysis yielded significant difference in attenuation changes between inspiration and expiration of unaffected lung parenchyma among all subject groups in all lung lobes. For IPF patients, the highest differences in densities were observed in the lower lobes, which is the predominantly affected site of usual interstitial pneumonia. In the chronic obstructive pulmonary disease group, the density remained rather equal in the entire lung.

Conclusions: High CT attenuation changes between inspiration and expiration in IPF patients might suggest altered lung parenchyma in normal-appearing tissue on CT. Density changes during the respiratory cycle might be explained by alveolar collapse of radiologically unaffected lung tissue possibly preceding fibrosis. These results support the concept of alveolar collapse preceding lung fibrosis in IPF.

Key Words: idiopathic pulmonary fibrosis, COPD, ACOS, emphysema, collapse induration, CT density, inspiratory density, expiratory density, alveolar collapse

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Idiopathic pulmonary fibrosis (IPF) is a devastating lung disease, characterized by a progressive fibrosis of the lung parenchyma. Radiological hallmark of IPF is the so-called usual interstitial pneumonia (UIP) pattern, which is characterized by reticular opacities, traction bronchiectasis, and commonly honeycombing, while ground glass is less predominant.[1] Usual interstitial pneumonia on high-resolution computed tomography (CT) is essential for IPF diagnosis, and imaging itself can be sufficient for diagnosis if a definite UIP pattern is diagnosed and there is no clinical suspicion of other diseases associated with an UIP pattern.[1] Further analysis of thoracic CT data of IPF patients using densitometric and histogram-based analyses has been proven to correlate with pulmonary function tests and was associated with transplant-free survival.[2]

The pathogenesis of IPF remains undetermined. Current hypotheses blame chronic lung injury and abnormal wound healing[3] for the excessive scarring observed in IPF lungs. In addition, impaired function with alveolar collapse might lead to collapse induration[4,5] and thus densified lung tissue.

In contrast to lung fibrosis, chronic obstructive pulmonary disease (COPD) is defined by chronic airflow limitation caused by a mixture of small airways disease (eg, obstructive bronchiolitis) and parenchymal destruction (emphysema).[6] It is commonly induced by tobacco smoking and prevalent in this population.[7] If the patient has an overlap syndrome with an asthmatic component, the term ACOS (asthma and chronic obstructive overlap syndrome) is used.[8] Radiological characteristics of COPD are thickened bronchial walls, whereas emphysema is characterized by rarefication of lung parenchyma.[9,10] Air trapping represents another hallmark in the COPD spectrum.

Having observed that normal-appearing parenchyma in the lung of IPF patients presents very dense in expiratory CT scans, we intended to investigate this phenomenon more in detail. The purpose of this study was to research the effects of inspiration and expiration on CT attenuation of the lung in IPF and COPD (including emphysema and ACOS subtypes) compared with patients with radiologically healthy-appearing lungs and no known lung disease.

MATERIALS AND METHODS

The study was approved by the Ethics Committee of Bern (BASEC No. 2016–01632).

Computed tomography chest scans of 15 patients with IPF, diagnosed according to the current ATS/ERS guidelines,[1] 13 patients with COPD, with or without radiological emphysema or ACOS (summarized as COPD for simplification), which were diagnosed in the presence of FEV1/FVC < 70% and/or with associated features of COPD and asthma (ACOS) according to current GOLD guidelines,[11,12] and 15 controls, who received CT scan for various medical reasons (eg, unclear dyspnea) without radiological lung parenchymal abnormalities, were retrospectively analyzed. All patients underwent CT scans for medical indications at our institution between February 01, 2015, and October 31, 2016, and were selected in a consecutive order.

Chest CT Examination and Acquisition

Non–contrast-enhanced CT scans were performed for all subjects using a 128-detector row CT scanner (Siemens SOMATOM Definition FLASH; Siemens Medical Solutions, Erlangen, Germany) or a 64-detector row CT scanner Philips Brilliance 64 (Philips Medical Systems, Best, the Netherlands) as part of routine clinical workup. Computed

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tomography scans were performed during end-inspiratory and end-expiratory breath-hold. Images were acquired in supine position from apex of the lung to the costodiaphragmatic recess. No intravenous contrast agent was administered.

