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

# Comparison of Different Quantitative Evaluations and Pulmonary Function Test

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*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 [ $\pm$  SD] age, 60  $\pm$  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 solftware. 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  $54\pm13\%$ , and it decreased to  $43\pm15\%$  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.

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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

C OPD 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.<sup>1</sup> Pulmonary emphysema is defined by the American

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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  $\alpha_1$ -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.  $^{3,4}$ 

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  $\mu$ m, which correspond to approximately the seventh to ninth bronchial generation.

Low-attenuation areas on CT scans have been reported<sup>9</sup> 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.<sup>10–12</sup>

Objective quantitation of emphysema can be obtained by measuring the relative lung area occupied by pixels with attenuation values below a predetermined threshold. <sup>13,14</sup> 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. <sup>15</sup> 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). <sup>16</sup>

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. 16,17 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.<sup>18,19</sup> Expiratory scans significantly improved diagnostic accuracy in patients with inhomogeneous attenuation on inspiratory HRCT scans, and helped in the diagnosis of diffuse lung disease.<sup>18</sup> This technique is particularly sensitive for the detection of diffuse lung diseases such as

bronchiectasis, bronchial asthma, and bronchiolitis obliterans.<sup>20</sup> 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<sup>21,22</sup> 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.<sup>23</sup> 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.<sup>24</sup>

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.<sup>8</sup> 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 [ $\pm$  SD] age, 60  $\pm$  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 FEV<sub>1</sub>, 35  $\pm$  11% predicted; FEV<sub>1</sub> range, 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  $\pm$  4 kg/m². (range, 19 to 34 kg/m²). All patients had a mean smoking history of 45  $\pm$  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.<sup>25</sup> 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). Selfwritten software (YACTA; Mainz, Germany) was used for the evaluation. The software was not used for diagnosis. 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 expertbased methods, and morphologic analysis. 23,26,27 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 detected as emphysema as they contain air with a density below -950 Hounsfield units (HU).

On the basis of the pulmonary landmarks, the lung is detected by a region growing with a N6 neighborhood system and an upper threshold of  $-500~\rm HU$ . This resulted in a "safe" segmentation of the lung parenchyma without surrounding thoracic structures. However, areas within the lung parenchyma-like vessels were not segmented. These areas were automatically included within the segmented lung area by a "closing" procedure.

All voxels marked as lung parenchyma were analyzed. Voxels below -950 HU were segmented as emphysema.<sup>7,28,29</sup> This was followed by a correction factor, which included all voxels from -950 to -910 HU if they were surrounded by emphysema voxels.

From this analysis, we received the total lung volume (LV), EV, emphysema index (EI), and mean lung density (MLD) for the whole lung, as well as for the right and the left lung separately.

Table 1—Results of the PFTs\*

Parameters	Values
TLC, L	$8.19 \pm 1.40$
ITGV, L	$6.12 \pm 1.30$
RV, L	$5.17 \pm 1.25$

<sup>\*</sup>Values are given as the mean ± SD.

Table 2—Results of the CT Evaluation for Inspiration and Expiration\*

Parameters	Inspiration	Expiration
LV, L	$7.21 \pm 1.30$	$6.23 \pm 1.26$
EV, L	$3.95 \pm 1.45$	$2.76 \pm 1.39$
EI, %	$52 \pm 15$	$41 \pm 16$
Cluster class 1, No.		
No.	$16,998 \pm 5,929$	$18,024 \pm 6,284$
L	$0.06 \pm 0.02$	$0.07 \pm 0.02$
Cluster class 2		
No.	$10,118 \pm 3,160$	$10,783 \pm 3,562$
L	$0.19 \pm 0.07$	$0.20 \pm 0.08$
Cluster class 3		
No.	$512 \pm 200$	$550 \pm 250$
L	$0.04 \pm 0.02$	$0.05 \pm 0.02$
Cluster class 4		
No.	$275 \pm 140$	$310 \pm 162$
L	$3.42 \pm 1.63$	$2.24 \pm 1.50$
All clusters		
No.	$27,903 \pm 9,090$	$29,667 \pm 9,870$
L	$3.71 \pm 1.51$	$2.56 \pm 1.46$

<sup>\*</sup>Values are given as the mean  $\pm$  SD.

