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Diagnostic Imaging in COPD

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Abstract

Chronic obstructive pulmonary disease (COPD) is a pathologic pulmonary condition characterized by expiratory airflow obstruction due to emphysematous destruction of the lung parenchyma and remodeling of the small airways. While spirometry is a very useful diagnostic tool for screening large groups of smokers, it cannot readily differentiate the etiologies of COPD and thus has limited utility in characterizing subjects for clinical and investigational purposes. There has been a longstanding interest in thoracic imaging and its role in the in-vivo characterization of smoking related lung disease. Research in this area has spanned readily available modalities such as chest x-ray and computed tomography to more advanced imaging techniques such as optical coherence tomography and magnetic resonance imaging. While chest x-ray is almost universally available, it lacks sensitivity in detecting both airway disease and mild emphysema, and is not generally amenable to objective analysis. Computed tomography has become the standard modality used for objective visualization of disease. It can provide useful measures of emphysema, airway disease, and more recently pulmonary vascular disease for clinical correlation. It does, however, face limitations in standardization across brands and generations of scanners, and the ionizing radiation associated with image acquisition is of concern to both patient and health care provider. Newer techniques such as OCT and MRI offer exciting in-vivo insight into lung structure and function that was previously available only in necropsy specimens and physiology labs. Given the more limited availability of these techniques, they are at present viewed as adjuncts to CT imaging.

Keywords

Emphysema; COPD; Imaging; computed tomography; airway disease

Introduction

Chronic obstructive pulmonary disease (COPD) is a pathologic condition of the lung characterized by emphysematous destruction of the lung parenchyma and remodeling of the small airways. The admixture of these two processes leads to what is clinically observed as expiratory airflow obstruction that is not completely reversible with the use of inhaled bronchodilating medications.(1) Despite ongoing refinements in the spirometric classification of disease, marked heterogeneity still exists in both subject symptoms and response to therapeutic intervention.(2, 3) This inconsistent association between lung

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function and disease manifestations has led to increasing interest in image based methods for the diagnosis and classification of COPD.

The following is a review of the role of chest imaging in the detection and quantification of the structural and functional abnormalities of a lung affected by COPD. The history of this effort extends from the use of the Roentgenologic exam, through the evolution of Computed Tomography (CT) and Optical Coherence Tomography (OCT), into more functional imaging modalities such as contrast enhanced (both intravenous and inhaled) Magnetic Resonance Imaging (MRI). The primary focus of this review will be applications of CT scanning in clinical investigation with lesser mention of additional techniques because of their more limited ability to be performed in very large cohorts of subjects with COPD.

Chest X-Ray

Posteroanterior and lateral chest x-ray (CXR) is a standard part of the clinical evaluation of subjects with COPD. Such images are inexpensive, easily obtained, and involve minimal radiation exposure. Prior work by several groups has led to several proposed criteria for the detection of emphysema on CXR (Table 1, Figure 1). These include

1. Increased radiolucency of the lung fields
2. Flattening of the diaphragms
3. Pruning of the peripheral vasculature
4. Increased retrosternal airspace
5. Widening of the intercostal spaces
6. Narrowed and more vertical cardiac silhouette.

While the application of such criteria to CXR for the detection of emphysema has historically had mixed success in correlations to histopathologic examination (4, 5), recent investigation suggests that the semi-objective visual interpretation of chest radiographic images may have clinical utility. In 2008, Miniati and colleagues demonstrated that both experienced and inexperienced viewers could identify the presence of moderate and severe emphysema with over 90% sensitivity and specificity with minimal training.(6) While such an approach is not amenable to the detection of subtle changes on longitudinal examination or a regional assessment of disease, it does suggest that in the clinical setting, CXR may provide useful subjective phenotypic information in subjects with COPD.

Computed Tomography: Emphysema—The introduction of computed tomographic imaging has facilitated the in-vivo examination of the most fundamental aspect of lung structure, the secondary pulmonary lobule. In it can be found the juxtaposition of the pulmonary vessels, airways, lymphatics, and lobular septa that maintain normal lung function. It is also the site most recognizable on CT scan for its appearance in both health and disease.(7)

Emphysema is defined as the abnormal enlargement of the airspaces distal to the respiratory bronchioles resulting from the destruction of the septal walls.(8) On CT scan, this process

results in visually apparent regions of low density tissue surrounded by more normal lung. The distribution of these regions of low attenuation and degree to which they involve the secondary pulmonary lobule can be characterized as centrilobular, panlobular, and paraseptal emphysema. As its name implies, centrilobular emphysema typically manifests as central destruction of the secondary pulmonary lobular parenchyma surrounding the centrilobular artery. In contrast, panlobular emphysema can be identified on CT scan as uniform destruction of the lobule. Finally, paraseptal emphysema is a form of panlobular emphysema localized primarily to the parenchyma adjacent to the pleural surface.(7) Examples of these conditions can be found in Figure 2.