A tube voltage of 120 kVp or 100 kVp was applied, which was kept constant between inspiratory and expiratory scans for each patient. A standard dose protocol was chosen for inspiratory scans and a low-dose protocol for the expiratory scans, both applying automated exposure control with tube current modulation (CARE Dose4D Siemens Health Care; DoseRight, Philips Healthcare). Consequently, tube current modulation resulted in a mean value of 105.3 mA (SD, 44.7) in inspiration and 55.7 mA (SD, 32.3) in expiration. Scans that covered the entire thorax were acquired with spiral acquisition and a slice thickness of 1 mm. The pixel matrix was 512 × 512, collimation was 128 × 0.6 mm, pitch was 0.6, and rotation time was 0.28 second. Siemens Sinogram-Affirmed Iterative Reconstruction (SAFIRE, strength 3) second-generation iterative reconstruction (kernel I31f) was used for image reconstruction on scans obtained using a Siemens SOMATOM Definition FLASH MDCT. For the scans acquired with Philips Brilliance 64, iterative reconstruction with iDose (strength 4, kernel Standard B) was applied.

Lobe-Based CT Densitometry

Lobe-based CT densitometry was performed for all lung lobes in both inspiration and expiration by 2 readers with 4 and 17 years of experience in reading CTs of the lung. A region of interest (ROI) with a diameter of 15 mm was drawn to measure the attenuation values of unaffected-appearing lung parenchyma in axial images of 1 mm thickness in the lung window (window level, −500 Hounsfield units [HU]; window width, 1500 HU).

In IPF and COPD subjects, the ROI was positioned as far as possible from the radiologically affected lung tissue, that is, into areas without features of fibrosis or emphysema. Vessels were excluded whenever possible.

Statistical Analysis

Statistical analysis was performed with IBM SPSS Statistics, version 21 (IBM, Armonk, NY). Normal distribution of data was tested using the Shapiro-Wilk test. One-factor analysis of variance (ANOVA) analysis was used to compare absolute attenuation values and attenuation changes between inspiration and expiration in all lung lobes between subject groups. A 2-tailed paired student *t* test was applied for comparing attenuation changes between the upper and lower lobe in different subject groups. The Mann-Whitney *U* test was performed for absolute HU values between IPF patients and controls as well as between IPF patients and COPD patients. Differences were considered statistically significant with a *P* value of less than 0.05.

Interobserver variability was tested with the intraclass correlation coefficient (ICC), an index of interrater reliability of quantitative data. For the generation of 3-dimensional receiver operating characteristic (ROC) surfaces, we used R (v. 3.4.0), boot (v.1.3-19), and plotly (v.4.7.0) with adapted scripts applying the methods of Nakas and Yiannoutsos[13] to generate and illustrate the empirical 3-dimensional ROC surfaces and their respective volume under the ROC surface (VUS). For the 95% confidence intervals, we used the bias-corrected and accelerated method as proposed by Efron,[14] based on R = 5000 bootstrap replicates.

RESULTS

Patients' Characteristics

The study included a total of 43 subjects, 15 patients with diagnosed IPF (mean age, 64.6 years; range, 53–83 years), 13 patients with a diagnosis of COPD of various degree including emphysematous subtypes and ACOS (mean age, 61.9 years; range, 44–79 years), and 15 subjects with no radiological features of an interstitial lung disease (ILD) or emphysema (mean age, 50.6 years; range, 24–78 years). Thirty-two male and 13 female patients were included. Eight of the IPF patients exhibited UIP pattern and 7 patients possible UIP pattern.

Pulmonary function tests were available for 12 patients of the control group, for 12 patients of the COPD group, and for all IPF patients (Table 1).

Absolute Attenuation Values

Hounsfield units were measured in all lobes in inspiration and expiration (Table 2). Attenuation values in inspiration of IPF patients are in the range of controls. In expiration, there is a marked increase in attenuation, especially in the lower lobes. Figure 1 illustrates the attenuation changes in a subject with IPF. To compare absolute HU values between groups, a Mann-Whitney *U* test was performed. In inspiration, there was no difference in the attenuation between IPF patients and controls ($P = 0.174$). On the contrary, in expiration, significant differences were observed ($P < 0.001$). A comparison between HU values of COPD patients and IPF patients yielded significant differences for inspiration and expiration ($P < 0.001$) (Fig. 2).

Comparison of Attenuation Changes Between Subject Groups in Inspiration and Expiration

Changes in the HU for all lung lobes between inspiration and expiration were highest in the IPF group, followed by controls, and lowest in the COPD group (Table 3). Representative images of 3 individuals

TABLE 1. Pulmonary Function Tests of Controls, COPD, and IPF Patients as Available (Control n = 12, Emphysema/COPD n = 12, and IPF n = 15, Other Numbers Are Reported in Parentheses)

Parameter	Control	COPD	IPF
FVC (l)	2.97 ± 1.05	3.93 ± 1.11	2.59 ± 0.8
FVC (%)	88.75 ± 26.15	96 ± 22.55	60.33 ± 15.95
TLC (l)	5.19 ± 1.8 (n = 9)	7.35 ± 1.09 (n = 9)	4.38 ± 1.16 (n = 13)
TLC (%)	92 ± 18.05 (n = 9)	113.33 ± 16.16 (n = 9)	60.31 ± 13.21 (n = 13)
FEV 1 (l)	2.33 ± 0.72	2.23 ± 1.08	2.18 ± 0.7
FEV 1 (%)	85.92 ± 25.25	69.33 ± 30.02	66.6 ± 19.12
corr DLCO	5.76 ± 2.06 (n = 10)	5.65 ± 1.93 (n = 11)	4.24 ± 1.28
DLCOc (%)	71.89 ± 21.27 (n = 10)	62.91 ± 17.33 (n = 11)	46.4 ± 12.93

Data present mean ± SD.

