Paired Inspiratory/Expiratory Volumetric Thin-Slice CT Scan for Emphysema Analysis*

Comparison of Different Quantitative Evaluations and Pulmonary Function Test

Julia Zaporozhan, MD; Sebastian Ley, MD; Ralf Eberhardt, MD; Oliver Weinheimer, MSc; Svitlana Iliyushenko, PhD; Felix Herth, MD, PhD; and Hans-Ulrich Kauczor, MD, PhD

**Purpose:** The aim of the study was to use three-dimensional high-resolution CT scan data sets in inspiration and expiration for the quantitative evaluation of emphysema. Using an advanced dedicated semiautomatic analysis tool, the functional inspiratory/expiratory shifts of emphysema volume and clusters were quantified. The pulmonary function test (PFT) served as the clinical “gold standard.”

**Materials and methods:** Thirty-one patients (9 women and 22 men; mean ± SD age, 60 ± 8 years) who had severe emphysema due to COPD (Global Initiative for Chronic Obstructive Lung Disease [GOLD] class III and IV) were included in the study. All patients underwent paired inspiratory/expiratory multidetector CT scans (slice thickness, 1/0.8 mm) and pulmonary function tests (PFTs). CT scan data were analyzed with self-written emphysema detection software. It provides lung volume (LV), emphysema volume (EV), emphysema index (EI), and four clusters of emphysema with different volumes (from 2, 8, 65, and 120 mm³). These results were correlated with total lung capacity (TLC), intrathoracic gas volume (ITGV), and residual volume (RV) derived from PFT results.

**Results:** Inspiratory LV correlated with TLC (r = 0.9), expiratory LV with ITGV (r = 0.87), and RV (r = 0.83). Expiratory EV correlated better with ITGV (r = 0.88) and RV (r = 0.93) than with inspiratory EV (r = 0.83 and 0.88, respectively). The mean inspiratory EI was 54 ± 13%, and it decreased to 43 ± 15% in expiration. However, the individuals showed a broad spectrum of changes of EI (mean, 11%; range, 1 to 28%), and no differences in inspiratory/expiratory EI and changes in EI or LV were found between GOLD III and GOLD IV patients. In expiration, there was a change from the large emphysema cluster (~37%) to the intermediate cluster (~15%) and small cluster (~13% and ~11%, respectively). The change of volume of the large emphysema cluster after expiration correlated well with the changes in LV (r = 0.9), EV (r = 0.99), EI (r = 0.85), and MLD (r = 0.76).

**Conclusion:** Emphysema volumes measured from expiratory MDCT scans better reflect PFT abnormalities in patients with severe emphysema than those from inspiratory scans. Volumetric cluster analysis provided deeper insights into the local hyperinflation and expiratory obstruction of large emphysematous clusters.

(CHEST 2005; 128:3212–3220)

**Key words:** emphysema detection software; lung emphysema; multidetector CT; pulmonary function test; three-dimensional volumetric analysis

**Abbreviations:** 3D = three-dimensional; EI = emphysema index; EV = emphysema volume; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HRCT = high-resolution CT; HU = Hounsfield units; ITGV = intrathoracic gas volume; LV = lung volume; MDCT = multidetector CT; MLD = mean lung density; PFT = pulmonary function test; RV = residual volume; TLC = total lung capacity

COPD is a major cause of morbidity and mortality throughout the world. This major public health threat is ranked 12th as a worldwide burden of disease and is projected to rank fifth by the year 2020 as a cause of lost quantity and quality of life.1 Pulmonary emphysema is defined by the American

*From the Department of Radiology E-010 (Drs. Zaporozhan, Iliyushenko, and Kauczor), German Cancer Research Center, Heidelberg, Germany; the Department of Pediatric Radiology (Dr. Ley), University Hospital for Children, Heidelberg, Germany; the Department of Pulmology (Drs. Eberhardt and Herth), Thoraxklinik, Heidelberg, Germany; and the Department of Radiology (Dr. Weinheimer), Johannes Gutenberg University, Mainz, Germany.
Thoracic Society as an abnormal permanent enlargement of the air spaces distal to the terminal bronchiole, accompanied by the destruction of their walls, most often caused by COPD or α₁-antitrypsin deficiency. The prevalence of COPD is highest in countries where cigarette smoking is very common, while the prevalence is lowest in countries where smoking is less common, or total tobacco consumption per individual is low.