Additionally, 3D emphysematous areas were sorted by their size. The classes were defined by their diameters (ie,  $\leq 2.5$ ,  $\leq 5$ ,  $\leq 7.1$ , and > 7.1 mm), as previously described.<sup>23</sup> These two-dimensional size classes of emphysema were transformed to the following corresponding 3D volume classes: 2 to 8 mm<sup>3</sup> (class 1); 8 to 65 mm<sup>3</sup> (class 2); 65 to 120 mm<sup>3</sup> (class 3); and > 120 mm<sup>3</sup> (class 4). The lower limit of 2 mm<sup>3</sup> 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

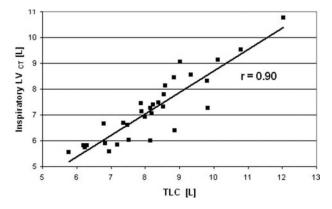


FIGURE 1. Correlation between inspiratory LV and TLC derived from PFT results.

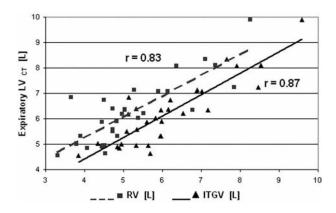


FIGURE 2. Correlation of expiratory LV with ITGV and RV.

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

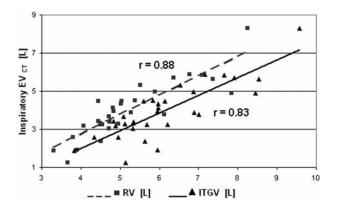


FIGURE 3. Correlation of inspiratory EV with ITGV and RV.

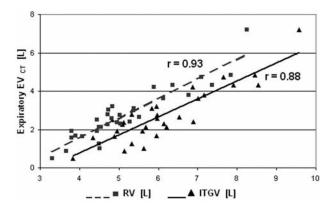


FIGURE 4. Correlation of expiratory EV with ITGV and RV.

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 FEV<sub>1</sub> (in liters or percent predicted).

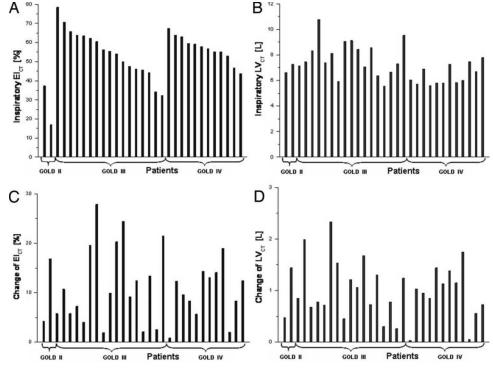


FIGURE 5. Individual inspiratory EI (top left, A) and the corresponding inspiratory LV (top right, B) depend on GOLD classification. Individual change of inspiratory EI after expiration (bottom left, C) and the corresponding exhaled LV (bottom right, D) depend on GOLD classification. No significant differences were found in any parameters between patients GOLD class III and IV.

#### DISCUSSION

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.<sup>22</sup> 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.<sup>8,9</sup> Thus, the acquisition of a spiral CT scan data set for the whole lung with thick slices and additional HRCT slices was recommended.<sup>17</sup>

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.<sup>20</sup> 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

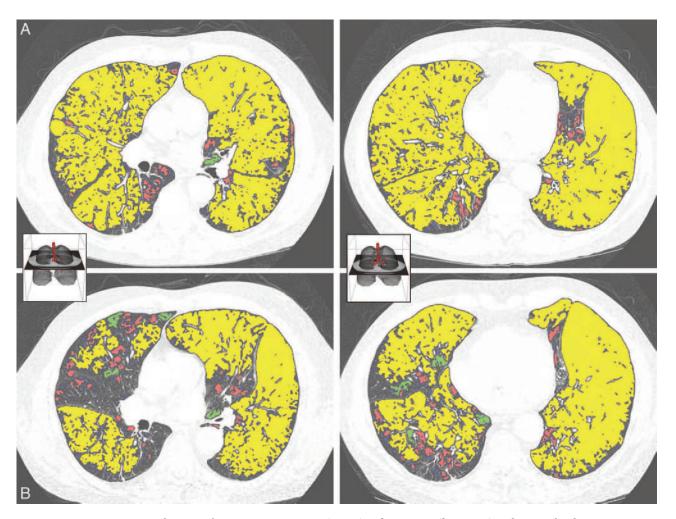


FIGURE 6. Color map of CT scan in inspiration (top, A) and expiration (bottom, B) at the same level of carina and lower lobes: clusters class 4 (yellow), class 3 (green), class 2 (red) and class 1 (blue). At the same anatomical level related to main bronchi and great vessels the lung parenchyma landmarks (like interlobar fissure) changed their position. Note the different change of fissure position for right and left lung and shift of the mediastinum corresponding to better expiration on the right that on the left side.

