

Imaging biomarkers for patient selection and treatment planning in emphysema

Emphysema is a disease that causes destruction of lung tissue and an overall reduction in lung compliance as air becomes trapped in the diseased regions. It affects an estimated 60 million people worldwide and up to 2 million Americans. As the disease progresses, the hyperinflated regions continue to expand, limiting the effective volume available for more viable lung tissue. New biomedical valves and stents are being developed that can be implanted in target airways to allow air to escape from the most diseased lung lobe, thereby reducing its volume and providing more space for the adjacent (healthier) lobe to expand. The challenge facing the clinician is to determine which patients are most likely to benefit from the treatment and which lobe/airway should be treated. This article describes imaging biomarkers and an automated computer-aided diagnosis system to perform patient selection and treatment targeting in emphysema.

KEYWORDS: computer-aided diagnosis • computed tomography • emphysema
• imaging biomarker • lung volume reduction

Emphysema is a disease that causes destruction of lung tissue and an overall reduction in lung compliance as air becomes trapped in the diseased regions, in turn reducing oxygen exchange [1]. Emphysema affects an estimated 60 million people worldwide and up to 2 million Americans and is considered a major cause of mortality and morbidity. As the disease progresses, the hyperinflated regions continue to expand, limiting the effective volume available for more viable lung tissue. As a result of these abnormalities in lung mechanics, patients exhibit a progressive increase in dyspnea, and reductions in exercise tolerance and quality of life.

Surgical treatments for emphysema include lung volume reduction surgery, where the most diseased and hyperinflated lung tissue is resected. It has been shown to benefit some patients with advanced emphysema, in particular patients with severe upper lobe-predominant emphysema and low baseline exercise capacity [2–6], but studies have shown a wide range of individual outcomes [2,7–11]. New biomedical valves and stents are being developed that can be implanted in target airways to allow air to escape from the most diseased lobe, thereby reducing its volume and providing more space for the adjacent (healthier) lobe or segment to expand [12–15]. Other interventions based on the same principals include airway sealants, and endobronchial spigots and plugs [16]. These minimally invasive techniques have the potential to improve the

quality of life for emphysema patients. The challenge facing the clinician is to determine which patients are most likely to benefit from the treatment and which lobe/airway should be treated. The selection of the target lobe is critical because the treatments are based on a reduction of lobar volume, or redistribution of ventilation away from the treated lobe, and a suitable diseased lobe must be identified if they are to be effective.

Lung volume and density measurements from CT play a prominent role in the diagnosis of emphysema [17–21]. Traditionally, the forced expiratory volume in 1 s (FEV_1) has been used to measure the progression of emphysema; however, destructive changes in lung parenchyma often precede the decline in FEV_1 by several years [22]. Quantitative assessment of the lungs using CT provides important complementary information to pulmonary function tests (PFTs) because it allows assessment of single and lobar lung volumes [23,24]. This ability for regional measurement of volumes is important in volume reduction treatments for emphysema [25]. Lung volumes and densities measured from imaging are now playing a key role in clinical trials of emphysema therapies [6,26,27] and changes in lobar volumes post-treatment are now being used as a primary outcome variable [27]. While this article focuses on device treatment trials, changes in density measures are also being employed in drug treatment trials as a measure of efficacy [28,29].

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This article describes the imaging biomarkers used in emphysema clinical trials, and the first use of an automated computer-aided diagnosis system to perform patient selection and device treatment targeting. We also describe surrogate outcome imaging biomarkers used to analyze trial data and gain insights into the mechanism behind functional improvements.

Quantitative image analysis

Advances in CT technology have resulted in the ability to obtain thin-section images with sub-millimeter resolution through the entire thorax in less than a single breath-hold (<10 s). This has resulted in exquisitely detailed descriptions of thoracic anatomy, including identification of areas of emphysema, as well as the ability to identify individual lobes and their fissures. The information obtained at pixel level is a measure of x-ray attenuation (measured in Hounsfield Units [HU]), which is an approximate measure of density. These values can be used to quantify disease burden, which has been particularly useful in emphysema patients.

