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Quantifying Heterogeneity in Emphysema from High Resolution Computed Tomography: A Lung Tissue Research Consortium Study

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Abstract

Rationale and Objective—To quantify spatial distribution of emphysema using high-resolution computed tomography (HRCT), we applied semi-automated analysis with internal attenuation calibration to measure regional air volume, tissue volume, and fractional tissue volume (FTV=tissue/[air+tissue] volume) in well-characterized patients studied by the Lung Tissue Research Consortium (LTRC).

Methods—HRCT was obtained at supine end-inspiration and end-expiration, and prone end-inspiration from 31 patients with mild, moderate, severe, or very severe emphysema (stages II–V, FEV₁>75%, 51–75%, 21–50% and 20% predicted, respectively). Control data were from 20 healthy non-smokers (stage I). Each lobe was analyzed separately. Heterogeneity of FTV was assessed from coefficients of variation (CV) within and among lobes, and the kurtosis and skewness of FTV histograms.

Results—In emphysema, lobar air volume increased up to 177% except in the right middle lobe. Lobar tissue volume increased up to 107% in mild-moderate stages then normalized in advanced stages. Normally, FTV was up to 82% higher in lower than upper lobes. In mild-moderate emphysema, lobar FTV increased by up to 74% above normal at supine inspiration. In severe emphysema FTV declined below normal in all lobes and positions in correlation with pulmonary function ($p<0.05$). Markers of FTV heterogeneity increased steadily with disease stage in correlation with pulmonary function ($p<0.05$); the pattern is distinct from that seen in interstitial lung disease (ILD).

Conclusion—CT-derived biomarkers differentiate the spatial patterns of emphysema distribution and heterogeneity from that in ILD. Early emphysema is associated with elevated tissue volume and FTV, consistent with hyperemia, inflammation or atelectasis.

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Keywords

CT scan; image analysis; fractional tissue volume; coefficient of variation; kurtosis; skewness

Introduction

Chest computed tomography (CT) is extensively utilized in the diagnosis and management of chronic lung disease. Clinical evaluation by CT is usually qualitative or semi-quantitative, resulting in unavoidable spatial, temporal, inter-observer and inter-scanner variability, particularly in the presence of volume change or local architectural distortion, making it difficult to match the same anatomical regions on successive scans. Currently, the large digital dataset generated by each CT study is routinely under-utilized. Given the widespread use of CT, its expense and the small but real risk of harm due to cumulative radiation exposure (1), there is a corresponding need for standardized imaging biomarkers to objectively characterize anatomical disease severity and distribution monitor pathological progression and assess response to therapy. By maximally exploiting the information content of CT datasets, quantitative image analysis has the potential to improve the precision of patient stratification, cross-sectional comparisons and longitudinal follow-up.

Both attenuation-based (2–10) and texture-based (11–16) image analysis algorithms have been used to quantify pulmonary emphysema. Attenuation-based methods commonly employ an arbitrary threshold value, e.g., –910 HU (8), to separate normal from emphysematous parenchyma (2, 4); these methods are relatively easy to use but highly sensitive to lung inflation. A range of threshold values has been reported (2, 17), and most studies do not take into account intra- or inter-lobar heterogeneity, a key feature in emphysema evolution. Texture-based methods rely on analysis of detailed morphologic patterns on high resolution CT (HRCT) (11, 13–16, 18), e.g., shape, skewness, kurtosis, gradient, contrast, correlation, circularity, aspect ratio, area, number of clusters. While offering more information, texture-based analysis involves greater computational complexity and higher cost.

To facilitate objective HRCT analysis, we developed a semi-automated, voxelwise method to quantify regional air volume, tissue volume, and fractional tissue volume (FTV) using each lobe as a natural reference unit to allow matching of corresponding regions and comparison of regional changes on different scans even among distorted lobes (19). FTV is derived using internal calibrated attenuations of intra-thoracic air and tissue to minimize potential temporal and inter-scanner variability. We (19) showed that this analysis objectively quantifies the severity and topographical distribution of parenchyma abnormalities in a cross-sectional cohort of patients with interstitial lung disease (ILD) who had been extensively characterized as part of the Lung Tissue Research Consortium (LTRC) sponsored by the National Heart, Lung and Blood Institute. Here we extended this analysis to a cross-sectional cohort of patients with emphysema who had also been extensively characterized by the LTRC. We tested the hypothesis that CT-derived parameters that reflect the magnitude and spatial heterogeneity of emphysema are physiologically relevant. Our results show that CT-derived parameters correlate significantly with lung function and could discriminate the disparate patterns of anatomical disease distribution and progression between emphysema and ILD.