The accurate diagnosis and quantification of pulmonary emphysema in vivo is important to understand the natural history, assess the extent of the disease, as well as evaluate and follow-up therapeutic interventions. High-resolution CT (HRCT) scanning is currently the method of choice for the noninvasive and sensitive assessment of pathologic changes in emphysema and has been shown to correlate well with pathologic grading. HRCT scanning can characterize anatomic details of the lung as small as 200 to 300 μm, which correspond to approximately the seventh to ninth bronchial generation.

Low-attenuation areas on CT scans have been reported to represent macroscopic and microscopic emphysematous changes of the lung. Qualitative evaluation is based on visual scoring of the size and extent of lung areas with low attenuation values. Objective quantitation of emphysema can be obtained by measuring the relative lung area occupied by pixels with attenuation values below a predetermined threshold. Objective methods are preferable over those based on visual scoring because they more precisely reflect the extent of macroscopic emphysema and are less operator-dependent. The determination of the percentage of the lung occupied by areas of low attenuation on CT scans correlates significantly with the results of pulmonary function tests (PFTs).

All past studies were based either on HRCT scans with slice thicknesses of 1 mm and large interslice gaps of up to 9 mm or thick spiral scans with slice thicknesses of 8 to 10 mm. Thus, either the whole lung parenchyma was not covered and no three-dimensional (3D) volumetric analysis was done, or the images were only obtained for volumetric purpose but were not useful for emphysema characterization.

As a powerful adjunct to inspiratory HRCT scanning, expiratory HRCT scanning reveals changes in lung attenuation that are related to the interplay of air in the alveoli, the pulmonary interstitium, and pulmonary blood volume. Expiratory scans significantly improved diagnostic accuracy in patients with inhomogeneous attenuation on inspiratory HRCT scans, and helped in the diagnosis of diffuse lung disease. This technique is particularly sensitive for the detection of diffuse lung diseases such as bronchiectasis, bronchial asthma, and bronchiolitis obliterans. In some subjects, the inspiratory HRCT scan might give a false-positive finding for emphysema when the hyperaeration observed at inspiration is no longer observed at expiration. Therefore, expiratory HRCT scans have been reported to be superior for quantitating emphysema and showed better correlation with PFTs than inspiratory scans.

Beside a pure analysis of the percentage of voxels below a certain threshold, CT scan data can be approached by a more sophisticated analysis tools. Contiguous emphysema areas can be clustered to obtain the volumes for small-sized, medium-sized, and large-sized emphysematous areas. The cluster distribution was reported to be useful in revealing the pattern of progression of emphysema. However, such advanced analysis tools were only applied to thick-slice CT scans, mostly during inspiration.

To distinguish static alterations (parenchymal) and dynamic alterations (functional) in patients with emphysema and to assess regional variations, high-resolution 3D techniques should be used. With the development of multidetector CT (MDCT) technology, this requirement can be fulfilled. Actual 16-detector CT scanners provide high-resolution, 1-mm thin, contiguous slices without a gap or even an overlap. These 3D data sets are well-suited for volumetric whole-lung evaluations of emphysema. Furthermore, these 3D data sets can also be acquired during expiration providing information on regional volumetric changes.

Thus, the aim of our study was to use novel 3D HRCT scan data sets obtained during inspiration and expiration for the quantitative evaluation of emphysema. Using an advanced dedicated semiautomatic analysis tool, the functional inspiratory/expiratory shifts of emphysema volume (EV) and clusters were quantified. PFTs served as the clinical “gold standard.”