There are several methods for both the detection and quantification of emphysema on CT scan. These can be preliminarily divided into two categories, visual detection schemes and more objective techniques based upon lung density. Typically, subjective approaches to analysis such as visual interpretation involve either a global or regional assessment of the lung using an ordinal scoring system (i.e. 0–4) to reflect disease severity. Using visual interpretation schemes, multiple investigators have demonstrated a correlation to histopathology (9–12), lung function (13, 14), and even response to therapeutic intervention. (3) Limitations to these approaches are, however, their susceptibility to intra and inter-observer variability (15), sensitivity to the viewing conditions such as window width and level (16, 17), and potential insensitivity for the detection of disease progression in longitudinal studies. Paradoxically, a potential strength to such analysis is that same ability of the user to be either consciously or unconsciously influenced by their visual perception of disease. Depending on the experience of the user, subtle patterns of disease may be observed that are not readily amenable to objective quantification.

In principle, a CT scanner is a densitometer where the brightness or attenuation of each pixel is a product of the density of the tissue it encompasses. These densities are expressed numerically in Hounsfield Units (HU) and generally range from −1000 HU (air) through 0 HU (water) to +1000 HU (bone) although the extremes can vary based upon CT scanner brand. Using this information, one can generate a histogram of the distribution of tissue densities in the lung, where each point is defined by the HU value of that pixel or voxel (3 dimensional pixel). Examples of these are shown in Figure 3. Multiple techniques for objectively identifying meaningful points on the CT lung histogram exist and include defining the mean lung density (18, 19), percentile points such as the Perc15 (HU threshold that delineates the lowest 15% of the histogram from the denser 85%) (20), and a fixed HU threshold such as −910 or −950 to identify the low attenuation regions of emphysema.(21, 22)

Since their inception over 30 years ago the afore mentioned methods of densitometric analysis have become standard for the detection and quantification of emphysema on CT scan and in the case of HU thresholding has been demonstrated on several occasions to offer correlates to the results of tissue necropsy.(21, 22) Through its application, investigators have found an objective tool for the prediction of surgical outcomes (23, 24) began to test drugs for their efficacy in the attenuation of disease progression (25), and have become increasingly aware of gender differences in the manifestations of smoking related lung disease.(26, 27) Despite these advances, lung densitometry is vulnerable to several

influences including the lung volume at which the CT scan was obtained (28, 29) and the protocol used to acquire and reconstruct the images.(30) While the former may be addressed by a calculated volume correction (28), the latter still offers an unanswered challenge to discover one or several “correction factors” by which one set of images can be adjusted so that they are comparable to those obtained by a different brand of scanner which has generated similar but not exactly the same set of images.

Computed Tomography: Airway Disease

The site of expiratory airflow obstruction in smokers is believed to be the peripheral small airways.(31) While the size of these airways precludes their direct assessment on clinical CT scans, recent investigation has demonstrated that the morphology of the central cartilaginous airways reflect the distal remodeling process. In 2000, Nakano and colleagues demonstrated that in smokers, subjects with the greatest degree of mural thickening and lumenal occlusion of the apical segment of the right upper lobe tended to have the lowest FEV_1 expressed as a percent of predicted (32) and a greater burden of distal small airway disease on histopathologic examination.(33) Further, the combination of CT measures of emphysema and densitometric measures of emphysema provided additive information when predicting lung function. Interestingly, there was no relationship between absolute airway wall thickness and lung function which alludes to the overall variability native airway morphology in this group. To address this issue investigators employed a measure called the Wall Area Percent (WA%) which is calculated as 100 times the airway wall area divided by the total bronchial cross sectional area.(32) This has become the standard CT based measure of airway disease in smokers.