Materials and methods

Subjects

The LTRC (<http://www.nhlbi.nih.gov/resources/ltrc.htm>) provided from its multi-center databank de-identified non-contrasted HRCT obtained at supine end-inspiration, supine end-expiration, and prone end-inspiration from 31 patients (age 36–76 years, 11–132 pack-years tobacco use) who had a clinical and pathological diagnosis of pulmonary emphysema, categorized by FEV₁ (% predicted): Stage II - mild (>75%), stage III - moderate: (50–75%), stage IV - severe (20–50%) and stage V - more severe (<20%). LTRC enrolled donor subjects who were anticipating lung surgery for suspected malignancy, lung volume reduction surgery or lung transplantation, collected blood and phenotypic data and processed lung tissue for research use. Phenotypic data include the clinical and pathological diagnosis, symptom questionnaires, pulmonary function tests (PFTs), and HRCT. Standardized protocols were followed to assure data quality and uniformity. All patients provided written informed consent to the LTRC. Patients with proven malignancy or primary infections such as tuberculosis were excluded. Data from one patient was excluded due to a large pneumothorax. Published HRCT analysis and PFTs of 20 healthy non-smokers (stage I, age 31–75 years) from a separate protocol approved by the Institutional Review Board of University of Texas Southwestern Medical Center (UT Southwestern) served as controls (19, 20). Spirometry and DL_{CO} were measured by a breath hold method following recommendations of the American Thoracic Society and the European Respiratory Society (21, 22).

HRCT

In LTRC patients, all LTRC participating centers used Gammex 464 CT phantom (Gammex, Middleton, WI) for scanner calibration. Three helical datasets (at supine inspiration, supine expiration and prone inspiration) were obtained using a multi-detector scanner (at least 8 detectors, 140 kVp, 324 mA) optimized for single breath acquisition in <15 s. Consecutive images (0.625mm) were rendered from apex to costophrenic angle. In healthy subjects studied at UT Southwestern (GE Lightspeed 16, Milwaukee, WI), Catphan500 (The Phantom laboratory, Salem, NY) was used for calibration. Discontinuous 1.25mm thick images (obtained at supine inspiration, supine expiration and prone inspiration) were rendered at 10mm intervals from apex to base. Consideration for minimal radiation exposure in healthy control subjects dictated the discontinuous imaging protocol. In all subjects, scout images were obtained to optimize the field of scan, and the standard reconstruction algorithm was used.

Image analysis

The DICOM images were analyzed using a PC-based semi-automated algorithm (Visual C++ 6.0 with OpenGL library) described in detail previously (19, 23–25). Briefly, the attenuation of each voxel was internally calibrated with respect to that of intra-thoracic air and tissue to derive standardized air and tissue volumes and FTV, which are mapped to the voxel position along the normalized span (0–100%) of reference coordinate axes (x,y,z) of each lobe. This approach has been used to characterize regional compensatory lung growth (23–25) and ILD (19) in the presence of non-uniform lobar distortion.

Lobar reconstruction

Lung area was outlined by thresholding, excluding trachea and the first 3 generations of large airways and blood vessels. Key points along inter-lobar fissures were manually identified every 10th image and fitted with cubic splines. On the intervening images the fissures were interpolated; then the interpolation and computer-generated pleural boundaries

were visually verified. Each lobe was analyzed separately. The lingula was included as part of the left upper lobe (LUL). Lobar volume was calculated as $\Sigma(\text{area} \times \text{slice thickness})$.

HRCT-derived indices

Attenuations of extra-thoracic air and water were set at $-1,000$ and 0 HU, respectively. In each subject, attenuation of intra-thoracic air (air CTn) was measured at 3 points in the tracheal column above carina (range -942 to -999 HU). Attenuation of air-free tissue was measured at 5 points within the right lobe of liver (liver CTn, range $+32$ to $+80$ HU). The average attenuations of air (air CTn), tissue (liver CTn) and each lung lobe (lobar CTn) were used to partition total lobar volume into air and tissue volumes:

$$\text{Lobar tissue volume} = \frac{\text{Lobar CTn} - \text{air CTn}}{\text{Liver CTn} - \text{air CTn}} \times \text{Total lobar volume}$$

$$\text{Lobar air volume} = \text{Total lobar volume} - \text{Lobar tissue volume}$$

$$\text{Fractional tissue volume} = \frac{\text{Lobar tissue volume}}{\text{Total lobar volume}}$$