■ Lung segmentation

There are a number of different lung CT segmentation methods available, with varying degrees of automation requiring different amounts of editing [25,30–36]. Most semiautomated techniques are based around the underlying principle of attenuation thresholding. The main clinical trial application described in this paper used a model-based image analysis system [30,31]. The system uses a parametric model of thoracic anatomy to guide automated segmentation based on attenuation thresholding (<500 HU for the lungs), region-growing and mathematical morphology. The results were manually edited as necessary, for example, to remove large central airways from the

segmentation. Other methods set the threshold by analyzing the histogram of the CT image [33,34].

For subdivision of the lungs into lobes, several automated methods have been developed for thin-section CT images. Most methods use the pulmonary airway and vascular trees to guide subdivision of the lungs into lobes [33,37,38]. Other methods use an atlas-based fissure identification for lobar segmentation [24]. The lobar segmentation shown in **FIGURE 1B** was performed using a semiautomated surface fitting approach [39].

■ Lung density analysis

To determine eligibility of a patient for treatment, the severity and interlobar heterogeneity of emphysema are important variables. Within a segmented lung or lobe the low attenuation relative area (RA) is a commonly accepted measure used to quantify the severity of emphysema on CT, based on the premise that regions of coalescent emphysema, as shown in **FIGURE 1A**, have lower density (HU values) than normal parenchyma. The RA is derived from the lung attenuation curve/histogram by computing the percentage of voxels below a particular HU threshold (-910 HU for thick-section or -950 HU for thin-section imaging). These techniques were originally validated against pathology [17,40]. Following thresholding, the percentage of emphysema destruction in each lobe is computed (**FIGURE 1C**). Another low attenuation measure often used is the 15th percentile of the lung attenuation curve [28]. The percentile in HU is typically converted to a density in g/l.

■ Lobar lung volume changes

To evaluate treatment efficacy, changes in lobar lung volumes are an important variable. By taking the product of the number of image voxels

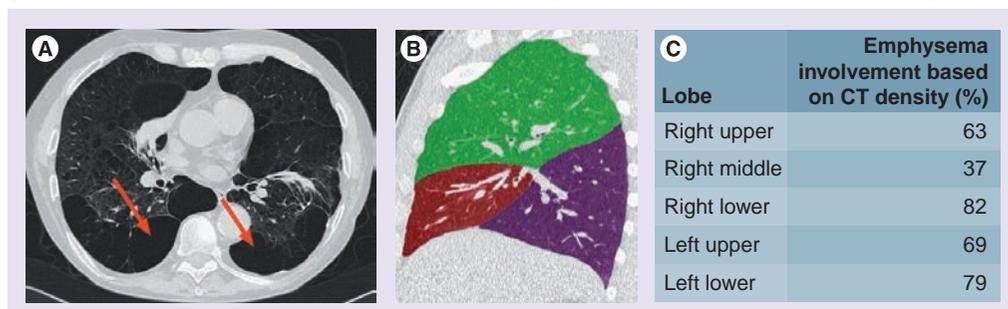


Figure 1. CT image from emphysema patient with lobar segmentation and quantitation. (A) Lung CT image showing paraseptal emphysema destruction, predominantly in the lower lobes. (B) Sagittal view of lobar segmentation results. (C) Computer-calculated emphysema involvement percentages in each lobe.