There have since been several similar investigations of the correlation between CT measures of airway disease and lung function.(34–36) Among the most notable of these was work done by Hasegawa and colleagues who demonstrated that the quantitative assessment of the WA% of more distal airway generations (5^{th}) provided stronger correlations to lung function than the proximal segmental airways (3^{rd} generation) suggesting that a more robust biological signal could be detected in the most peripheral aspects of the bronchial tree.(34) This finding has been further extended by demonstrating that distal measures of WA% provided the strongest correlate to inhaled bronchodilator response. (37)

To this point, CT measures of airway disease have been defined as mural thickening with encroachment on the lumen. While useful for functional correlation, their relationship to another clinically significant occurrence, acute exacerbations of COPD, is currently undefined. In contrast, another radiographic form of airway disease, bronchiectasis, is increasingly being recognized for its association with elevated biomarkers of inflammation and the severity of respiratory events.(38)

Bronchiectasis is characterized radiographically as the abnormal dilation of the airway lumen with concomitant wall thickening.(39, 40) Its prevalence in the general population of smokers with COPD is unknown. In one of the largest reported CT based studies of smokers to date, Patel and colleagues found that approximately 2.5% of subjects had moderate to severe disease.(41) In contrast, Parr and colleagues found that almost 95% of their study cohort of subjects with AATD exhibited some bronchiectatic changes in their airways.(42)

There are 2 notable differences to these studies. The first is that the prevalence estimate published by Parr and colleagues included subjects with even mild, regionally limited disease while those estimates reported by Patel and colleagues were based on severe disease that precluded quantitative airway analysis. The second is related to the unique pulmonary manifestations of smoking related lung disease in smokers with or without AATD. Further investigation is needed to determine the prevalence and clinical associations of bronchiectatic airway disease detected on CT scan in smokers.

Computed Tomography: Expiratory/Dynamic Imaging

While HRCT images provide detailed structural information, they are generally acquired in a single breath hold at full inflation. To fully exploit the potential of CT, investigators have begun to utilize static expiratory scans and in the case of more central airway disease such as tracheobronchomalacia, dynamic expiratory imaging.(43) One of the most striking findings on expiratory CT imaging in subjects with expiratory airflow obstruction is mosaic perfusion of the secondary pulmonary lobule (Figure 4). Regions of low attenuation represent relative oligemia due to local obstruction of either the vasculature or small airway which in the latter case results in focal gas trapping.(44) While recognized visually, little has been done to objectively quantify this distinct radiographic pattern.

Computed Tomography: Pulmonary Vascular Disease (PVD)

Clinicians and investigators have long recognized the significance of pulmonary vascular disease in subjects with COPD. In 1972, Burrows and colleagues performed right heart catheterization in 50 subjects with severe COPD revealing that 26% of them had resting mean pulmonary artery (Ppa) pressures ≥ 26 mmHg.(45) Subsequent investigations have estimated the prevalence of elevated pulmonary vascular pressures to be between 35% and 90%, the higher estimates reported in subjects with severe emphysema.(46, 47) In addition to the disabling dyspnea on exertion ascribed to pulmonary hypertension in subjects with COPD, the presence of pulmonary vascular disease in this cohort has been demonstrated to be a poor prognostic determinant of survival (45, 46, 48, 49) and is associated with increased utilization of healthcare resources.(50)

While CT scanning is a standard of care for the investigation of pulmonary thromboembolic disease, there has been little application of CT to conditions such as PVD associated with COPD. Recently, Matsuoka and colleagues conducted an investigation of the relationship between CT burdens of emphysema and PVD in smokers using a metric termed the CSA or cross sectional area.(51) In an axial image, the authors hypothesized that some of the apparent high density structures are small vessels captured orthogonal to their long axis. By examining the cross sectional area of those round structures, one may have an objective measure of the aggregate small pulmonary vasculature available for lung perfusion. Further, when constraining this analysis to those structures that are each less than 5 mm^2 in cross sectional area, one can assess the CSA of the sub-sub segmental pulmonary vessels.

