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

Valentina Petroulia, MD,* Manuela Funke, MD,† Pascal Zumstein,‡ Sabina Berezowska, MD,‡ Lukas Ebner, MD,* Thomas Geiser, MD,† Nenad Torbica, MD,§ Johannes Heverhagen, MD,* and Alexander Poellinger, MD*

Objective: 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 concomitant 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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From the Departments of *Diagnostic, Interventional, and Pediatric Radiology, and †Pulmonary Medicine, Bern University Hospital, University of Bern, Bern; ‡Institute of Pathology, University of Bern, Bern; and §University Institute of Clinical Chemistry, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland. Drs Petroulia and Funke contributed equally to this manuscript.

Address correspondence to: Alexander Poellinger, MD, Department of Diagnostic, Interventional and Pediatric Radiology, Inselspital, University Hospital Bern, Freiburgistrasse, CH-3010 Bern, Switzerland. E-mail: alexander.poellinger@insel.ch.

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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,† 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,‡† ‡‡ 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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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 thicknesses 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 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>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>COPD</th>
<th>IPF</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (l)</td>
<td>2.97 ± 1.05</td>
<td>3.93 ± 1.11</td>
<td>2.59 ± 0.8</td>
</tr>
<tr>
<td>FVC (%)</td>
<td>88.75 ± 26.15</td>
<td>96 ± 22.55</td>
<td>60.33 ± 15.95</td>
</tr>
<tr>
<td>TLC (l)</td>
<td>5.19 ± 1.8 (n = 9)</td>
<td>7.35 ± 0.99 (n = 9)</td>
<td>4.38 ± 1.16 (n = 13)</td>
</tr>
<tr>
<td>TLC (%)</td>
<td>92 ± 18.05 (n = 9)</td>
<td>113.3 ± 16.16 (n = 9)</td>
<td>60.31 ± 13.21 (n = 13)</td>
</tr>
<tr>
<td>FEV 1 (l)</td>
<td>2.33 ± 0.72</td>
<td>2.23 ± 1.08</td>
<td>2.18 ± 0.7</td>
</tr>
<tr>
<td>FEV 1 (%)</td>
<td>85.92 ± 25.25</td>
<td>69.33 ± 30.02</td>
<td>66.6 ± 19.12</td>
</tr>
<tr>
<td>corr DLCO</td>
<td>5.76 ± 2.06 (n = 10)</td>
<td>5.65 ± 1.93 (n = 11)</td>
<td>4.24 ± 1.28</td>
</tr>
<tr>
<td>DLCo (%)</td>
<td>71.89 ± 21.27 (n = 10)</td>
<td>62.91 ± 17.33 (n = 11)</td>
<td>46.4 ± 12.93</td>
</tr>
</tbody>
</table>

*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.
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.

### 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

### 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

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>COPD</th>
<th>IPF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inspiration, HU</td>
<td>Expiration, HU</td>
<td>Inspiration, HU</td>
</tr>
<tr>
<td>Upper lobe</td>
<td>(-874.5 \pm 28.4)</td>
<td>(-800.7 \pm 42.2)</td>
<td>(-899.5 \pm 19.9)</td>
</tr>
<tr>
<td>R1</td>
<td>(-880 \pm 29.6)</td>
<td>(-807 \pm 42.8)</td>
<td>(-901.4 \pm 31.8)</td>
</tr>
<tr>
<td>R2</td>
<td>(-881.8 \pm 32.9)</td>
<td>(-815.6 \pm 40.6)</td>
<td>(-900.2 \pm 33.5)</td>
</tr>
<tr>
<td>Middle lobe/lingula</td>
<td>(-881.6 \pm 30.0)</td>
<td>(-809.7 \pm 44.1)</td>
<td>(-891.1 \pm 41.3)</td>
</tr>
<tr>
<td>R1</td>
<td>(-858.3 \pm 46.4)</td>
<td>(-733.2 \pm 81.2)</td>
<td>(-881.0 \pm 45.7)</td>
</tr>
<tr>
<td>R2</td>
<td>(-854 \pm 45.0)</td>
<td>(-720.9 \pm 84.6)</td>
<td>(-881.8 \pm 32.9)</td>
</tr>
</tbody>
</table>

HU indicates Hounsfield units; COPD, 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. They provide functional and dynamic information on lung parenchyma, small airways, and interstitium that would otherwise (ie, only by means

| 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.
Interpretation of 5 < 0.001. It has been shown that air trapping of emphysema and in analogy, we observe increased density in CT densitometry in IPF patients that slow down disease progression, treatment might be found in patients with COPD 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 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.

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. 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. Idiopathic pulmonary fibrosis patients are known to have defective surfactant production, and mutations of surfactant protein have been detected in some patients. Surfactant dysfunction has been associated with fibrosis and could contribute to increased collapsibility followed by collapse induration as a precursor of fibrosis.

As histopathological staining for fibrogenic pathways was altered with histologically proven IPF can present without the typical CT findings of UIP. With the availability of new antifibrotic drugs such as pirfenidone and nintendan® that slow down disease progression, treatment response needs to be measured. However, the most commonly used...
outcome measurement based on FVC is difficult to assess\textsuperscript{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...
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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REFERENCES


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