**Materials and Methods**

From December 2003 until December 2004, we examined 31 consecutive patients (9 women and 22 men; mean [± SD] age, 60 ± 8 years; age range, 41 to 76 years). All patients had severe emphysema due to COPD. Classification was performed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), as follows: GOLD class II, 2 patients; GOLD class III, 17 patients; and GOLD class IV, 12 patients (mean FEV₁, 35 ± 11% predicted; FEV₁/FVC, 64 to 20%). They presented with shortness of breath, repeated exacerbations, or the presence of chronic respiratory failure. The mean body mass index of our study population was 24 ± 4 kg/m² (range, 19 to 34 kg/m²). All patients had a mean smoking history of 45 ± 21 pack-years (range, 10 to 120 pack-years).

All patients underwent PFTs that were performed on a body plethysmograph (MasterScreen Body; Jaeger; Wuerzburg, Germany) according to the guidelines of the European Respiratory Society. The following volume measurements were chosen for...
correlation with CT evaluation: total lung capacity (TLC), intrathoracic gas volume (ITGV), and residual volume (RV).

CT was performed using a 16-detector CT (Aquilion-16; Toshiba Medical Systems; Tochigi, Japan) as part of a standard clinical investigation. The scanner was calibrated regularly using a water phantom to allow for reliable measurements and comparison between examinations. CT scanning was done during deep inspiratory and expiratory breath-hold with the patient in the supine position. Every patient was carefully instructed how to breathe before the study and again right before the scan. The breath-hold period ranged between 9 and 13 s (mean duration, 11 s) for the inspiratory scan and 8 to 13 s (mean duration, 10 s) for the expiratory scan, depending on the individual lung size.

MDCT scan parameters for both scans were as follows: collimation, 1 mm; 120 kV; 150 mA/s; gantry rotation time, 0.5 s; pitch, 1.5; and large scan field. All images were reconstructed using a high-frequency reconstruction algorithm (standard lung kernel, FC 51) with a slice thickness of 1 mm and a reconstruction interval of 0.8 mm. For thoracic coverage, 311 to 509 images (mean number, 422 ± 38 images) were reconstructed. No IV contrast medium was administered.

**Image Analysis**

All images were transferred via a picture-archiving and communication system to a personal computer (Intel Pentium 4 processor; Intel; Palo Alto, CA; 2.7 GHz; 768 MB of RAM; Windows XP Professional; Microsoft; Redmond, WA). Self-written software (YACTA; Mainz, Germany) was used for the evaluation. The software was not used for diagnosis. The reading was performed by a radiologist. The software was applied to all inspiratory and expiratory CT scan images. The reading of the CT scan images was routinely performed by a radiologist. The software combined different techniques for semiautomatic segmentation like region growing, threshold-based, and expert-based methods, and morphologic analysis. A denoising filter was applied to all images. Important morphologic thoracic landmarks (ie, trachea, right lung, and left lung were automatically detected. The trachea and the bronchi up to the eighth generation were automatically segmented and excluded from lung parenchyma evaluation as they contain “dead respiratory space.” Without this segmentation, the airways would have been evaluated as they contain air with a density below

### Table 1—Results of the PFTs*

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
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<tbody>
<tr>
<td>TLC, L</td>
<td>8.19 ± 1.40</td>
</tr>
<tr>
<td>ITGV, L</td>
<td>6.12 ± 1.30</td>
</tr>
<tr>
<td>RV, L</td>
<td>5.17 ± 1.25</td>
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*Values are given as the mean ± SD.

Additionally, 3D emphysematous areas were sorted by their size. The classes were defined by their diameters (ie, ≤ 2.5, ≤ 5, ≤ 7.1, and > 7.1 mm), as previously described. These two-dimensional size classes of emphysema were transformed to the following corresponding 3D volume classes: 2 to 8 mm³ (class 1); 8 to 65 mm³ (class 2); 65 to 120 mm³ (class 3); and > 120 mm³ (class 4). The lower limit of 2 mm³ in the smallest cluster was used to minimize the influence of noise on the evaluation.