CT-derived tissue volume includes extravascular tissue and microvascular blood. Air volume, tissue volume and FTV were plotted along 3 reference coordinate axes: x (medial-to-lateral), y (posterior-to-anterior) and z (cephalad-to-caudal). To compare the position of a region, the distance across a lobe along each axis was divided into bins: 0–10%, 10–30%, 30–50%, 50–70%, 70–90% and 90–100%, of the total span (Figure 1) and analyzed with respect to average bin positions along a given axis i.e., 5, 20, 40, 60, 80 and 95%. Regional heterogeneity was assessed from the coefficients of variation ($CV = SD/\text{mean}$) of FTV within and among lobes, and the kurtosis (peakness) as well as skewness (symmetry) of whole-lung FTV distributions along each coordinate axis.

Analyzing images with and without gaps

Initially, every image in emphysema patients (0.625mm apart) was analyzed exhaustively. In 4 emphysema patients we repeated the analysis using every 10th image (6.25mm apart). These two methods resulted in $< 4\%$ difference in derived indices. For emphysema stage II, III, IV, and V, the respective maximum percent error was as follows: air volume (0.7%, 0.7%, 2.0%, 3.8%); tissue volume (1.0%, 1.4%, 3.3%, 3.0%); and FTV (1.3%, 1.3%, 1.5%, 2.6%). Therefore, subsequent analysis in the patients utilized gap images 6.25mm apart.

Statistical analysis

Results were expressed as mean and SD, or mean and 95% confidence interval, and compared with respects to posture, inflation and disease severity (stages I to V) using factorial ANOVA. Intra- and inter-lobar gradients of CT-derived indices were compared with respect to position along each references axis, and compared with respect to posture, inflation and disease severity using repeated measures ANOVA. Post-hoc test was performed using Fishers protected least significant difference. $P < 0.05$ was considered significant.

Results

Emphysema patients were older than control subjects. Airflow obstruction, air trapping and hyperinflation worsened with emphysema stage (Table 1). Mean tracheal air and liver attenuations were lower in patients (-983 ± 13 and 58 ± 9 HU, respectively) than in controls (-969 ± 9 and 64 ± 9 HU, $p < 0.0001$ and $p = 0.03$, respectively) (Table 2). At prone and supine end-inspiration, mean lung FTV was 22–45% above normal in mild-moderate emphysema (stages II–III) then declined ~25% below normal in severe and more severe emphysema (stages IV–V); the changes were less pronounced at supine end-expiration. In individual groups, kurtosis and skewness of FTV histogram were within normal range. However, combining all emphysema groups (II–V), kurtosis and skewness were normal at prone end-inspiration but above the critical range at supine end-inspiration while skewness was elevated at end-expiration.

Figure 2 shows representative axial images and color FTV maps from the upper (1st–2nd rows) and lower (3rd–4th rows) lobes, in addition to 3D surface FTV maps (5th row) for one subject per group at supine end-inspiration. In mild-moderate emphysema, lobar FTV is modestly elevated especially in lower lobes. With increasing severity FTV declined to or below normal values in all lobes and positions. In severe emphysema, lower attenuation is most pronounced at the apex but also at the base where large bullae may compress adjacent parenchyma. Lobar (Figure 3) and whole-lung (Figure 4) air volumes increased with emphysema severity, except in the right middle lobe (RML). Lobar and whole-lung tissue volume increased modestly but significantly in mild-moderate emphysema, then normalized in advanced emphysema. Average FTV in lower lobes and whole-lung FTV also increased in mild-moderate emphysema, then decreased below normal in advanced emphysema. Gradients among lobes and disease stages were most pronounced at supine end-expiration.

Intra-lobe gradients of air volume (Figure 5) and FTV (Figure 6) are shown at supine end-expiration. Air volume increased with disease severity in all lobes except RML; changes were most pronounced at supine end-expiration with differential directional gradients within different lobes (Figure 5). In mild-moderate emphysema, FTV was modestly but significantly elevated along each coordinate axis of all lobes especially in the periphery. In severe emphysema, FTV decreased below normal in all central intra-lobe regions (Figure 6). For all lobes and whole-lung, FTV correlated significantly with PFTs at supine end-expiration (Table 3) but not supine or prone end-inspiration (*not shown*).

At all positions and inflation levels, CV of FTV within lobes increased steadily with emphysema severity (Figure 7) in correlation with multiple PFT parameters (Table 3, *supine end-inspiration is shown*). At prone end-inspiration only, CV of FTV among lobes increased steadily with emphysema severity (Figure 7) in correlation with PFTs (Table 3). Thus, regional heterogeneity of FTV increased with emphysema progression.