COPD indicates chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; FVC, forced vital capacity; TLC, total lung capacity; FEV 1, forced expiratory volume in 1 second; DLCO, diffusion capacity of the lung for carbon monoxide.

TABLE 2. Absolute Attenuation in HU in the Upper Lobes, Middle Lobe/Lingula, and Lower Lobes With Standard Deviation for the Different Groups in Inspiration and Expiration

		Controls		COPD		IPF	
		Inspiration, HU	Expiration, HU	Inspiration, HU	Expiration, HU	Inspiration, HU	Expiration, HU
Upper lobe	R1	−874.5 ± 28.4	−800.7 ± 42.2	−899.5 ± 19.9	−838.9 ± 50.2	−852.9 ± 37.5	−712.0 ± 72.7
	R2	−880 ± 29.6	−807 ± 42.8	−899.9 ± 22.8	−846.3 ± 46.9	−852.6 ± 41.3	−711.1 ± 87.7
Middle lobe/lingula	R1	−881.6 ± 30.0	−809.7 ± 44.1	−901.4 ± 31.8	−839.6 ± 56.6	−858.2 ± 37.9	−718.0 ± 79.1
	R2	−881.8 ± 32.9	−815.6 ± 40.6	−900.2 ± 33.5	−853.7 ± 52.4	−848.2 ± 40.0	−715.7 ± 67.3
Lower lobe	R1	−858.3 ± 46.4	−733.2 ± 81.2	−891.1 ± 41.3	−819.7 ± 73.3	−837.5 ± 53.6	−605.6 ± 115.4
	R2	−854 ± 45.0	−720.9 ± 84.6	−881.0 ± 45.7	−819.6 ± 70.4	−816.4 ± 61.7	−555.1 ± 121.5

HU indicates Hounsfield units; COPD, chronic obstructive pulmonary disease; R1, reader 1; R2, reader 2.

are presented in Figure 3. A 1-factor ANOVA analysis yielded significant differences of the density changes between the groups for each lung lobe (for all lobes: $P < 0.001$) (Fig. 4). The highest differences in the attenuation changes between inspiration and expiration were observed in the lower lobes of IPF patients, which represent the lung areas predominantly affected by UIP.

Comparison of Upper Versus Lower Lobes Attenuation Changes

A 2-tailed paired *t* test was used to compare attenuation changes between upper and lower lobes in inspiration and expiration for each group. Idiopathic pulmonary fibrosis patients and controls exhibited significant attenuation changes in inspiration and expiration with the highest attenuation differences seen in the lower lobes for both groups ($P < 0.005$), in accordance with the predominant affected area of UIP, whereas the comparison of upper and lower lobes attenuation changes yielded no significant difference in COPD patients ($P = 0.241$) (Fig. 5).

Attenuation Values of Air Ventral to the Patient

As an internal control, the air ventral to the patient was measured at the level of the carina both at inspiration and expiration for the IPF patients. Mean HU values of these measurements were −1001 (SD, 2.11) HU in inspiration and −999.7 (SD, 2.36) HU in expiration. The highest difference for a pair of inspiration/expiration measurements was 3 HU.

Interobserver Variability

Interobserver variability, tested with single score intraclass correlation, yielded an ICC of 0.968. An ICC of greater than 0.90 indicates excellent reliability.[15]

ROC Analysis

For the assessment of the 3-class discriminative power of CT density changes, we generated 3-dimensional ROC surfaces and computed the respective VUS as the equivalent of the 2-dimensional ROC area under the curve (AUC) (Fig. 6A). The exemplary VUS for the difference in attenuation changes (for Reader 2) is 0.7265 (95% confidence interval, 0.4068–0.8876, a random predictor would yield 0.1667).