The software was applied to all inspiratory and expiratory MDCT data sets. The results were correlated to the parameters of PFTs, as described above. Data analysis was done using a spreadsheet program (Excel 2002 SP 2, version 10.43; Microsoft). For correlation between different results, linear regression analysis was applied. For evaluation between different GOLD levels, the Mann-Whitney U test was used (SPSS for Windows, version 11.5; SPSS; Chicago, IL). A local level of significance (p value) of < 0.5 was assumed to be significantly different.

### Results

All examinations were eligible for evaluation. In all cases, the leading CT scan diagnosis was severe

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![Figure 1. Correlation between inspiratory LV and TLC derived from PFT results.](image-url)
centrilobular emphysema with architectural destruction. No large emphysema bullae or areas of ground-glass opacity, which could suggest other disease patterns such as alveolitis or bronchiolitis obliterans, were detected.

The results of PFTs are summarized in Table 1. The results of the CT scan evaluation for inspiration and expiration are presented in Table 2. Beside the volumes, the absolute number is given for each cluster. The volume of each cluster is in the range defined above. Thus, the absolute number of clusters is not directly associated with the volume. In inspiration, the sum of the volume of all clusters is 3.71 L, and in expiration it is 2.56 L. The difference with the EV was 0.24 L for inspiration and 0.2 L for expiration.

We found a high correlation between inspiratory LV and TLC $(r = 0.9)$ [Fig 1]. The expiratory LV correlated well with the ITGV $(r = 0.87)$ and RV $(r = 0.83)$ [Fig 2]. We found a high correlation between inspiratory EV and ITGV and RV $(r = 0.83$ and 0.88, respectively) [Fig 3]; however, expiratory EV correlated even better with ITGV and RV $(r = 0.88$ and 0.93, respectively) [Fig 4].

The change of LV between inspiration and expiration correlated well with the change of MLD $(r = -0.83)$. The mean inspiratory EI for all patients was $54 \pm 13\%$, the mean expiratory EI was $43 \pm 15\%$. For two GOLD II patients, the mean inspiratory EI was $27\%$ and the expiratory EI was $17\%$, for GOLD class III patients inspiratory EI was $55\%$ and the expiratory EI was $43\%$, for GOLD class IV patients the inspiratory EI was $57\%$ and the expiratory EI was $46\%$ (Fig 5, top left, A). However, the individuals showed a broad spectrum of changes in EI (mean, $11 \pm 7\%$; range, 1 to $28\%$) and LV (mean, $1 \pm 0.55$ L; range, 0.03 to 2.3 L) from inspiration to expiration (Fig 5, bottom left, C, and bottom right, D). No significant differences in inspiratory EI, expiratory EI, change of EI, or change of LV were found between GOLD III and GOLD IV patients $(p = 0.7, 0.53, 0.76, and 0.79$, respectively). Some GOLD IV patients could barely exhale, so the changes in LV and EI were small.

The change in EV and EI after expiration correlated well with the amount of air exhaled $(r = 0.94$ and 0.75, respectively) and the change in MLD $(r = -0.84$ and $-0.94$, respectively).

During expiration, there was a change from the large emphysema cluster $(37\%)$ to the intermediate cluster $(+15\%)$ and the small clusters $(+13\%$ and $+11\%)$. An example of the change in emphysema clusters after expiration is given as a color map in Figure 6. A 3D volume of the large emphysema cluster class 4 is shown in Figure 7 for inspiration and expiration. The change in the volume of cluster class 4 after expiration correlated well with the change in LV $(r = 0.9)$ [Fig 8], EV $(r = 0.99)$, EI $(r = 0.85)$, and MLD $(r = -0.79)$ [Fig 9]. All other cluster classes showed no correlation. The change in the volume of clusters showed no significant correlation with FEV₁ (in liters or percent predicted).
We found a high correlation between quantitative parameters derived from MD scans that obtained at deep inspiration and deep expiration, and the results of PFT. The EV at expiration correlated even better with ITGV and RV than the EV at inspiration. During expiration, there was a volume loss in the large emphysema cluster, which corresponded to an increase in volume in the intermediate and small clusters. The absolute change in EV was attributed to the large cluster.