At supine end-expiration, kurtosis and skewness of FTV distributions along medial-to-lateral and cephalad-to-caudal directions increased with emphysema severity (Figure 8). Kurtosis and skewness of FTV in the cephalad-to-caudal direction correlated directly with all PFT parameters except total lung capacity (TLC) (Table 3). This non-random, directional increase in end-expiratory FTV heterogeneity is consistent with progressive air trapping. Weak to no correlations were observed at supine or prone end-inspiration.

Discussion

Summary of results

This study quantifies the progression in magnitude and heterogeneity of FTV, a readily obtained and internally calibrated imaging biomarker, in emphysema. We mapped regional air volume, tissue volume and FTV along standard coordinate axes in each lobe severity to test whether these metrics objectively track disease severity and distribution. The main findings are: a) In mild-to-moderate emphysema, supine tissue volume and FTV were modestly elevated in lower lobes; in advanced emphysema these parameters declined to or below normal in all lobes and positions, b) whole lung air volume increased with emphysema severity. Whole lung tissue volume increased in mild-moderate emphysema, then normalized in advanced emphysema. Whole lung FTV was normal to modestly elevated in mild-moderate emphysema but declined below normal in advanced emphysema, c) in all lobes except RML, air volume increased with emphysema severity, suggesting that the RML is prone to atelectasis, d) lobar and whole lung FTV correlated significantly with resting lung function at supine end-expiration but not supine or prone end-inspiration, d) CV of FTV within lobes increased steadily with emphysema severity in all positions and lung volumes, indicating increasing parenchyma heterogeneity. CV of FTV among lobes increased steadily with emphysema severity only at prone end-inspiration, e) kurtosis and skewness of FTV histograms increased with emphysema severity along medial-to-lateral and cephalad-to-caudal directions, indicating directional gradients of heterogeneity that is accentuated by end-expiratory air trapping, f) the above indices of heterogeneity broadly correlated with function (airflow limitation, air trapping, and alveolar diffusion), and g) these patterns in emphysema are distinct from that in interstitial lung disease (ILD) where inter- and intra-lobar heterogeneity increased up to a plateau in mild-moderate ILD and did not increase further with more severe ILD (19) (*discussed below*).

Significance of the findings

Heterogeneity of parenchyma pathology, an intrinsic feature of emphysema, is readily appreciated during qualitative CT evaluation but notoriously difficult to quantify. Our approach, using relatively simple and robust statistical metrics (CV, kurtosis and skewness of regional FTV), can quantitatively follow the evolution of heterogeneity on a local (lobar) or whole lung scale in correlation with lung function, thereby supporting the physiological relevance of regional CT biomarkers in distorted lobes. These biomarkers are able to differentiate between emphysema and other lung diseases.

Critique of methods

Few patients were in the “mild” emphysema group (n=3), but the combined mild-moderate groups (stages II–III, n=10) showed similar increases in tissue volume and FTV. End-inspiration and end-expiration points were not verified by transpulmonary pressures. In severe emphysema the definition of lobar fissures was not always obvious; hence, computer-detected fissures were manually verified. Microvascular blood and extra-vascular parenchyma tissue could not be differentiated on non-contrasted scans. Our analysis is sensitive in detecting normal apex-to-base gradients of increasing FTV at supine end-inspiration and end-expiration in control subjects (19). The use of internal calibration of attenuation within each subject to derive FTV could minimize potential variability resulting from the use of different CT scanners across different participating centers. Whether the images were analyzed consecutively or with gaps had no significant impact on the analytical results in patients with emphysema, a finding in agreement with that previously reported in ILD (19) or; thus, a more radiation-intensive imaging protocol in healthy control subjects is not justified and would not have been approved. We did not separately analyze textural patterns such as bullae or parenchyma collapse. Bullae were included in regions of high air

volume, low tissue volume and low FTV, while collapsed parenchyma was included in regions of low air volume, high tissue volume and high FTV. Additional textural analysis (12) may complement and extend the analysis of bullae. Variability in liver attenuation among subjects (± 30 HU) causes $<4\%$ error while variability in air attenuation among subjects (± 10 HU) causes $<10\%$ error in whole lung FTV. A similar variability also causes 3%–4% errors in patients with ILD (19). Because average whole lung attenuation is lower in emphysema than in ILD, a given variability in air attenuation constitutes a slightly larger fraction of total lung attenuation in emphysema than in ILD. We previously found that the reference attenuation of air-free tissue obtained from liver is less variable compared to that from skeletal muscle (19); the latter may be influenced by atrophy, fatty infiltration, inflammation or steroid use (26). None of the subjects had clinical or radiological evidence of liver disease. Finally, the study is limited by its cross-sectional nature; future longitudinal follow-up will be needed to verify the reproducibility of CT-derived metrics.