Using this metric of disease, Matsuoka and colleagues found that the CSA of those pulmonary vessels less than $5mm^2$ was inversely related to the CT burden of emphysema. (51) Not surprisingly, subjects with greater burdens of parenchymal destruction tended to

have lower aggregate cross sectional area of the small pulmonary vasculature. In a subsequent investigation, the same CSA measure was applied to a subset of subjects enrolled in the National Emphysema Treatment Trial (NETT) who underwent high resolution CT scanning and right heart catheterization for the invasive assessment of pulmonary artery pressures. In this cohort of subjects with severe emphysema, there was a marked inverse relationship between the vascular CSA and PA pressures while there was no evidence of a similar relationship between CT burdens of emphysema and PA pressures.(52) Further work needs to be done to replicate and validate these findings but CSA may prove to be a minimally invasive CT based assessment of pulmonary vascular disease in smokers.

Computed Tomography: Summary and Limitations

There are several technical as well as biologic limitations to the use of CT as a measure of lung disease in subjects with COPD. The first pertains to such considerations as the lack of manufacturer standardization of CT acquisition and reconstruction protocols across multiple brands and generations of scanners. Such systematic issues can bias data so that subjects at a given center may appear to have more or less emphysema for a given degree of tobacco smoke exposure or expiratory airflow obstruction. A second well documented limitation of quantitative CT scan analysis is the resolution imposed by clinical imaging protocols. Standard theory in image analysis states that structures smaller than 2 pixel widths in size cannot be resolved with accuracy. (53) Since the wall thicknesses of the 4^{th} and 5^{th} generation airways tend to fall in this range, consideration must be given to the accuracy of such measures prior to clinical application despite their providing a more robust biologic signal.

Additional seemingly simple biologic considerations that must be acknowledged include the level of inspiratory effort a subject exerts to achieve a full inflation scan. The lung (and in turn the airways) expand isotropically with inflation (54) so that for a given subject, the greater the degree of inflation, the greater the apparent burden of emphysema (by a corresponding reduction in lung density) and potentially diminished CT burden of airway disease (by dilating the airway lumen used to calculate cross-sectional measures of WA%). While the impact of such variability is recognized, and efforts are being made to adjust CT measures of emphysema for inspiratory effort (55), thus far there are no similar adjustments for CT measures of airway disease.

Finally, while CT imaging is a relatively safe, non-invasive tool that can be used on a large scale for genetic and epidemiologic studies, as a modality, it is limited in its ability to asses such things as the detailed mural remodeling process found in airway disease or the regional function of seemingly emphysematous tissue. In addition, general tendencies for subjects with thicker walls and smaller airway lumens to have greater expiratory airflow obstruction have been reproduced, but a single reported value of WA% at a single site in a single subject has little clinical meaning. Because of this, there is great interest in additional imaging modalities such as optical coherence tomography (OCT) and magnetic resonance imaging (MR) that may provide more detailed structural information and possibly insight into tissue function without the potential risks of ionizing radiation exposure inherent in CT.(56)

Optical Coherence Tomography (OCT)

Optical coherence tomography is a newer imaging technique that can provide detailed information of mural structures to a depth of several mm with a resolution of less than 5 μm. (57–59) By advancing a fiber optic probe bronchoscopically, investigators can selectively examine detailed regions of the tracheobronchial tree. OCT functions very similarly to ultrasound in that a tissue or region of interest is exposed a signal (in this case infrared light) and the reflected or back-scattered signals are reconstructed to generate an image. Again, similar to ultrasound, the density and depth of these tissues will influence the back-scattered signal such that they can be differentiated on the final reconstructed image.

Clinical application of this technique in subjects with COPD has provided new insight into the mural remodeling process characteristic of airway disease. Given the orders of magnitude increase in image resolution offered by OCT over CT, Coxson and colleagues were able to demonstrate the degree of overestimation of CT measures of airway disease and were further able to demonstrate that OCT may be a more sensitive imaging modality to assess disease progression.(60) Additional investigation is ongoing in such areas as the use of Doppler and OCT in objectively examining microvascular blood flow (61, 62) and the spectroscopic examination of in-vivo molecular structure.(63)

Magnetic Resonance Imaging

Unlike CT, magnetic resonance imaging does not require exposure to ionizing radiation; rather it is dependent upon the application of an external magnetic field to align the nuclear magnetization of the hydrogen atoms in a structure of interest. The resulting behavior of these atoms can then be detected by the scanner and reconstructed to generate an image. A major limitation of MRI imaging of the lung is the relatively high ratio of air to tissue. The resulting low density of pulmonary hydrogen atoms limits image resolution for the quantitative assessment of structure without the use of intravenous or inhaled contrast enhancing agents.(64)

The discovery and implementation of new contrast agents for MRI is an area of ongoing research. Some of the newest and most exciting agents under investigation are the hyperpolarized noble gases such as helium (^{3}He) and xenon (^{129}Xe). While both gases provide detailed images of the tracheobronchial tree and allow global and regional measurement of surface to volume ratio(65, 66), ^{129}Xe has the added property of being diffusible across the alveolar capillary membrane and can therefore be used to examine the septal thickness and diffusion capacity.(66–68) Further work is needed using these and other contrast agents however such techniques may truly allow in-vivo assessment of lung function in both health and disease.