Until now, spiral CT scan data sets with slice thicknesses between 5 and 10 mm were used for the evaluation of LVs during inspiration and expiration. The obtained CT scan LVs correlated well with static LVs (ie, TLC, ITGV, and RV) derived from PFT. These data sets did not allow for further textural analysis of the lung parenchyma due to the thick slices. The parameters EI and MLD represent the loss of tissue in patients with emphysema. These parameters can only be measured appropriately using HRCT scan slices. Thus, the acquisition of a spiral CT scan data set for the whole lung with thick slices and additional HRCT slices was recommended.

MDCT scanners (16-slice) provide high-resolution volumetric data since they allow for an acquisition of 1-mm HRCT scan slices covering the whole lung. In this study, we were able to merge the advantages of both acquisitions, volume and high resolution, into a single volumetric data set. These volumetric data sets were acquired during inspiration and expiration providing a 3D approach for high-resolution analyses of lung parenchymal structures. Using up-to-date scanner technology increases image quality, while examination time is kept to a minimum. All patients, even GOLD IV patients, were able to hold their breath during inspiration and expiration for the study as the longest examination time was as short as 13 s. Until now, the evaluation of the advantage of those 3D data sets comprised just the visual assessment of airtrapping. The use of volumetric and advanced 3D analysis approaches for the segmentation and classification of different LVs, and the assignment to different emphysema clusters is unique in the literature.

The quality of LV determination is reflected by the excellent correlation between LVs during CT scanning and LVs measured in PFTs. This was found for inspiratory and expiratory scans. Also, EVs, which were determined by CT scanning, correlated well with the respective PFT parameters. An analysis of expiratory CT scans showed a better correlation with
PFT results than did inspiratory CT scans, which is in agreement with the findings of other publications. We carefully instructed every patient how to breathe before undergoing the scans, because no advantage was described for spirometric gating over nonspirometric gating, especially in patients with obstructive lung function impairment due to emphysema.

Usually, quantitative CT scan parameters comprise MLD and EI. By using a semiautomatic quantification tool, the MLD of the whole lung parenchyma was measured. Therefore, in our study the MLD reflects the real MLD of the whole lung. During expiration, the MLD increases, reflecting the loss of air. We found a high correlation between the increase in MLD and the decrease in LV determined by CT scanning. Using a threshold-based technique, we quantified the volume of all voxels below a threshold of −950 HU. The volume of this simple approach is referred to as the EI. In former studies, these parameters were based on either thick slices or only a few single slices.

Facilitated by the volumetric approach, it is possible to determine the EI of the whole lung. For functional assessments, we also evaluated the changes in tissue density and EI during expiration. We used the value of −950 HU for inspiratory and expiratory CT scans in order not to measure the same aspects during both inspiration and expiration. The individual change in EI neither correlated with the severity of emphysema (ie, GOLD category class) nor the severity level of EI.
However, the reduction of EI is closely related to the amount of air exhaled. These data provide an illustration of the whole lung, but there may be some regions that change more than others. In this study, no local (ie, segmental) analysis was performed.

Until now, emphysema analysis was mainly based on a straightforward threshold technique measuring the MLD, the EI, or different percentiles. A new classification and morphologic analysis approach was introduced by Blechschmidt et al.23 We adopted this approach and applied it to volumetric data sets with our own software. Therefore, the already determined EV was further classified into four different volumetric size classes. The ability of the program has
already been demonstrated\textsuperscript{27} by another group using the same software and comparing it with commercially available software tools.