HRCT in emphysema

Emphysema is defined histologically by “abnormal permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls” (27), and physiologically by irreversible airflow obstruction and reduced DL_{CO} signifying alveolar-capillary obliteration. While subjective expert CT evaluation can fully describe and semi-quantify these abnormalities in correlation with pathology (10, 28), inter-observer variability is unavoidable and disparate regional changes may be difficult to follow on serial scans across platforms or centers, especially in the presence of irregular architectural distortion. There is a need to supplement subjective evaluation with objective, standardized quantification to improve the precision and reproducibility of image analysis (29), maximize information yield, and justify the risks of radiation exposure. These are important issues for multi-center clinical trials as well as routine medical management of chronic lung disease as patients often undergo serial scans in different centers over prolonged follow-up. Currently most reports use a predetermined threshold, e.g., -910 or -950 HU, to identify the fractional volume of emphysematous lung (13, 17, 29, 30). Because of a wide range of “normal” attenuation values (2, 7), the threshold approach is less sensitive than our method in discriminating graded changes. In addition, the fractional volume of regions with sub-threshold attenuation correlates better with measures of hyperinflation and airflow obstruction than with gas exchange (31).

Comparison to ILD

In a previous LTRC-sponsored study of HRCT datasets obtained by the same imaging protocols from ILD patients, analyzed using the same methodology and compared to the same control subjects as in the present study, we mapped a peripheral-to-central progression of increased FTV in all lobes with advancing ILD, and quantified the heterogeneity of FTV within and among lobes (19). In both ILD and emphysema, the magnitude and heterogeneity of FTV correlate significantly with lung function; correlations are stronger in ILD than emphysema. Furthermore, our analysis distinguishes the disparate patterns of progression between emphysema and ILD (19), summarized in Figure 9: 1) With advancing ILD whole lung air volume declined while tissue volume rose until the very severe stage; with advancing emphysema air volume progressively increased while tissue volume increased initially then declined. 2) FTV increased steadily with advancing ILD whereas FTV increased slightly in mild-moderate emphysema then declined below normal in severe emphysema. 3) The elevated inter- and intra-lobe CVs of FTV peaked in mild-moderate ILD and did not increase further in severe ILD. In contrast, inter- and intra-lobe CVs of FTV increased steadily with emphysema severity without a plateau. 4) In ILD the abnormalities in CT-derived parameters and correlations with PFTs tended to be most

pronounced at prone end-inspiration while in emphysema they tended to be most pronounced at supine end-expiration.

Physiological correlates

The elevated FTV in mild-to-moderate emphysema likely reflects pulmonary hyperemia, inflammation, and/or atelectasis in early disease, consistent with previous report that a subset (~8%) of smokers (32) display interstitial abnormalities on HRCT associated with greater tobacco exposure, lower TLC, and lower percentage of low attenuation regions; these smokers are less likely to meet the diagnostic criteria for chronic obstructive pulmonary disease (COPD) than smokers without interstitial abnormalities.

Compared to ILD, the CVs of FTV within and among lobes are larger in magnitude and increase relentlessly with advancing emphysema. This is not surprising because air trapping by bullae and compression of adjacent parenchyma lead to large irregular regions of low as well as high attenuation. In contrast, ILD is associated with predominantly elevated lung attenuation with smaller areas of parenchyma collapse or hyperinflation. The greater heterogeneity in emphysema partly explains the weaker correlations of FTV with respect to lung function compared to that in ILD.

Emphysema patients exhibited medial-to-lateral and apex-to-base gradients of increasing skewness and kurtosis in FTV histograms at supine end-inspiration and end-expiration that correlated with disease stage, airflow limitation, air trapping, and DL_{CO} . Increasing skewness indicates that above-average FTV regions largely account for the variability in FTV. Elevated kurtosis indicates a more peaked distribution with most data points clustered around the mean and fewer data points accounting for the variability in FTV. The directionality reflects greater FTV heterogeneity in lateral and caudal lung regions with advancing emphysema, that is, a nonrandom increase in FTV heterogeneity is intrinsic to emphysema pathophysiology. These findings are consistent with that in another LTRC-sponsored study of smokers (33) where expiratory kurtosis and skewness correlated significantly with airflow limitation and air trapping.