Conclusions

Imaging and image analysis offers new insight into pulmonary disease processes that were previously available only on tissue necropsy. Current techniques can offer detailed measures of lung structure and with newer modalities previously immeasurable things like regional lung function. Imaging in the context of clinical investigation may offer the ability to define more homogeneous subsets of subjects with COPD and to potentially provide an

intermediate biomarker of disease progression in lieu of a declining FEV_1. In the case of CT, there are several limitations that must be overcome prior to its universal adoption in clinical investigation. These include the noise introduced by such non-disease related variables as subject inspiratory level and inter scanner reproducibility. Newer modalities such as OCT and MRI have distinct advantages to CT in such areas as image resolution and functional assessment of lung tissue. They, however, suffer for requiring more training to perform and are more burdensome for clinical study. Despite acknowledged limitations in all techniques, there is tremendous opportunity for further application of multimodality imaging in ongoing large clinical investigations.

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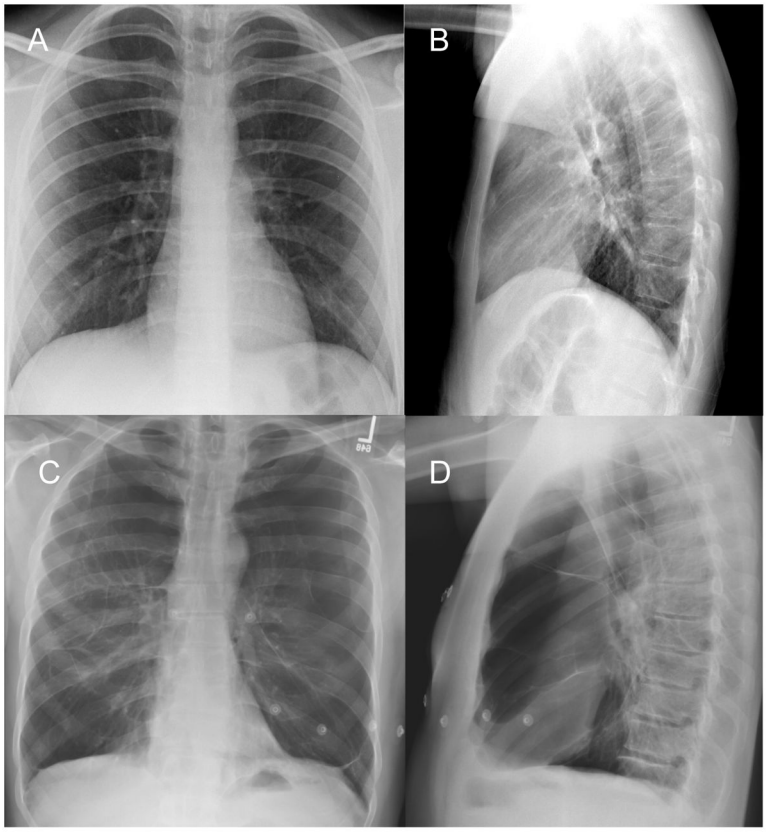

Figure 1.
Posteroanterior and Lateral CXR of a normal healthy subject (panels A and B) and one with several emphysematous destruction of the lung parenchyma (Panels C and D).