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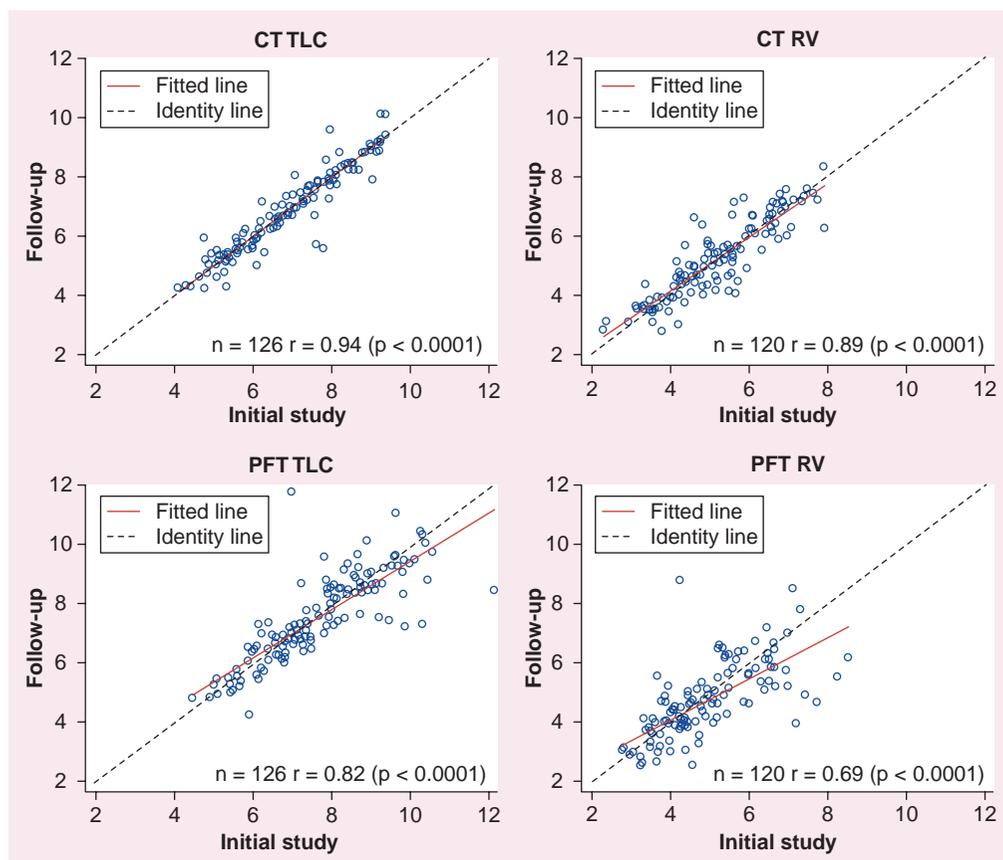


Figure 2. Plots of lung volumes measured at follow-up versus baseline, with regression (solid) and identity (dashed) lines. Clockwise from top left are the correlations from CT at TLC, CT at RV, PFT at RV and PFT at TLC. PFT: Pulmonary function test; RV: Residual volume; TLC: Total lung capacity. Reproduced with permission from [39].

within a segmented lobe with the volume of an individual voxel, the volume of the lobe can be estimated. With careful attention to breathing instructions at the time of scanning, lung volume measurements have been shown to be highly reproducible and correlate with PFTs. In one study, CT imaging and body plethysmography were performed at baseline and after a 9-month interval in multicenter emphysema treatment trials [39]. Lung volumes were measured at total lung capacity (TLC) and residual volume (RV). Correlations between CT and PFT lung volumes for 486 subjects at baseline were 0.86 at TLC and 0.67 at RV. The CT volumes at TLC were systematically lower than the PFT volumes by 0.6 l, similar to other studies [41]. This has been attributed to measurement in the supine versus sitting position and differences in airspace included by the PFT measurement [39]. Reproducibility was assessed in terms of the intraclass correlation coefficient (ICC) for 126 subjects from the control group at TLC and 120 subjects at RV (FIGURE 2). At TLC, ICC was 0.943 for CT and 0.814 for PFT. At RV,

ICC was 0.886 for CT and 0.683 for PFT. CT lobar volumes showed high reproducibility (ICC ≥ 0.845 for the five lobes).

Application of imaging biomarkers in clinical trials

These biomarkers have been used for patient eligibility, treatment targeting and efficacy assessment in minimally invasive emphysema treatment device trials [25,26]. As an example, we will focus on the Endobronchial Valve for Emphysema Palliation Trial (VENT), the first computer-aided diagnosis (CAD)-targeted emphysema trial [25]. The trial used the Zephyr valve (Pulmonx, Inc.) and the treatment involves placing the one-way endobronchial valve (EBV) in the lobar or segmental airways of the most diseased lobe to prevent air from entering these portions of the lung, while still allowing air to exit.

■ Clinical trial data acquisition

When performing quantitative image analysis in multicenter clinical trials it is important that imaging protocols be standardized to ensure

comparability and reproducibility of image analysis results. The major factors affecting lung density and volume measurements are patient breath-hold and CT acquisition parameters, such as slice thickness and reconstruction kernel [42].