PFT results than did inspiratory CT scans, which is in agreement with the findings of other publications. <sup>21</sup> 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. <sup>30,31</sup>

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.<sup>32</sup> In former studies,  $^{17,32-34}$  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, and give away the chance to obtain information on function from the difference between inspiration and expiration.<sup>33</sup> The individual change in EI neither correlated with the severity of emphysema (*ie*, GOLD category class) nor the severity level of EI

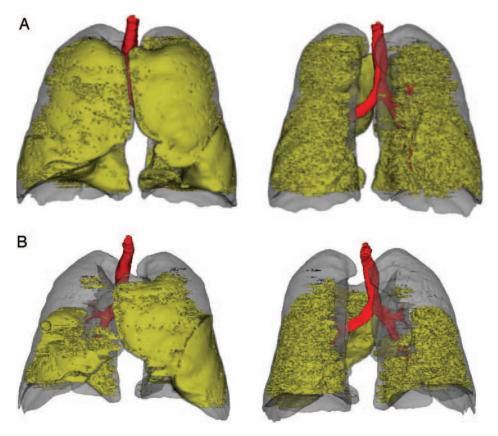


FIGURE 7. 3D rendering of CT scan in inspiration (top, A) and expiration (bottom, B) with tracheobronchialtree (red), lungs (gray) and large emphysema cluster (class 4; yellow). View from anterior (left) and posterior (right).

(Fig 5). 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.<sup>23</sup> 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

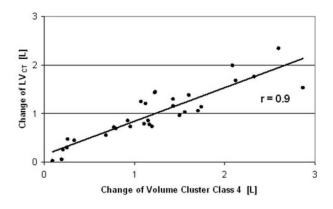


FIGURE 8. Correlation between change of LV and change of volume of cluster class 4 after expiration.

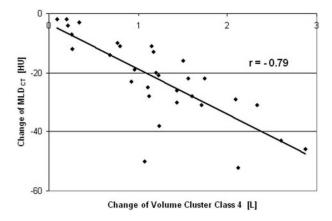


FIGURE 9. Correlation between change of MLD and change of volume of cluster class 4 after expiration.

already been demonstrated<sup>27</sup> 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  $-950~\mathrm{HU}$  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 mm³) 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 (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 (ie, LV reduction surgery or new treatment options like endobronchial valve placement).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<sup>21</sup> have used different thresholds for emphysema quantification. Other authors,<sup>22</sup> 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.

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# REFERENCES

- 1 Murray CJ, Lopez AD. Evidence-based health policy: lessons from the Global Burden of Disease Study. Science 1996; 274:740-743
- 2 Snider G, Kleinerman J, Thurlbeck WM, et al. The definition of emphysema: report of a National Heart, Lung, and Blood Institute, Division of Lung Diseases workshop. Am Rev Respir Dis 1985; 132:182–185
- 3 Pauwels RA, Buist AS, Ma P, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD); executive summary. Respir Care 2001; 46:798–825
- 4 GOLD. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Executive summary, updated 2004. Available at: http://www.goldcopd.com/es2004clean.pdf. Accessed September 2004
- 5 Bankier AA, Madani A, Gevenois PA. CT quantification of pulmonary emphysema: assessment of lung structure and function. Crit Rev Comput Tomogr 2002; 43:399–417
- 6 Gurney JW. Pathophysiology of obstructive airways disease. Radiol Clin North Am 1998; 36:15–27
- 7 Gevenois PA, de Maertelaer V, De Vuyst P, et al. Comparison of computed density and macroscopic morphometry in pulmonary emphysema. Am J Respir Crit Care Med 1995; 152:653–657
- 8 Goldin JG. Quantitative CT of the lung. Radiol Clin North Am 2002; 40:145–162
- 9 Nakano Y, Muro S, Sakai H, et al. Computed tomographic measurements of airway dimensions and emphysema in smokers: correlation with lung function. Am J Respir Crit Care Med 2000; 162:1102–1108
- 10 Bergin CJ, Muller NL, Miller RR. CT in the qualitative assessment of emphysema. J Thorac Imaging 1986; 1:94–103
- 11 Foster WL Jr, Pratt PC, Roggli VL, et al. Centrilobular emphysema: CT-pathologic correlation. Radiology 1986; 159: 27–32
- 12 Kuwano K, Matsuba K, Ikeda T, et al. The diagnosis of mild emphysema: correlation of computed tomography and pathology scores. Am Rev Respir Dis 1990; 141:169–178
- 13 Sakai N, Mishima M, Nishimura K, et al. An automated method to assess the distribution of low attenuation areas on chest CT scans in chronic pulmonary emphysema patients. Chest 1994; 106:1319–1325
- 14 Gould GA, MacNee W, McLean A, et al. CT measurements of lung density in life can quantitate distal airspace enlargement: an essential defining feature of human emphysema. Am Rev Respir Dis 1988; 137:380–392
- 15 Bankier AA, De Maertelaer V, Keyzer C, et al. Pulmonary emphysema: subjective visual grading versus objective quantification with macroscopic morphometry and thin-section CT densitometry. Radiology 1999; 211:851–858
- 16 Kinsella M, Muller NL, Abboud RT, et al. Quantitation of emphysema by computed tomography using a "density mask" program and correlation with pulmonary function tests. Chest 1990; 97:315–321
- 17 Orlandi I, Moroni C, Camiciottoli G, et al. Spirometric-gated computed tomography quantitative evaluation of lung emphysema in chronic obstructive pulmonary disease: a comparison of 3 techniques. J Comput Assist Tomogr 2004; 28:437–442
- 18 Arakawa H, Webb WR, McCowin M, et al. Inhomogeneous lung attenuation at thin-section CT: diagnostic value of expiratory scans. Radiology 1998; 206:89–94
- 19 Slone RM, Gierada DS, Yusen RD. Preoperative and postoperative imaging in the surgical management of pulmonary