Research and clinical applications

Currently there is a paucity of accurate reliable imaging biomarkers for tracking the regional heterogeneity of anatomical involvement. We demonstrate that FTV, a standardized and functionally relevant imaging biomarker, could be used to quantify emphysema severity and heterogeneity in the presence of anatomical distortion, and to distinguish diverging patterns of disease progression between emphysema and ILD. This analysis has immediate applications in clinical research and multi-center clinical trials to non-invasively stratify subjects, monitor disease evolution and assess therapeutic response. The analysis may help to diagnose local emphysema and may be applied to characterize other pathology, e.g., malignancy. Further studies will need to evaluate a larger patient sample and examine the reproducibility as well as longitudinal assessment in relationship to lung function. Additional texture-based metrics (12) could complement and enhance this analysis. Applications of this analysis to conventional chest CT remain to be examined.

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Figure 1.

Representative reconstruction of the right upper lobe from a normal subject (upper panels) and a patient with severe emphysema (lower panels) illustrates the analysis of intra-lobe gradients along standard x,y,z coordinate axes. Each lobe was divided into 6 regions along the span (0–10%, 10–30%, 30–50%, 50–70%, 70–90% and 90–100%) of a given axis. The results were expressed with respect to the average positions of a region (5, 20, 40, 60, 80 and 95%) along the span of a given axis.

Figure 2.

Representative axial HRCT images and the corresponding color maps of FTV from comparable regions of the upper (1st and 2nd rows) and lower (3rd and 4th rows) lobes, with three-dimensional surface color maps of FTV (5th row) from one subject in each severity category: normal, mild, moderate, severe and more severe emphysema (stages I–V respectively) shown at supine end-inspiration.

Figure 3.

Lobar air and tissue volumes and FTV are shown at prone end-inspiration, supine end-inspiration and supine end-expiration in each emphysema stage: normal, mild, moderate, severe and more severe (stages I–V, respectively). Mean $\pm$ SD or $\pm$ SD. In the left upper panel all the lobes are indicated for identification. In other panels the lobes are indicated only to show significant differences. $P < 0.05$ * $p < 0.05$ vs. I (normal); § vs. II (mild), † vs. III (moderate); ‡ vs. IV (severe); a vs. RML; b vs. RLL; c vs. LUL; and d vs. LLL, by repeated measures ANOVA. Air volume increased with disease stage in all lobes except the small RML. FTV was higher in both lower lobes than upper lobes in supine but not prone position; the difference is exaggerated in mild-moderate emphysema due to a higher FTV at supine inspiration. In all lobes, FTV does not decline below normal until stages IV–V.

Figure 4.

Whole lung air volume, tissue volume, and average FTV are shown at prone endinspiration, supine end-inspiration and supine end-expiration for each emphysema stage: normal, mild, moderate, severe and more severe (stages I–V, respectively). Solid lines: average; dashed lines: 95% confidence interval. * $p < 0.05$ vs. I (normal); § vs. II (mild), † vs. III (moderate); ‡ vs. IV (severe) by repeated measures ANOVA.

Figure 5.

Intra-lobe distribution of air volume at supine end-expiration is shown with respect to the position (% of the total span) along a given axis in each lobe and emphysema stage: normal, mild, moderate, severe and more severe (stages I–V, respectively). Mean +SD or –SD. * $p < 0.05$ vs. I (normal); § vs. II (mild), † vs. III (moderate); ‡ vs. IV (severe) by repeated measures ANOVA. With increasing emphysema severity, air volume increased asymmetrically in different regions within the left and right upper (RUL and LUL) and lower (RLL and LLL) lobes. In contrast, regional air volume increased minimally in the right middle lobe (RML).

Figure 6.

Intra-lobe distribution of FTV at supine end-expiration is shown with respect to the position (% of the total span) along a given axis in each lobe and emphysema stage: normal, mild, moderate, severe and more severe (stages I–V, respectively). Mean +SD or –SD. * $p < 0.05$ vs. I (normal); § vs. II (mild), † vs. III (moderate); ‡ vs. IV (severe) by repeated measures ANOVA. In stages II and III, regional FTV was unchanged or mildly elevated above normal. In stages IV and V, regional FTV declined below normal in the central regions of all lobes.

Figure 7.

Coefficients of variation (CVs) of FTV among lobes (*left panels*) and within lobes (*right panels*) at prone end-inspiration (*upper*), supine end-inspiration (*middle*), and supine end-expiration (*lower*) are shown with respect to emphysema severity: normal, mild, moderate, severe and more severe (stages I–V, respectively). Mean +SD or –SD. * $p < 0.05$ vs. I (normal); § vs. II (mild), † vs. III (moderate); ‡ vs. IV (severe) by factorial ANOVA.