Classical ROC analyses were calculated for percent attenuation changes between inspiration and expiration in IPF and controls. When considering the whole lung, the AUC was 0.811 for reader 1 and 0.814 for reader 2 (Fig. 6B). For the lower lobes alone, the AUC was 0.830 for reader 1 and 0.872 for reader 2 (Fig. 6C). Based on the measurements of reader 2, an attenuation change in HU of approximately

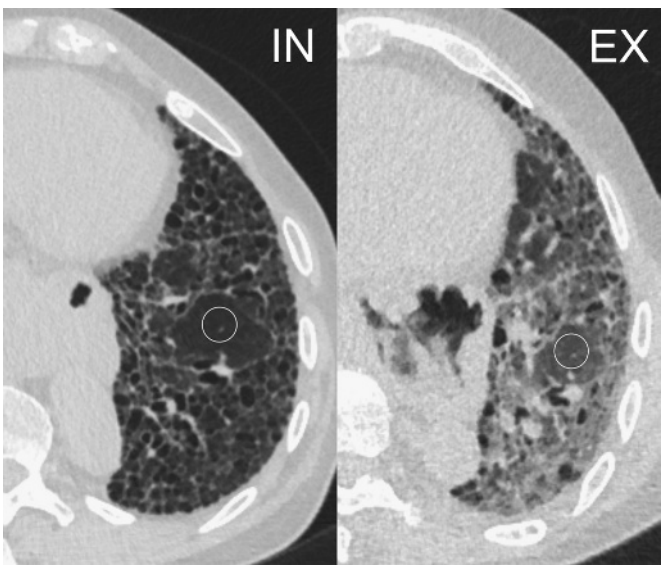

FIGURE 1. Attenuation in an unaffected-appearing lung area in the lower lobe of an idiopathic pulmonary fibrosis patient. During inspiration, attenuation was –874 HU; during expiration, HU –612 HU.

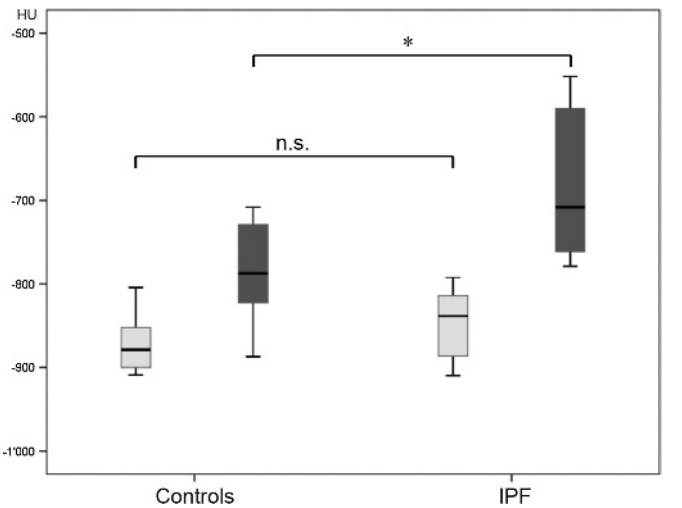

FIGURE 2. Absolute Hounsfield units (HU) values for inspiration and expiration between controls and patients with idiopathic pulmonary fibrosis (for all lobes). There was no significant difference in the inspiration HU values between these 2 groups (light-colored boxes; $P = 0.174$). However, for expiration, the HU differences were statistically significant (dark-colored boxes; $P < 0.001$). *$P < 0.001$; n.s. not significant.

TABLE 3. Average Density Differences in Percent in the Upper Lobes, Middle Lobe/Lingula, and Lower Lobes With Standard Deviation for the Different Groups

		Controls, %	COPD, %	IPF, %
Upper lobe	R1	9.3 ± 4.3	7.5 ± 4.9	23.2 ± 10.1
	R2	9.2 ± 4.2	6.7 ± 3.7	21.6 ± 14.3
Middle lobe/lingula	R1	8.9 ± 5.5	7.7 ± 4.6	20.9 ± 12.1
	R2	8.3 ± 4.1	5.6 ± 3.8	19.5 ± 9.3
Lower lobe	R1	18.0 ± 10.6	9.2 ± 5.6	43.2 ± 23.6
	R2	19.7 ± 11.1	7.9 ± 4.8	54.1 ± 29.9

COPD indicates chronic obstructive pulmonary disease; R1, reader 1; R2, reader 2.

27% between inspiration and expiration in the lower lobe could be used as a discriminator between IPF and controls with a sensitivity of 80% and a specificity of 83%.

When based on the absolute HU values in expiration, there was an AUC of 0.778 for reader 1 and 0.846 for reader 2. Here, a discriminator at a HU of −658 could be established for the expiratory scans with a sensitivity of 73% and a specificity of 73%.

DISCUSSION

Computed tomography attenuation in the lungs of IPF patients seems high in expiratory scans. We thus decided to further analyze this phenomenon and investigated absolute CT lung density and density changes during inspiration and expiration in areas with no or minimal abnormalities in IPF patients in comparison to those of COPD patients and patients with no radiological signs of ILD. We found that lungs of IPF patients exhibited significantly higher attenuation values in expiration than those of controls, whereas there was no significant difference in HU between the lungs of IPF patients and controls during inspiration. Attenuation changes between inspiration and expiration were significantly different among all the 3 groups. To our knowledge, this is the first study systematically analyzing lung density of IPF patients during inspiratory and expiratory CT scans.