In VENT, image acquisition protocols were tailored based on the specific CT scanner model used at each site, and were designed to maintain as consistent image quality performance (slice thickness, spatial resolution and image noise) as possible across all scanners. CT imaging of the lung was performed at TLC and RV, pre- and post-treatment (nominally at an interval of 9 months), with 5–10 mm slice thickness, 120 kVp, 140–300 mAs and a pitch ranging from 0.984 to 1.5. Subjects were carefully coached to reach TLC and RV static breath-holds during scanning and validity checks confirmed excellent breath-hold reproducibility [39]. Methods have been developed that aim to correct RA measurements for differences

in patient breath-hold in longitudinal studies. These methods are based on linear regression or mixed-effects models and correcting using images acquired at two different breath-holds [43].

■ Patient eligibility & treatment targeting

Eligibility for minimally invasive emphysema trials is typically based on heterogeneity of disease as assessed by RA [25,26]. In VENT, the RA percentage was converted to an emphysema score from 0–4 as shown in FIGURE 3. The eligibility and lobe to be treated were then determined by the CAD system and a report was automatically generated as shown in FIGURE 3. The CAD system uses rule-based algorithms to make these diagnostic decisions. The eligibility criteria (shown in FIGURE 3) require an emphysema score of greater than three in one lobe, and an emphysema score at least one point lower in the adjacent lobe (i.e., interlobar heterogeneity of emphysema). The CAD system selects the most severely diseased lobe for treatment (volume reduction) using the algorithm shown in FIGURE 4. The criteria used in the VENT study were determined by the study investigators [26], based on an emphysema scoring system developed by Goddard *et al.* [44].

■ Imaging surrogate outcomes

Changes in RV and RV/TLC are associated with changes in lung function [45]. As airway obstruction moves from borderline (90% of predicted FEV₁) to moderate (50% of predicted FEV₁), the mean RV increases from 100 to 140% of its predicted value. Previous studies with the EBV found that overall there were post-treatment reductions in TLC and RV (measured by PFT), with RV having greater reduction [46]. The lessening of hyperinflation and associated improvements in chest wall mechanics and elastic properties of the lung may be partly responsible for symptomatic improvements [46,47].

A retrospective research study was conducted using RV changes as a surrogate outcome biomarker, which included subjects from VENT [48]. The cohort was comprised of 274 subjects treated with the EBV and 126 matched controls with available CT scans acquired at RV. Subjects were imaged pre- and 6-months post-treatment. The treatment group target lobe volume change had a mean (and standard deviation) of -300 (460) ml, with the control group having a change of six (180). The treatment group had a statistically significant volume reduction (p < 0.0001) compared with the

The screenshot shows the 'INTERNATIONAL VENT HRCT Scoring Form' with the UCLA logo. It includes fields for 'Site #' and 'Patient Initials:'. Below is 'SECTION 2 continued: SCORING RESULTS:'. It features two tables: 'Severity Scale' and 'Emphysema Scores (ES)'. The 'Severity Scale' table maps 'Parenchymal Destruction' percentages to 'Emphysema Score' values (0 to 4). The 'Emphysema Scores (ES)' table shows scores for 'Right Lung' and 'Left Lung' across 'Upper Lobe', 'Middle Lobe', and 'Lower Lobe'. Below the tables are 'RADIOLOGICAL INCLUSION CRITERIA' with four numbered questions and checkboxes for 'Yes' and 'No'. The form indicates 'Patient Not Eligible' for questions 1, 2, and 3. Question 4 asks for the lobe to be treated, with checkboxes for LUL, LLL, RUL, and RLL.

Parenchymal Destruction	Emphysema Score
0	0
1-25%	1
26-50%	2
51-75%	3
>75%	4

	Right Lung	Left Lung
Upper Lobe	3	3
Middle Lobe	3	N/A
Lower Lobe	3	2

Figure 3. Web-based report form showing computer-aided diagnosis output: emphysema scores based on density mask and lobe to be targeted for valve placement.

LLL: Left lower lobe; LUL: Left upper lobe; RLL: Right left lobe; RUL: Right upper lobe.

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control cohort. In patients who achieved substantial target lobe volume reduction (>15%), there were significant overall (whole lung) RV reductions accompanied by some redistribution of volume to nontreated lobes. FIGURE 5 shows an example of a subject treated with the EBV pre- and post-treatment with lobar collapse in the right upper lobe and volume redistribution to right middle and lower lobes. This patient had a positive outcome in terms of the lobar volume decrease variable. Similar lobar volume reductions and redistributions have been found in other EBV studies [26,49].