During inspiration, we found a difference between the EV as detected by the simple threshold approach and the sum of the four volumes of the emphysema clusters. Nearly the same result was found for expiration. This may indicate that the simple threshold technique overestimated the amount of emphysema. The threshold-based calculation of the volume below \(-950\) HU is an important first step in all quantification analysis. This volume also contains random single-voxel noise. To reduce the impact of noise, a minimum of coupled voxels (2 mm\(^3\)) was required for the smallest cluster. By use of the cluster analysis, the influence of noise voxels was reduced.

Comparing the inspiratory and expiratory measurements, we were able to determine a shift in volumes between different clusters. Our results suggest that the decrease in EV is mainly due to the reduction of volume in the large emphysema cluster. The small clusters showed only a marginal change in absolute volume. Therefore, it can be assumed that during inspiration the EV is mainly trapped in large clusters, while in expiration they collapse either to smaller clusters or even to an area of normal attenuation and therefore are not represented in the clusters.

Besides the absolute volume of each emphysema cluster in inspiration and expiration, the number of clusters in each size class is another characteristic feature. While the emphysema cluster volume decreased during expiration, the absolute number of clusters increased during expiration (Table 2). Therefore, the mean volume of each cluster, independent of its size, decreased even more. On the other hand, this demonstrated that the number of small and intermediate clusters grew due to a shift of volume from the large clusters. During expiration, the absolute number of cluster class 4 increased, which may be due to the division of formerly very large clusters. The volume of the cluster class 4 had no upper limit. Thus, very large clusters (containing more than double the lower limit of the volume of cluster class 4) can become smaller during expiration, but still remain large enough to be in class 4. This means that our study has given a first glance at the detailed changes of textures during breathing. We showed that patients with severe emphysema show the biggest changes in large clusters. Thus, future studies have to focus on a more detailed analysis of the large clusters.

Due to the high-resolution coverage of the whole lung, we were further able to assess and quantify different areas of textural distortion. The visual analysis of the mechanism mentioned above is illustrated in Figure 6. In the upper row, the inspiratory segmented images of one patient are shown. Looking at the segmentation of the large cluster (yellow), you will notice that the right middle lobe does not show yellow areas during expiration (lower row). The left lung in contrast shows only a marginal change in the number of large clusters. The mediastinal anatomic landmarks (\textit{ie}, carina and lower lobe bronchi) are accompanied by different lung parenchymal areas, as can be appreciated by the shift of interlobar fissures. By comparing only a few single inspiratory/expiratory image pairs, this information cannot be perceived correctly. This example demonstrates the necessity for 3D whole-lung quantitative analysis. This information could be important for therapy (\textit{ie}, LV reduction surgery or new treatment options like endobronchial valve placement).\textsuperscript{35,36} 3D scans provide valuable information, especially for the evaluation of the heterogeneity of emphysema. Paired 3D information gives a better opportunity to evaluate the regional contribution of lung parenchyma to ventilation. This information could be used to generate maps of parenchymal change for the fast and easy visualization of regions with need for therapy.

Some limitations of this study have to be noted. CT scanning was performed only in a small, but well-defined patient population to selectively recruit patients with severe centrilobular emphysema who might undergo further surgical or interventional therapy. Therefore, these results should be confirmed in patients with less severe or bullous emphysema. For the segmentation of emphysema, the same threshold was used for inspiratory and expiratory CT scan data sets. Some studies\textsuperscript{21} have used different thresholds for emphysema quantification. Other authors,\textsuperscript{22} however, have used the same setting for both measurements and have found excellent correlations with the results of PFTs. Therefore, further investigations should be conducted to evaluate the influence and performance of the selected thresholds.

**Conclusion**

EVs measured from expiratory MD better reflect PFT result abnormalities in patients with severe emphysema than those from inspiratory MDCT scans. Cluster analysis provides deeper insights into local hyperinflation and the expiratory obstruction of large emphysematous clusters.

ACKNOWLEDGMENT: The authors are grateful to Emphasys Medical Inc to be able to participate in the VENT Trial. Many thanks to Mrs. A. Fuxa for technical assistance. The data are part of the doctoral thesis of Ms. Serap Erdogan, MS.
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