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# CT-Definable Subtypes of Chronic Obstructive Pulmonary Disease: A Statement of the Fleischner Society[1]

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The purpose of this statement is to describe and define the phenotypic abnormalities that can be identified on visual and quantitative evaluation of computed tomographic (CT) images in subjects with chronic obstructive pulmonary disease (COPD), with the goal of contributing to a personalized approach to the treatment of patients with COPD. Quantitative CT is useful for identifying and sequentially evaluating the extent of emphysematous lung destruction, changes in airway walls, and expiratory air trapping. However, visual assessment of CT scans remains important to describe patterns of altered lung structure in COPD. The classification system proposed and illustrated in this article provides a structured approach to visual and quantitative assessment of COPD. Emphysema is classified as centrilobular (subclassified as trace, mild, moderate, confluent, and advanced destructive emphysema), panlobular, and paraseptal (subclassified as mild or substantial). Additional important visual features include airway wall thickening, inflammatory small airways disease, tracheal abnormalities, interstitial lung abnormalities, pulmonary arterial enlargement, and bronchiectasis.



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The term *chronic obstructive pulmonary disease* (COPD), currently defined on the basis of spirometric evidence of airway obstruction, encompasses several distinct but overlapping obstructive syndromes, including emphysema, chronic bronchitis, and reversible or irreversible small airways obstruction (1). The Global Obstructive Lung Disease (GOLD) system has been widely used to identify and classify the severity of postbronchodilator airflow limitation in COPD, with GOLD stage I referring to subjects with a ratio of forced expiratory volume in 1 second ($FEV_1$) to forced vital capacity (FVC) of less than 0.7 but with preserved $FEV_1$, and GOLD stages II, III, and IV when the $FEV_1$/FVC ratio is less than 0.7 and $FEV_1$ is less than 80%, 50%, and 30% of predicted, respectively (2). Individuals with identical GOLD stages may have different morphologic appearances at computed tomography (CT) (3). Some have extensive emphysema, whereas others with equal functional impairment have an airway-dominant phenotype with little or no emphysema. These morphologic differences may reflect important differences in the underlying pathophysiology and genomic profile of COPD. Furthermore, individual subtypes of emphysema may have different pathophysiologic importance. For example, Smith et al (4) showed that smokers with predominantly centrilobular emphysema (CLE) had a higher level of cigarette exposure, higher lung volumes, and lower lung diffusing capacity than those without emphysema. Conversely, smokers with a predominantly "panlobular" pattern of emphysema had a relatively lower body mass index than smokers without emphysema.

In addition, morphologic changes of emphysema and airways disease are found in a substantial proportion of subjects who do not meet the spirometric criteria for COPD (5). Standardized characterization of COPD and other smoking-related lung changes at CT is particularly important given the emerging role of reduced-dose CT in screening for lung cancer in cigarette smokers (6).

COPD is associated with irreversible structural pulmonary changes, including parenchymal destruction (emphysema), large airway remodeling, and reduction in the caliber and number of small airways in the lung (7). CT is a well-validated technique to visually and quantitatively assess the in vivo presence, pattern, and extent of emphysema (8–11). Bronchial wall thickness and the extent of emphysema at quantitative CT in patients with COPD are independent determinants of the degree of airflow obstruction at pulmonary function testing (12) and the risk of COPD exacerbations (13). Emphysema assessed quantitatively is also associated with increased all-cause mortality in patients with COPD (14). Quantitative CT assessment of expiratory gas trapping is emerging as a powerful predictor of the severity of airway obstruction in COPD (12,15,16). Furthermore, the observation that expiratory gas trapping correlates only weakly with histologic severity of emphysema strongly suggests that it is caused by obstruction in the smaller airways rather than emphysema (17). Quantification of low-attenuation areas, expiratory gas trapping, and airway wall thickness can help define specific COPD phenotypes with differing clinical and physiologic features (18).

The purpose of this statement is to define the phenotypic abnormalities recognizable at visual and quantitative evaluation of CT images in subjects with COPD. Although these abnormalities often overlap, we believe that identification and quantification of the predominant morphologic findings and their grouping into defined subtypes of COPD will improve diagnostic accuracy, help optimize treatment, facilitate genetic analysis, and provide a framework for data comparison in clinical trials. Given the focus on COPD and related phenotypes, discussion of other smoking-related lung conditions such as pulmonary Langerhans cell histiocytosis, lung cancer, and usual interstitial pneumonia is beyond the scope of this article. Although COPD unrelated to smoking (eg, COPD related to biomass fuel exposure) is not discussed herein, the same concepts likely apply to these conditions.