- emphysema. Radiol Clin North Am 1998; 36:57-89
- 20 Nishino M, Boiselle PM, Copeland JF, et al. Value of volumetric data acquisition in expiratory high-resolution computed tomography of the lung. J Comput Assist Tomogr 2004; 28:209–214
- 21 Arakawa A, Yamashita Y, Nakayama Y, et al. Assessment of lung volumes in pulmonary emphysema using multidetector helical CT: comparison with pulmonary function tests. Comput Med Imaging Graph 2001; 25:399–404
- 22 Kauczor H-U, Hast J, Heussel CP, et al. CT Attenuation of paired HRCT scans obtained at full inspiratory/expiratory position: comparison with pulmonary function tests. Eur Radiol 2002; 12:2757–2763
- 23 Blechschmidt RA, Werthschutzky R, Lorcher U. Automated CT image evaluation of the lung: a morphology-based concept. IEEE Trans Med Imaging 2001; 20:434–442
- 24 Mishima M, Hirai T, Itoh H, et al. Complexity of terminal airspace geometry assessed by lung computed tomography in normal subjects and patients with chronic obstructive pulmonary disease. Proc Natl Acad Sci USA 1999; 96:8829–8834
- 25 Siafakas NM, Vermeire P, Pride NB, et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD): the European Respiratory Society Task Force. Eur Respir J 1995; 8:1398–1420
- 26 Mayer D, Bartz D, Fischer J, et al. Hybrid segmentation and virtual bronchoscopy based on CT images. Acad Radiol 2004; 11:551–565
- 27 Achenbach T, Weinheimer O, Buschsieweke C, et al. Fully automatic detection and quantification of emphysema on thin section MD-CT of the chest by a new and dedicated software. Rofo 2004; 176:1409–1415
- 28 Gevenois PA, De Vuyst P, de Maertelaer V, et al. Comparison of computed density and microscopic morphometry in pulmonary emphysema. Am J Respir Crit Care Med 1996; 154:187–192
- 29 Baldi S, Miniati M, Bellina CR, et al. Relationship between extent of pulmonary emphysema by high-resolution computed tomography and lung elastic recoil in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001; 164:585–589
- 30 Kauczor HU, Heussel CP, Fischer B, et al. Value of spirometry-gated high resolution computerized tomography of the lung during inspiration and expiration. Rofo 1998; 169:658– 661
- 31 Gierada DS, Yusen RD, Pilgram TK, et al. Repeatability of quantitative CT indexes of emphysema in patients evaluated for lung volume reduction surgery. Radiology 2001; 220:448– 454
- 32 Cederlund K, Tylen U, Jorfeldt L, et al. Classification of emphysema in candidates for lung volume reduction surgery: a new objective and surgically oriented model for describing CT severity and heterogeneity. Chest 2002; 122:590–596
- 33 Kauczor HU, Heussel CP, Fischer B, et al. Assessment of lung volumes using helical CT at inspiration and expiration: comparison with pulmonary function tests. AJR Am J Roentgenol 1998; 171:1091–1095
- 34 Cerveri I, Dore R, Corsico A, et al. Assessment of emphysema in COPD: a functional and radiologic study. Chest 2004; 125:1714–1718
- 35 Toma TP, Hopkinson NS, Hillier J, et al. Bronchoscopic volume reduction with valve implants in patients with severe emphysema. Lancet 2003; 361:931–933
- 36 Yim AP, Hwong TM, Lee TW, et al. Early results of endoscopic lung volume reduction for emphysema. J Thorac Cardiovasc Surg 2004; 127:1564–1573