Conclusion

Computer-aided diagnosis systems are being used to extract quantitative imaging biomarkers from CT to assess emphysema. In this article we described their use to determine patient eligibility and treatment targeting in therapeutic trials for emphysema. Quantitative imaging is expected to play a greater role as a predictive and surrogate outcome biomarker. These biomarkers have the potential to reduce the numbers of patients in clinical trials and provide insights into the mechanism behind functional improvements.

Future perspective

Previous studies have shown statistically significant overall reductions in RV using the targeting algorithms described in this article, but the reductions are modest from a clinical standpoint. However, responder analyses have identified a subgroup with clinically significant RV reductions of more than 0.5 l [48]. Research suggests that the new predictive imaging biomarkers described in this section can be used to identify these responders prospectively, thus increasing the overall treatment efficacy.

■ Fissure integrity as a biomarker for treatment efficacy

Recent research on data from completed trials has shown that there is a difference in imaging features between subgroups who benefited from treatment and those who did not. For example, a closed system in the target lobe is important to achieve desired volume loss [46,50,51], and studies have shown that patients with complete interlobar fissures assessed on CT (a marker of no collateral ventilation between lobes) benefit from treatment more than patients with incomplete fissures [52,53]. Therefore, a quantitative measure of fissure integrity may be an important biomarker for treatment planning.

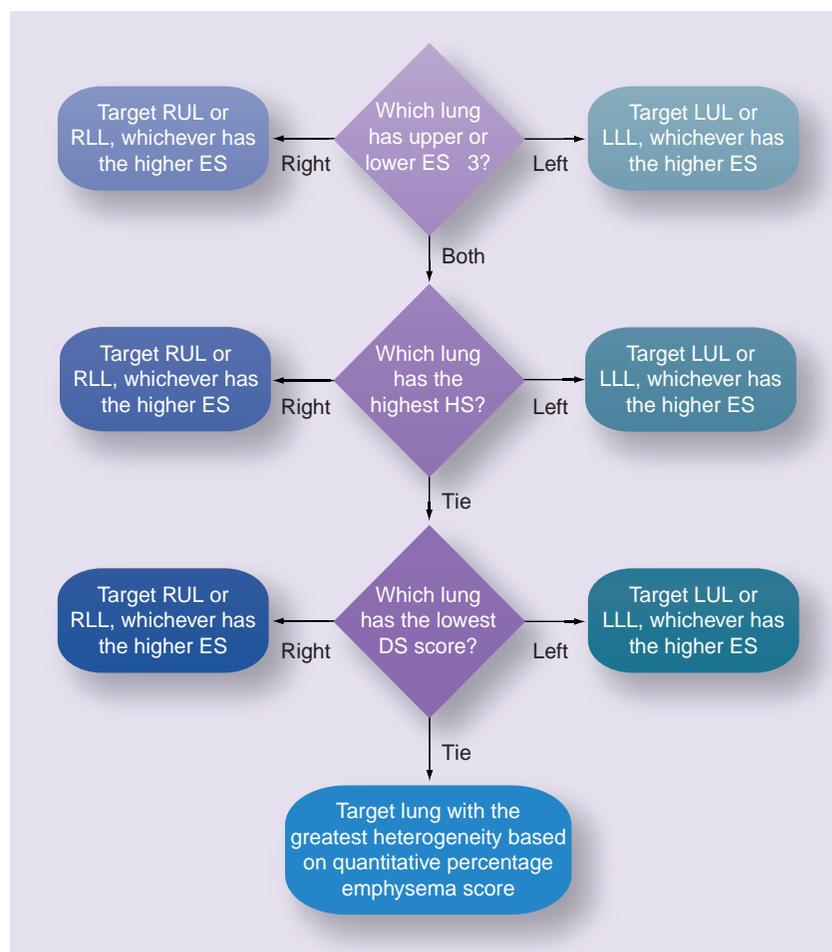


Figure 4. Computer-calculated lobar treatment targeting algorithm.

DS: Density score; ES: Emphysema score; HS: Heterogeneity score; LLL: Left lower lobe; LUL: Left upper lobe; RLL: Right lower lobe; RUL: Right upper lobe. Reproduced with permission from [26].

