Quantitative CT analysis in COPD: do coexisting fibrotic changes influence pulmonary function in patients with advanced emphysema?

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Purpose

Chronic obstructive pulmonary disease (COPD) typically presents with decreased lung function caused by hyperinflation and reduced gas exchange. With high morbidity and mortality, it is the fourth leading cause of death in the world (1).

Chronic lung inflammation histologically results in irreversible destruction and dilatation of terminal air spaces, chronic bronchiolitis and varying fibrotic changes of the smaller airways. These structural pulmonal pathologies result in decreased gas exchange, airflow limitation and air trapping. In lung function tests, patients typically present with reduced forced expiratory volume per second (FEV1), decreased FEV1/FVC-ratio and increased total lung volume [2].

HRCT imaging often shows a typical pattern of centrilobular emphysema. Amongst others, in the COPD Gene Study Group a coexistence of interstitial pulmonary abnormalities with higher attenuation patterns (ground-glass, reticular or nodular opacities) has been reported in a high percentage of patients with COPD [3,4]. More severe and characteristic fibrotic changes in combination with emphysema are summarized in the entity of combined pulmonary fibrosis and emphysema (CPFE), which was first described by Auerbach et al. in 1974 [5]. In this entity, upper lobe emphysema and especially lower lobe fibrosis with mostly patterns of IPF/UIP (as honeycombing and bronchiectasis) are characteristic [6]. In addition to this, well defined HR-CT findings and their distribution the COPD Gene Study Group showed a high prevalence of unspecific interstitial shadowing and interstitial pneumonia in patients with COPD [2]. Chronic fibrotic patterns due to smoking can for example occur in patients with non-specific interstitial pneumonia (NSIP), smoking related interstitial pneumonia (SRIF) or UIP as a distinct entity [7, 8].

In COPD as well as in CPFE qualitative and quantitative HRCT measures of total lung capacity (total volume or percentage of expected lung volume) and the extent of emphysema (threshold-based identification of low attenuation areas) are well described and performed [2, 9-13]. Recent studies compared HRCT-findings with clinical symptoms and tried to find a relationship between CT metrics and pulmonary function. Ando et al. suggested a higher impact of fibrotic compared to emphysematous changes on disease progression of CPFE [14]. Choi et al. underlined that the severity of fibrosis is an important prognostic factor of disease progress in biopsy proven CPFE [15]. In CPFE there is evidence of a counterbalancing effect between restrictive and obstructive spirometric values due to traction of the smaller airways as well as hyperinflation in emphysematic lesions. As a result, FEV1 and total lung capacity (TLC) can be measured within relatively normal ranges [16, 17, 21, 23] in CPFE. Kitaguchi et al. showed a lower decrease of FEV1 in patients with CPFE than in a group of patients with emphysema only [16]. Another trial
on 2416 HRCT-scans of smokers found lower total lung capacity and a lower percentage of emphysema in patients with interstitial lung abnormalities [20].

In our study, we tried to find out whether there is significant decrease of lung function (especially FEV1%) of no further specified fibrotic changes represented by higher attenuation areas in patients with advanced COPD (GOLD 3-4). Is High Attenuation Volume (HAV) a useful parameter to show a significant influence on lung function in severe emphysema?

Methods and materials

A total of 86 patients (figure 1) with COPD and pulmonary emphysema (all clinically classified GOLD stadium 3-4) underwent CT-scans followed by pulmonary function tests. Patients with active lung disease or acute exacerbation of COPD were excluded. All CT-scans were performed with identical scanning parameters (2 scans of the whole lung in full inspiratory and expiratory breath hold, standardized scanning parameters (1,25 mm, 120 kV, 100 mA, soft tissue kernel). Quantitative analysis of CT-data was performed with MeVisPULMO 3D v3.42 (Fraunhofer MEVIS, Bremen, Germany; figure 2) to detect low (LAV) and high (HAV) attenuation volumes, defined by a threshold (LAV: <-950HU; HAV: >-700HU) as it was used in previous studies [19, 20]. HAV was considered the measurable correlate of fibrotic changes of lung tissue. The HAV-extent was classified in three groups (<7%, 7-10%, >10% of lung volume). Peripheral lung volumes within a subpleural space of 2cm width were considered as the lungs "peel", central volumes were defined as "core" volumes. In multivariate and simple regression-analysis results were correlated with FEV1% (FEV1 percentage of the predicted value of FVC) and LAV. p-values of less than .05 were considered to indicate statistical significance.
**Fig. 2:** Quantitative analysis of HRCT-data in full inspiration (left) and full expiration (right) breath hold, performed with MeVisPULMO 3D v3.42 (Fraunhofer MEVIS, Bremen, Germany)