Figure 8.

Kurtosis (*upper panels*) and skewness (*lower panels*) of whole-lung FTV distribution along each axis (x, medial to lateral: *left panels*; y, posterior to anterior: *middle panels*; and z, cephalad to caudal: *right panels*) are shown at supine end-expiration with respect to emphysema severity: normal, mild, moderate, severe and more severe (stages I–V, respectively). Mean +SD or –SD. * $p < 0.05$ (a $p = 0.065$) vs. I (normal); § vs. II (mild), † vs. III (moderate); ‡ vs. IV (severe) by factorial ANOVA.

Figure 9.

Side-by-side comparison of selected imaging biomarkers during progression of ILD and emphysema. Whole lung air volume, tissue volume, FTV, and CV of FTV among and within lobes are shown at prone end-inspiration. Mean $\pm$ 95% confidence interval. Published ILD data are from a separate LTRC study (19) that used the same imaging and analytical methods and the results compared to the same control subjects (stage I) as in the present study. ILD severity was categorized by FVC (% predicted): mild (stage II, 80%), moderate (stage III, 50–80%), severe (stage IV, 30–50%), more severe (stage V, <30%). * $p < 0.05$ vs.

I (normal); § $p<0.05$ and # $p=0.06$ vs. **II** (mild); $p<0.05$ † vs. **III** (moderate) and ‡ vs. **IV** (severe) by factorial ANOVA.

Table 1

Demographic data and lung function.

Stage	I	II	III	IV	V
Emphysema severity	Normal	Mild	Moderate	Severe	More Severe
Number of subjects	20	3	7	10	10
Male/female	11/9	3/0	5/2	6/4	6/4
Age, yrs	51±12	67±8 *	62±9 *	61±12 *	59±6 *
Height, cm	171±12	173±11	171±13	170±13	168±7
Weight, kg	79±23	92±30	78±19	76±21	75±12
BMI, kg m ⁻²	28.8±11.7	30.5±7.3	25.7±4.0	25.8±4.5	26.3±2.5
Hemoglobin, g dL ⁻¹	13.7 ± 1.4	13.3±1.2	14.1±2.6	13.6±0.8	13.3±1.1
FEV ₁ , L	3.33±0.90	2.57±0.06	2.21±0.47 *	1.11±0.46 *§†	0.61±0.25 *§†‡
FEV ₁ , % predicted	105±14	85±9 *	65±8 *§	31±4 *§†	17±5 *§†‡
FVC, L	4.28±1.10	4.47±0.35	3.77±0.62	2.91±0.74 *§	2.02±0.76 *§†‡
FVC, % predicted	111±15	108±15	86±7 *	67±11 *§†	54±18 *§†
FEV ₁ /FVC	0.78±0.04	0.58±0.05 *	0.59±0.05 *	0.37±0.10 *§†	0.31±0.09 *§†‡
FEV ₁ /FVC, % predicted	95±5	79±7 *	76±10 *	47±10 *§†	34±8 *§†‡
DL _{CO} , mL/[min mmHg] ⁻¹	23.3±5.9	14.0±6.1 *	14.5±7.5 *	10.5±7.7 *	6.5±1.3 *
DL _{CO} , % predicted	88±17	53±11 *	62±22 *	44±22 *†	30±8 *†
TLC, L	5.77±1.28	6.70±0.26	6.42±1.08	7.19±1.35 *	7.20±1.28 *
RV, L	1.48±0.52	2.07±0.40	2.57±0.33 *	3.86±0.72 *§†	4.40±0.88 *§†
RV/TLC	0.26±0.08	0.31±0.05	0.41±0.06 *	0.54±0.07 *§†	0.61±0.09 *§†‡

Mean±SD. FEV₁: forced expiratory volume at 1 s, FVC: forced vital capacity, DL_{CO}: lung diffusing capacity for carbon monoxide, RV: residual volume, TLC: total lung capacity.

* p<0.05 vs. I (normal);

§ vs. II (mild),

† vs. III (moderate);

‡ vs. IV (severe) by factorial ANOVA.