Assessment of fissure integrity using high resolution CT imaging has previously been carried out by visual inspection and subjective grading into three categories: complete, incomplete and absent [53–55]. This is a tedious and difficult task requiring review of a large number of images under multiplanar reformats, which has motivated the development of an automated quantitative system to assess fissure integrity. An automated quantitative system could be of tremendous benefit in making assessment of fissure integrity more discriminative, reproducible and broadly applicable. A variety of methods have been introduced for fissure detection [38,56–61], and more recently classification techniques have been used to quantify fissure integrity [62].

The Hessian matrix of second-order partial derivatives (EQUATION 1) was used to characterize the variations in intensity around a point, and features were computed to detect the image gradient changes associated with a fissure. The computation has been described in greater detail

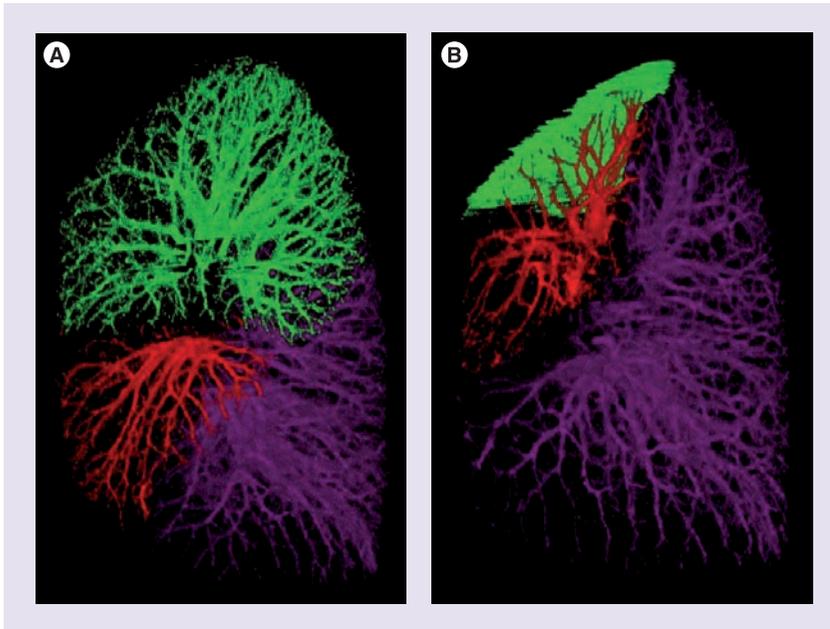


Figure 5. 3D visualization of lung vasculature from CT pre- and post-treatment. (A) Lobar segmentation pre-treatment; right upper lobe is green, right middle lobe is red and lower lobe is purple. **(B)** Post-treatment placement in the right upper lobe, showing upper (emphysematous) lobe collapse and lower lobe expansion reflecting partial redistribution to nontarget lobes. Reproduced with permission from [69].

by other authors [56,63]. These features were used to develop a voxel-wise fissure classification model by unsupervised k-means clustering. The number of clusters was set to three based on the premise that three classes are expected: fissure, nonfissure and bronchovascular bundle (near the hilum). The CAD system was also applied to each case and automatically classified voxels along the fissural path into the same three categories. The fissure integrity was then assessed by calculating the percent completeness of the fissure:

$$\text{Completeness} = \frac{N_{\text{Fiss}}}{N_{\text{Fiss}} + N_{\text{NonFiss}}} \times 100 \quad (1)$$

where N_{Fiss} is the number of voxels classified as fissure and N_{NonFiss} is the number of voxels classified as nonfissure.

Based on previous studies involving visual assessment, a completeness percentage of 90% or more was considered as a complete fissure for potential treatment planning. The performance of the system was then evaluated using 84 randomly selected fissure images. The test cases were also independently contoured by two observers to form a reference standard for fissural completeness. Analysis of the results showed that there was no statistically significant difference between the CAD system and the human observers in calculating fissure

percentage completeness (t-test $p > 0.05$). Pairwise comparisons of CAD–reader and reader–reader assessment of fissure completeness showed comparable levels of agreement of 77% or more.