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<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Median Age (years)</td>
<td>66 (SD 6,6)</td>
</tr>
<tr>
<td>Female sex</td>
<td>33 (38%)</td>
</tr>
<tr>
<td>FEV1 % post BS (percent of predicted)</td>
<td>28,8 (SD 8,1)</td>
</tr>
<tr>
<td>Total lung capacity (TLC, percent of predicted)</td>
<td>121,8% (SD 14,0)</td>
</tr>
<tr>
<td>Vital capacity (VC, percent of predicted)</td>
<td>69% (SD 15,8)</td>
</tr>
<tr>
<td>COPD GOLD stage 3</td>
<td>34 (39,5%)</td>
</tr>
<tr>
<td>COPD GOLD stage 4</td>
<td>52 (60,5%)</td>
</tr>
</tbody>
</table>

**Fig. 1:** Characteristics of the study participants

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Results

Of 86 participants 33 (38%) were women, the average age was 66.1 (SD 6.6) years with a range from 45 to 79 years. All patients fulfilled the GOLD criteria for stage 3 or 4 (FEV1% ranged from 13-50 % with a mean of 28.8% and a SD of 8.1; figure 2).

Impact of HAV on FEV1:

There was no significant correlation of HAV as a quantitative correlate of fibrotic lung tissue and FEV1% compared to LAV (i.e. emphysema index). In total lung volumes and inspiration breath hold only low attenuation volumes showed a significant negative correlation with FEV1% (r= -.309, R²=.096, p=.008) in contrast to high attenuation volumes (no correlation, p=.786; figure 4). The highest negative correlation of LAV with FEV1% was registered in expiration-CT scans and regarding core volumes (r= -.377, p<.001 vs. HAV with p=.376). Neither in in-/expiration series nor in core-/peel-volumes HAV showed a significant correlation with FEV1% (figure 3).

Images for this section:
Fig. 3: Results of multivariate and simple regression analysis: Correlation between HAV and LAV with FEV1% (FEV1/VC). No correlation (p<.05) between HAV and FEV1% in peel, core or total lung volumes as well as in in- or expiration breath hold HR-CT scans.

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Fig. 4: Correlation in full inspiration breath hold of LAV (r=-.309, R²=.096, p=.008/.003) and HAV (p=.786) with FEV1% in total lung volumes compared to HR-CT scans in expiration (LAV: r=-.369, R²= 0.136, p=.091/<.001)

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Conclusion

All patients in our study group matched the GOLD criteria for stages 3 and 4. Emphysematous, low attenuation areas prevailed (even in exhalation and collapsed lung tissue) the HAV extend by approximately 2.5-4 times. However, in single cases there is up to 30.8% of HAV, especially in peel areas.

Although we found more areas with high attenuation due to collapsed bronchioles/lung tissue in expiration breathhold HRCT scans, even under this condition there was no significant impact of HAV on the lung function. Incidentally, there seems to be no difference between CT-scans of core or peel volumes. LAV still is the only parameter associated significantly with the reduction of FEV1.

As a conclusion, for HRCT-classification of severe COPD and its impact on lung function LAV as a measurable correlate of emphysema still seems to be most important. As another conclusion we found no evidence for a counterbalancing effect of fibrotic lesions in advanced emphysema as it has been reported in CPFE or low-grade fibrosis in smokers [16, 17, 21].

We tend to regard the disproportionally high degree of emphysema as a reason for the missing effects of fibrotic patterns on lung function in our study group. In CPFE, the ratio between these patterns seems to be more balanced [21, 22].

Limitations:

There are several limitations of this study. First, we did not evaluate other parameters of lung function as e.g. diffusion capacity of carbon monoxide, total lung capacity or restrictive parameters as residual volume. These other preserved lung volumes might be the subject of further research on this item. Second, this study involved only a small number of subjects. Third, a qualitative analysis of the HAV-patterns was not performed although we excluded patients with acute pneumonia or relevant dyselephasias. Furthermore, up to the date of the HR-CT scans no UIP or other specific interstitial fibrosis was diagnosed in our patients.

Despite these limitations, our results show that in patients with severe emphysema only emphysematous changes show a statistically negative correlation with FEV1 and coexisting fibrotic changes do not.

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References