Expiratory chest CT scans have been proven to be useful for the evaluation of certain diffuse lung diseases such as emphysema or ILD.[16] They provide functional and dynamic information on lung parenchyma, small airways, and interstitium that would otherwise (ie, only by means

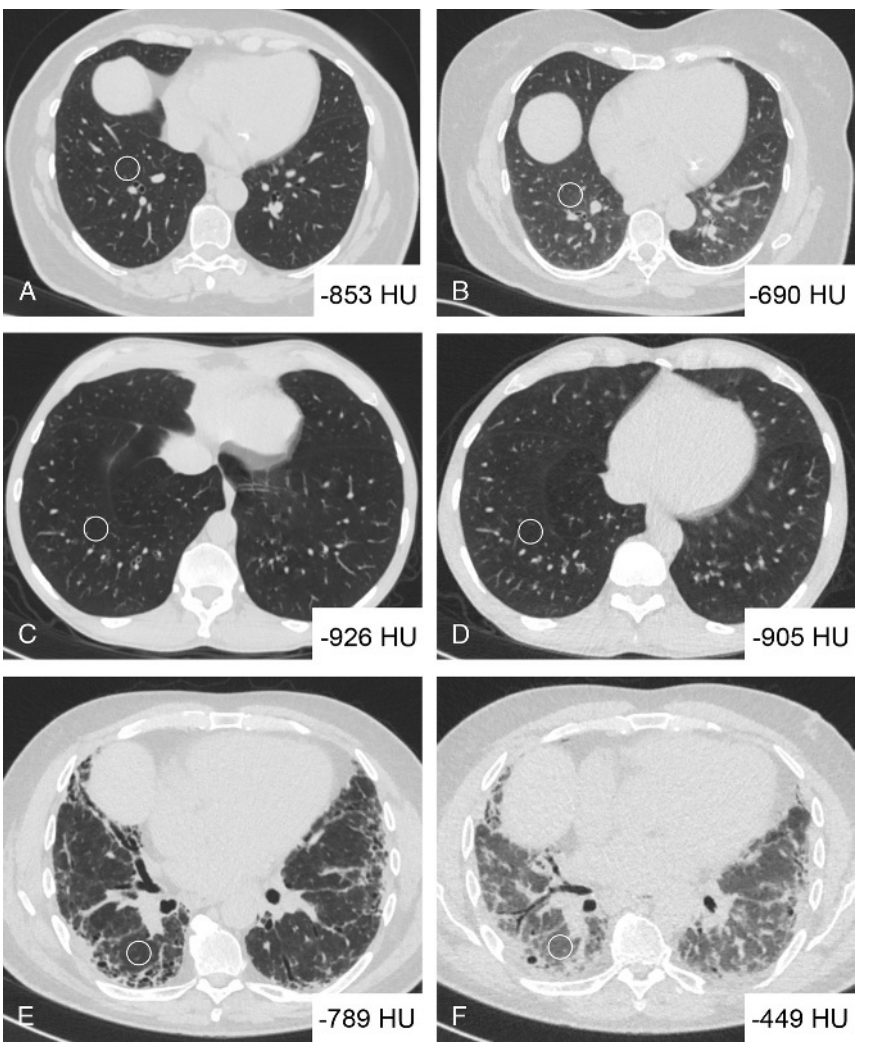

FIGURE 3. Representative computed tomography density measurements of lower lung lobes in inspiration (left) and expiration (right) in (A and B) a control subject, (C and D) COPD patient, and (E and F) idiopathic pulmonary fibrosis patient. White circle depicts region of interest.