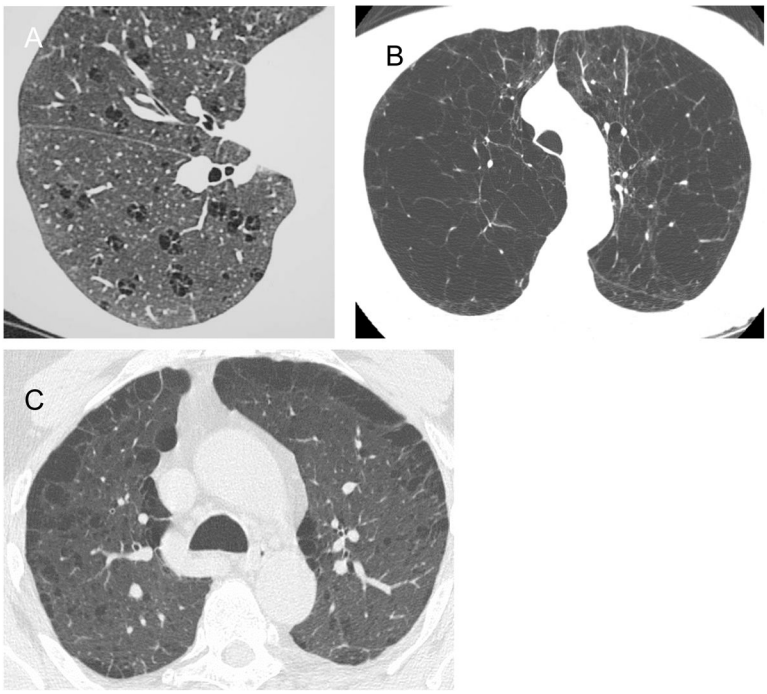

Figure 2.
Examples of centrilobular (A), panlobular (B), and paraseptal emphysema (C). Images provided courtesy of the COPDGene® Study.