Table 2

Whole lung attenuation values and Histogram of FTV

Stage Emphysema severity	I Normal (N=20)	II Mild (N=3)	III Moderate (N=7)	IV Severe (N=10)	V More severe (N=10)	II-V All Emphysema (N=30)
<i>Attenuation (HU)</i>						
Tracheal Air	-969±9	-974±19	-975±13	-985±8 *	-989±2 * ^{§†}	-983±13 *
Liver	64±9	60±3	57±10	57±11	59±6	58±9 *
<i>Histogram of FTV</i>						
Prone end-inspiration						
Mean lung FTV	0.106±0.029	0.138±0.011	0.130±0.042	0.101±0.022	0.077±0.013 * ^{§†‡}	0.104±0.033
Kurtosis	-0.558	1.513	-1.112	0.756	-0.025	0.620
Skewness	0.368	1.303	0.247	0.666	-0.376	0.727
Supine end-inspiration						
Mean lung FTV	0.106±0.030	0.154±0.015 *	0.126±0.047	0.096±0.017 ^{§†}	0.078±0.017 * ^{§†}	0.102±0.035
Kurtosis	0.304	-0.708	2.526	-0.765	-0.692	2.590 #
Skewness	0.671	0.817	1.528	0.431	-0.342	1.283 #
Supine end-expiration						
Mean lung FTV	0.201±0.046	0.191±0.020	0.210±0.066	0.120±0.033 * ^{§†}	0.096±0.021 * ^{§†}	0.140±0.060 *
Kurtosis	-0.604	-1.603	0.156	-0.897	-0.488	1.601
Skewness	0.467	0.462	0.849	0.207	-0.078	1.071 #
Critical values (p<0.05, 2 sided)						
Kurtosis (range of normality)	-1.27 to 2.56	-3.64 to 4.36	-2.79 to 4.10	-1.81 to 3.58	-1.71 to 3.44	-1.12 to 2.22
Skewness	1.03	1.83	1.68	1.44	1.37	0.894

FTV, fractional tissue volume calculated using tissue attenuation of the liver; HU, Hounsfield units. Mean±SD.

* p<0.05 vs. I (normal);

[§] vs. II (mild),

[†] vs. III (moderate);

[‡] vs. IV (severe) by factorial ANOVA.

Outside of critical range of normality.

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Table 3

Pearson correlation coefficients (r) and 95% confidence interval (CI) for the correlations of whole lung FTV, the coefficients of variation (CV) of FTV within and among lobes, and the kurtosis and skewness of FTV, with respect to pulmonary function

	FTV		CV of FTV within lobes		CV of FTV among lobes		Kurtosis †		Skewness †	
	r	95 % CI	Supine end-expiration	Supine end-inspiration	Prone end-inspiration	Supine end-inspiration	Supine end-expiration	Supine end-expiration	Supine end-expiration	Supine end-expiration
FEV₁, % pred	0.67 *	0.47 to 0.80	-0.88 *	-0.93 to -0.79	-0.59 *	-0.75 to -0.37	-0.66 *	-0.79 to -0.46	-0.63 *	-0.77 to -0.41
FVC, % pred	0.55 *	0.31 to 0.72	-0.75 *	-0.85 to -0.59	-0.56 *	-0.72 to -0.33	-0.58 *	-0.75 to -0.36	-0.55 *	-0.72 to -0.31
DL_{CO}, % pred	0.52 *	0.28 to 0.70	-0.79 *	-0.88 to -0.65	-0.46 *	-0.66 to -0.20	-0.59 *	-0.75 to -0.37	-0.63 *	-0.77 to -0.41
FEV₁/FVC, % pred	0.73 *	0.57 to 0.84	-0.88 *	-0.93 to -0.79	-0.59 *	-0.75 to -0.37	-0.65 *	-0.79 to -0.44	-0.64 *	-0.78 to -0.44
RV, L	-0.75 *	-0.85 to -0.59	0.79 *	0.64 to 0.88	0.64 *	0.43 to 0.58	0.52 *	0.27 to 0.71	0.45 *	0.18 to 0.66
TLC, L	-0.42 *	-0.63 to -0.15	0.37 *	0.09 to 0.60	0.46 *	0.20 to 0.66	0.25	-0.05 to 0.51	0.04	-0.26 to 0.33
RV/TLC	-0.74 *	-0.85 to -0.57	0.81 *	0.68 to 0.89	0.55 *	0.31 to 0.73	0.54 *	0.29 to 0.72	0.54 *	0.29 to 0.72

FEV₁ forced expiratory volume at 1 s, FVC: forced vital capacity, DL_{CO}: lung diffusing capacity for carbon monoxide, RV: residual volume, TLC: total lung capacity.

* p 0.005.

† Kurtosis and skewness of FTV were calculated along the cephalo-caudal direction.