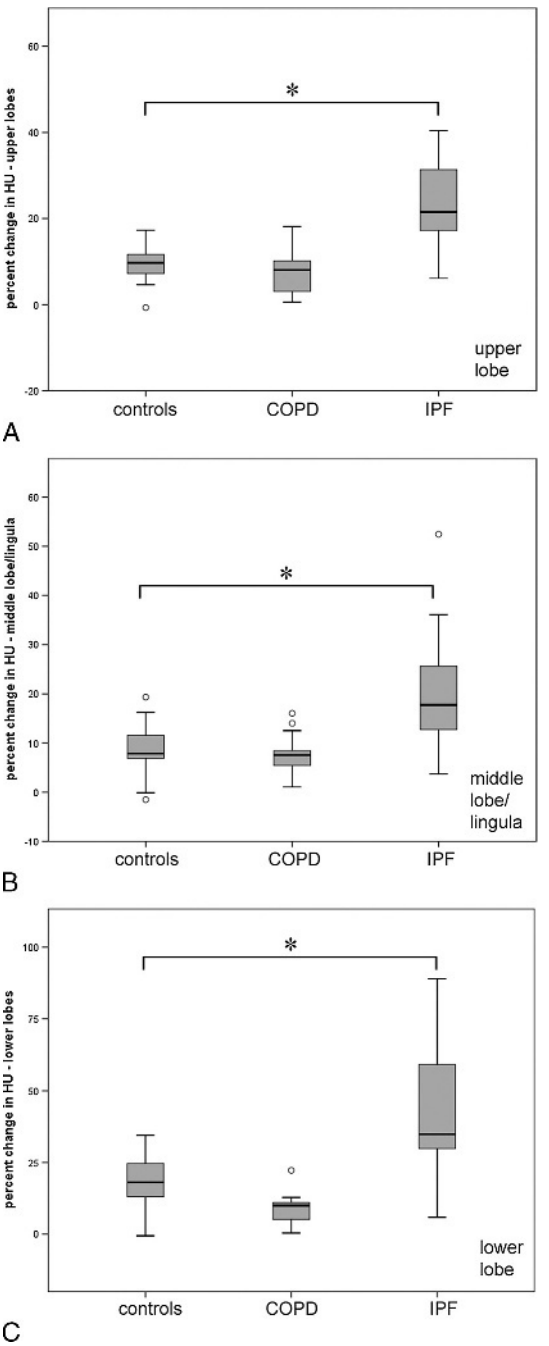

FIGURE 4. One-factor ANOVA analysis yielded significant difference in attenuation changes between inspiration and expiration of unaffected lung parenchyma among all the subject groups in all lung lobes ($P < 0.001$) (A: upper lobes; B: middle lobe/lingula; C: lower lobes). For idiopathic pulmonary fibrosis patients, highest differences in densities were observed in the lower lobes (C), which is the predominant affected site of UIP. *$P < 0.001$.

of an inspiratory CT scans) be unavailable.[17,18] In patients with COPD and emphysema, expiratory scans help to identify lung areas with fixed hyperinflation versus areas that still take part in the volume change of a respiratory cycle and thus facilitate planning of local therapy.[19,20]

Earlier densitometry studies focusing on COPD patients reported mean lung density ranging from −880 to −813 HU in inspiration and from −840 to −736 HU in expiration.[21–23] The density we measured in the lungs of COPD patients ranged from −901 to −881 HU in inspiration and from −854 to −820 HU in expiration. These values are at the lower range or below those of earlier studies. A possible explanation for this difference—besides a different set of patients—might be found in a different measurement technique; although the aforementioned authors measured the whole lung, we measured small ROIs with a minimal amount of included blood vessels that might have lowered the attenuation values.

For controls, we found attenuation values between −882 HU in inspiration and −721 HU in expiration, which is in the range of earlier publications.[22]

Many studies have correlated lung function tests and quantitative parameters such as lung volume or mean density in inspiratory and expiratory CT scans.[24] It has been shown that air trapping of emphysema and hyperinflated areas correlates with functional loss of lung parenchyma.

Expiratory scans are part of the established workup in lung diseases with bronchiolitis such as hypersensitivity pneumonitis or constrictive bronchiolitis after lung transplantation.[25] Interpretation of mosaic pattern present on inspiratory CT scans is further refined by expiratory CT scans. Lobulated areas of lower attenuation, which represent retained gas in the secondary pulmonary lobules, are translated as an obstruction of the expiratory airflow, seen in many obstructive diseases, such as asthma, emphysema, bronchiolitis, and many others.[17,26]

Although expiratory CT scans are routinely performed for the aforementioned lung diseases, no such approach exists for patients with IPF. It is still debated when an expiratory CT scan should be acquired in terms of additional information gained as well as radiation concerns, varying between volumetric and noncontiguous CT scans. Some radiologists perform expiratory CTs for ILD patients with the sole purpose to exclude air-trapping and thus to be able to exclude a pattern that is incompatible with the diagnosis of UIP. In a survey among members of the European Society of Thoracic Imaging, only 58% of respondents stated to routinely perform expiratory scans in patients with ILD.[16] The common paradigm indicates that expiratory scans do not provide further information than to exclude air-trapping. Possibly due to this untested assumption, there is a lack of systematic studies having analyzed expiration in IPF and other ILD patients.