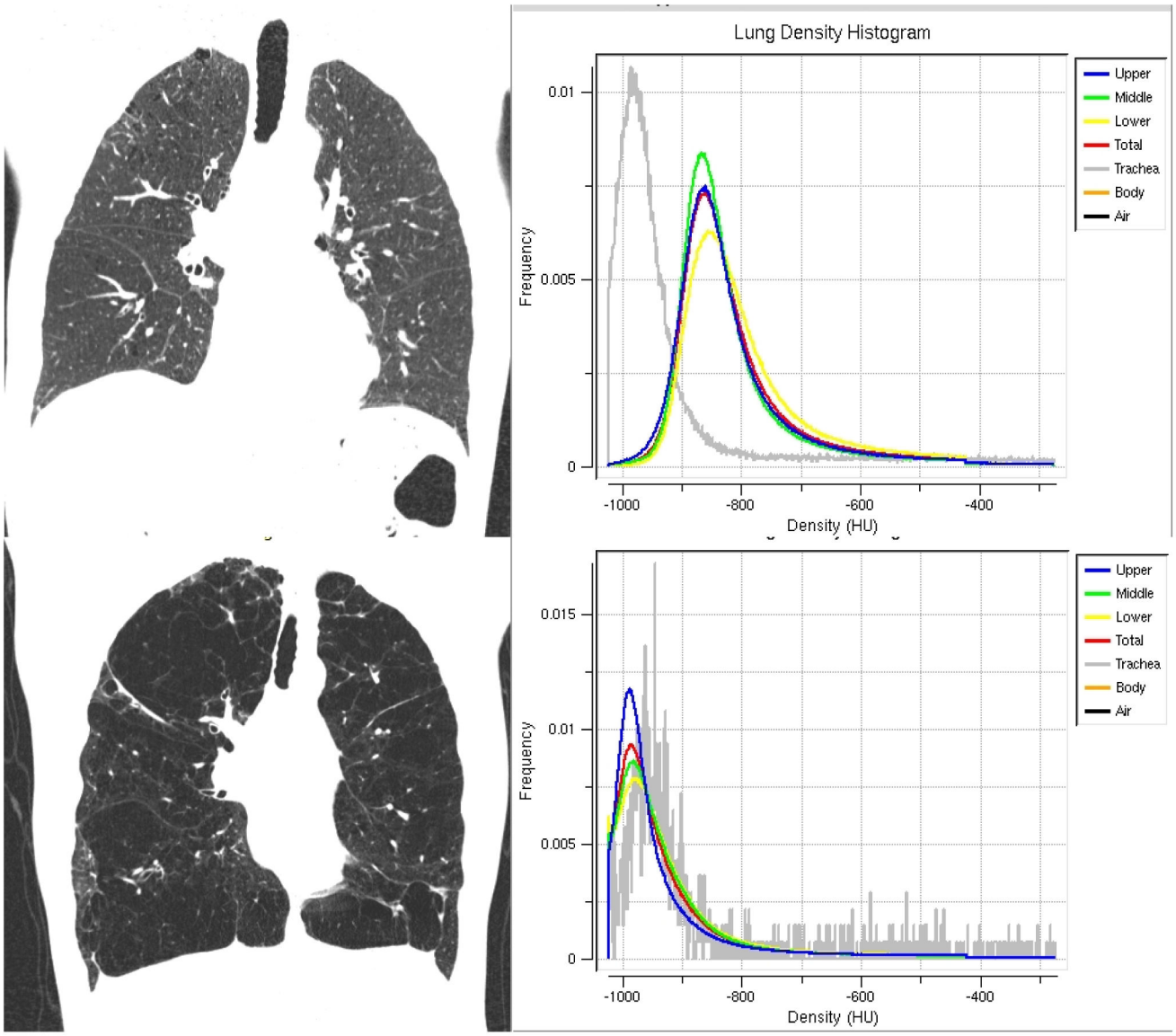

Figure 3.

Coronal images of a subject with minimal emphysema (top panels) and severe emphysema (bottom panels). For each subject, density histograms are presented for the upper (blue), middle (green), and lower (yellow) regions of lung divided by lung volume. Note the leftward shift in the density histograms of the subject with severe emphysema compared to the more normal smoker.

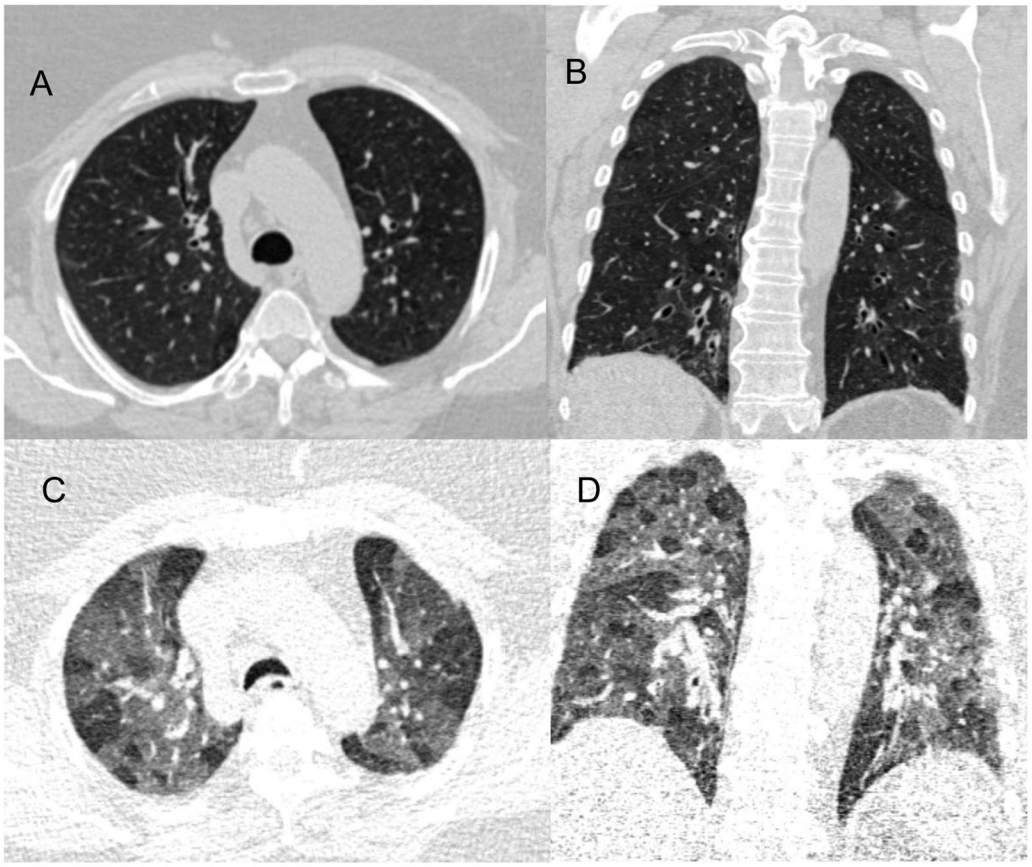

Figure 4.

Examples of axial and coronal CT images obtained at full inflation (panels A and B) and at relaxed exhalation (panels C and D). Note the mosaic attenuation of the bottom 2 expiratory panels suggesting oligemia or gas trapping within the secondary pulmonary lobule.