■ Chronic obstructive pulmonary disease characterization: airways disease versus emphysema

Patient selection may also be enhanced by better characterization of chronic obstructive pulmonary disease (COPD), by distinguishing between emphysema and airways disease, and further in terms of emphysema phenotype. Emphysema treatments may not be appropriate for COPD patients with a predominance of airways disease and *vice versa*. Also, some studies have shown that surgical lung volume reduction surgery treatments may be most effective in patients with upper lobe-predominant emphysema [64].

Airway morphometry is one avenue for improved COPD characterization. Studies are beginning to show an association between CT airway measurements of lumen area and wall thickness with clinical measures of airflow limitation [65]. Airway analysis steps typically include detection of the airway lumen, extraction of the centerline of the airway tree and segment labeling [66]. This is followed by morphometric measurement by reformatting the image data orthogonal to the airway centerline, detection of the inner and outer airway wall boundaries, and computation of lumen area and wall thickness for each segment [67]. There are a number of challenges that complicate this analysis, including the comparable size of airway walls and point spread function of the CT scanner, as well as partial voluming effects, all of which cause blurring and make detection of the airway wall edges difficult. These effects vary from scanner to scanner and with acquisition parameters in multicenter clinical trials. Current research aims to increase automation of airway segmentation and labeling, and increase measurement reproducibility.

Emphysema patterns are being characterized through CT image texture analysis and low attenuation cluster analysis. In texture analysis, features are extracted within the lung parenchyma and pattern classifiers are trained to recognize patterns such as centrilobular, panlobular and paraseptal emphysema [68]. In low attenuation cluster analysis, the severity of emphysema is characterized by constructing a histogram of the sizes of clusters of pixels that are contiguous in the 2D image plane. Mild

disease is thought to have a larger number of small low attenuation clusters, while more advanced disease will have a smaller number of large low attenuation clusters, representing coalescent emphysema. It is expected that these research efforts will enable better characterization of emphysema and provide an opportunity to better target patients who are most likely to benefit from specific therapies.

Financial & competing interests disclosure

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Executive summary

Emphysema patient selection & treatment target challenges

- Emphysema causes destruction of lung tissue and an overall reduction in lung compliance as air becomes trapped in the diseased regions, which in turn reduces oxygen exchange.
- Hyperinflated regions limit the effective volume available for more viable lung tissue.
- New biomedical valves and stents are being developed that can be implanted in target airways to allow air to escape from the most diseased lung lobe, thereby reducing it in volume and providing more space for the adjacent (healthier) lobe to expand.
- The challenge facing the clinician is to determine which patients are most likely to benefit from the treatment and which lobe/airway should be treated.

CT imaging biomarkers

- Quantitative assessment of the lungs using CT provides important complementary information to pulmonary function tests because it allows regional assessment of the lung lobes.
- Lobar lung volumes and densities measured from imaging are now playing a key role in clinical trials of emphysema therapies.
- They are being used to determine patient eligibility and select the target lobe for treatment, based on lobar disease severity and heterogeneity.
- Treatment decisions based on these biomarkers are being made using automated computer-aided diagnosis systems.

Lung density analysis

- To determine eligibility of a patient for treatment, the severity and interlobar heterogeneity of emphysema are important variables.
- Density measurements used to quantify emphysema severity on CT include low attenuation relative area and 15th percentile of the lung attenuation histogram.
- Eligible patients typically have one lobe with a high relative area value (severe disease), with other lobes having lower values, and this most severe lobe is targeted for treatment.

Lobar lung volume changes

- To evaluate treatment efficacy, changes in lobar lung volumes post-treatment are an important variable, and are being used as a primary outcome variable in clinical trials.
- Lobar lung volume measurements from CT have been shown to be highly reproducible and correlate with pulmonary function tests.
- Changes in the residual volume/total lung capacity ratio are also used as a measure of hyperinflation, which is expected to be lessened post-treatment.

Conclusion

- Computer-aided diagnosis systems are being used to extract quantitative imaging biomarkers from CT to assess emphysema, and determine patient eligibility and treatment targeting in therapeutic trials.
- By correctly identifying the patients most likely to benefit from treatment and targeting the most appropriate lobe, these biomarkers have the potential to reduce the numbers of patients in clinical trials and provide insights into the mechanisms behind functional improvements.

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▪ **Describes the information system used to perform image data management and analysis in emphysema treatment trials.**