Our finding of increased density during expiration in radiologically healthy-appearing tissue of IPF lungs fits to the concept of alveolar collapse and collapse induration of IPF pathogenesis.[4] Idiopathic pulmonary fibrosis patients are known to have defective surfactant production,[5] and mutations of surfactant protein have been detected in some patients.[27] Surfactant dysfunction has been associated with fibrosis and could contribute to increased collapsibility followed by collapse induration as a precursor of fibrosis.[4]

As histopathological staining for fibrogenic pathways was altered in apparently healthy lung tissue, the fibrotic process affects the entire lung of IPF patients.[28] In analogy, we observe increased density in healthy-appearing tissue, which might indicate increased collapsibility.

Recently, Mai et al[29] reported that even in areas with no or minimal abnormalities on CT images, there were islands of increased attenuation located in or near the interlobular septa on micro-CT scans. These areas corresponded to fibroblastic foci (ie, active, very recently formed fibrotic areas) at histologic analysis. The authors further found an abnormal adjacency of alveolar walls suggesting alveolar collapse. Because we also focused on normal-appearing lung areas, it seems possible that the increased density we perceived on expiratory scans might be attributable to alveolar collapse. Thus, areas of increased attenuation in expiration that seem to be normal on inspiratory CT might already be affected by fibrotic changes. Previous studies have shown that patients with histologically proven IPF can present without the typical CT findings of UIP.[30]

With the availability of new antifibrotic drugs such as pirfenidone and nintendanib[31,32] that slow down disease progression, treatment response needs to be measured. However, the most commonly used

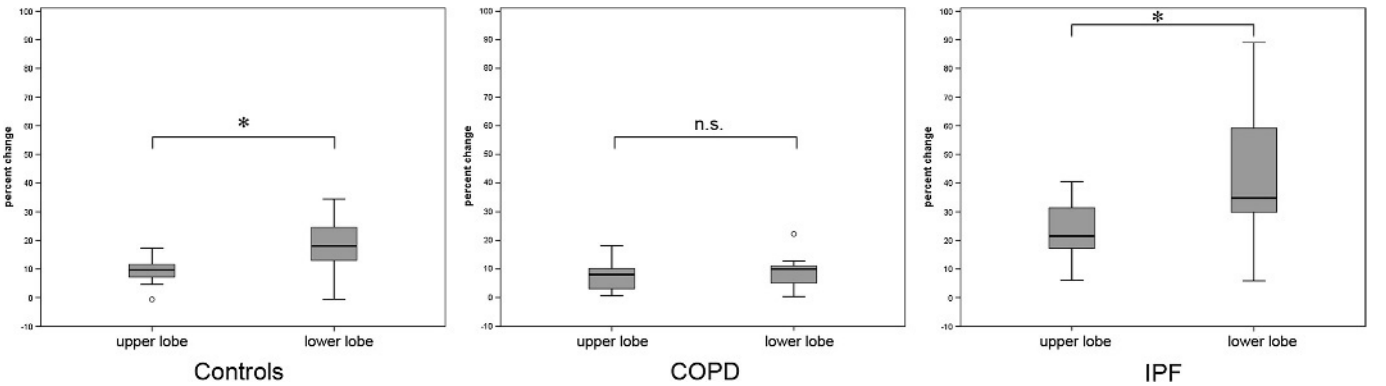

FIGURE 5. Differences in density between upper lobe and lower lobe for controls, COPD, and idiopathic pulmonary fibrosis. *T* test revealed significant differences between upper lobe versus lower lobe for idiopathic pulmonary fibrosis patients and controls but not for COPD patients. *$P < 0.001$; ns, not significant.

outcome measurement based on FVC is difficult to assess[1,33] and new methods to evaluate treatment response are urgently required. Our findings that apparently unaffected lung parenchyma in IPF lungs has altered density in inspiration and expiration might be an earlier outcome marker to evaluate drug effects before radiological fibrosis or lung functional FVC changes become apparent, if treatments affect alveolar collapsibility. Additional studies in larger cohorts are required to validate our findings.

This study has several limitations. There was no objective control of the degree of inspiration and expiration. Although all patients were instructed in the same way and CT scans were performed in maximal end-inspiration and end-expiration, there is a possibility that

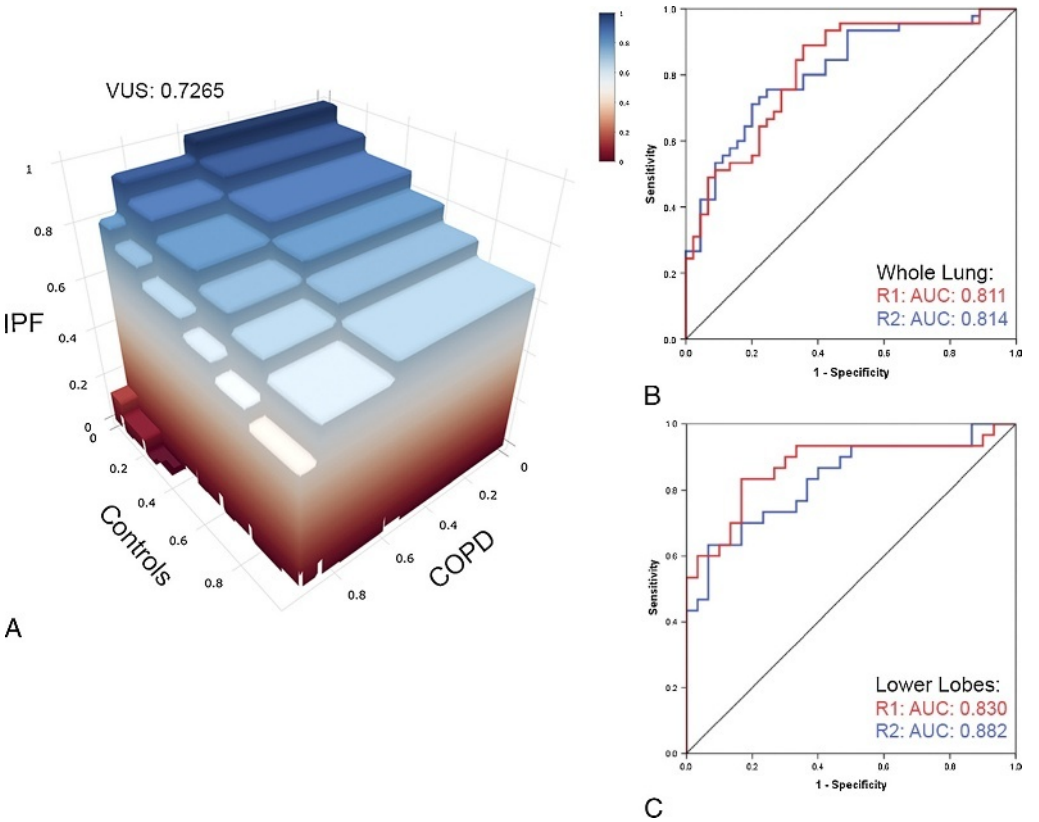

FIGURE 6. A, Three-dimensional ROC curves surfaces for the assessment of the 3-class discriminative power. The respective volume under the ROC surface as the equivalent of the 2-dimensional ROC area under the curve (AUC) was computed. The exemplary volume under the ROC surface for the relative difference in lung attenuation between inspiration and expiration is 0.7265 (95% confidence interval, 0.4068–0.8876; a random predictor would yield 0.1667). B, ROC curve for attenuation changes between inspiration and expiration for idiopathic pulmonary fibrosis (IPF) in comparison to controls. For the whole lung, the AUC was 0.811 for reader 1 (R1) and 0.814 for reader 2 (R2). C, ROC curve for attenuation changes between inspiration and expiration for IPF in comparison to controls. For the lower lobes alone, the AUC was 0.830 for reader 1 (R1) and 0.872 for reader 2 (R2). Based on the measurements of reader 2, an attenuation change in HU of approximately 27% between inspiration and expiration in the lower lobe could be used as a discriminator between IPF and controls with a sensitivity of 80% and a specificity of 83%. Figure 6 can be viewed online in color at www. investigativeradiology.com.

interindividual variations might have occurred. Lung density varies according to the degree of inspiration and expiration. For future studies, the use of portable spirometers could be applied to control for these subjective variations.

The CT protocol used in this study consisting of an inspiratory scan at standard dose and an expiratory scan at low dose might have had an impact on the density units. It is known, however, that changes in tube current (milliampere) alter the amount of noise but do not affect the HU. In an additional measurement, we evaluated the air ventral to the patient at the level of the carina both at inspiration and expiration to control for any systematic error. The mean HU values showed virtually the same HU (−1001 [SD, 2.11] HU in inspiration and −999.7 (SD, 2.36) HU in expiration). Because the difference in attenuation between inspiration and expiration in the lung parenchyma was in the order of 50 to 350 HU, this extremely small difference is very unlikely to have had an influence on the results. For consistency, all patients, that is, also the control and COPD groups, were examined in the same way.

Finally, the small number of patients is a limitation for the statistical power of this study. However, a power analysis conducted before this study revealed that the contrasts in CT density between IPF patients and the other 2 groups were so large that a statistically significant result was achieved.

In conclusion, expiratory lung density is increased in IPF in normal-appearing tissue as opposed to COPD and controls. The common paradigm indicates that expiratory scans do not provide further information than to exclude air-trapping. Possibly due to this untested assumption, there is a lack of systematic studies having analyzed expiration in ILD patients. We suggest that the increased density observed in expiratory scans in IPF patients might indicate early changes in the development of this disease.

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