### Advance in Knowledge

- Visually based classification of the CT appearances in chronic obstructive pulmonary disease (COPD) provides complementary information to quantitative CT.

### Implication for Patient Care

- Combined quantitative and visual assessment of CT may contribute to improved personalized care of patients with COPD.

## Technical Approach

### CT Image Acquisition and Evaluation

CT is currently the most widely available and precise imaging method for the characterization of COPD. Chest radiography does not allow accurate morphologic assessment of COPD owing to

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**Abbreviations:**
CLE = centrilobular emphysema
COPD = chronic obstructive pulmonary disease\
$FEV_1$ = forced expiratory volume in 1 second
FVC = forced vital capacity
GOLD = Global Obstructive Lung Disease
PLE = panlobular emphysema
PSE = paraseptal emphysema

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Guarantors of integrity of entire study, D.A.L., J.D.C.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, D.A.L., J.H.M.A., P.A.G., H.U.K., A.A.B., R.G.B., T.V.C., J.R.G., P.A.G., H.C., E.A.H., J.D.N., M.P., J.D.C.; clinical studies, D.A.L., J.H.M.A., P.A.G., H.U.K., E.K.S., J.D.C.; statistical analysis, J.D.C.; and manuscript editing, D.A.L., J.H.M.A., J.C.H., P.A.G., H.U.K., A.A.B., R.G.B., T.V.C., P.A.G., H.C., E.A.H., J.D.N., M.P., E.K.S., J.D.C.

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Conflicts of interest are listed at the end of this article.

limited resolution and superimposition of overlapping structures. Although magnetic resonance (MR) imaging, particularly with use of hyperpolarized gases, offers exciting possibilities for measuring alveolar dimensions (19–23), technical issues currently limit wide acceptance. With advances in fluorine MR imaging, some of these limitations may be eliminated (24). Other potentially promising MR imaging techniques, such as ultrashort echo time pulse sequences, oxygen-enhanced MR imaging, or the use of fluorinated gases, require validation in multicenter studies.

The appropriate CT technique for the evaluation of COPD should optimize visual assessment of the lung structure for emphysema and airways disease and help identify other complications of cigarette smoking, such as lung cancer, lung fibrosis, and Langerhans cell histiocytosis. Moreover, CT should facilitate quantitative evaluation of emphysema and airway wall thickening while using the minimum possible radiation dose. CT images should be viewed at window level settings suitable for lung evaluation (typically a window level of −700 HU and window width of 1500 HU). A narrower window width (750–1000 HU) may be useful for detecting or excluding early emphysema (25). Minimum intensity projections may help show the presence and extent of emphysema (26). Standard images from subjects with normal and abnormal findings may improve observer agreement in the visual characterization of CT changes (27).

Unenhanced volumetric thin-section CT is generally recommended for COPD characterization (28). Precise scanner calibration, ideally with a standardized CT phantom (29), is important for ensuring the accuracy of CT numbers (30,31). Scanner-specific protocols have been designed to compare quantitative CT indexes of parenchymal and airway status (32). A high-spatial-resolution reconstruction algorithm is better for visual assessment of the lungs (28), whereas a smoother reconstruction algorithm facilitates computerized analysis by reducing image noise (33,34). Submillimeter z-axis resolution, with overlapping section reconstructions, is recommended for optimal airway analysis (35,36). Expiratory CT, performed at functional residual capacity or at residual volume, is a powerful tool for determining the severity of airway obstruction in cigarette smokers (12,16,37,38) and can suggest tracheobronchomalacia, although this condition is better shown with dynamic expiratory imaging (39). In the absence of lung volume control with a pneumotachometer (40,41), it is critically important for the CT technologist to rehearse breathing instructions with the patient, encouraging a full deep inspiration to total lung capacity for the inspiratory acquisition and expiration to functional residual capacity or residual volume for the expiratory acquisition (42).

The CT radiation dose level used for the evaluation of COPD is driven by the balance between radiation dose and image quality. Adequate visual characterization can be achieved with reduced-dose CT acquisition techniques, as used for lung cancer screening (43,44). Excessive image noise with a reduced CT dose can simulate emphysema, particularly at quantitative CT (45,46), and may impair segmentation of the airways and quantitative evaluation of airway wall thickness. Given the older age profile of subjects with COPD and the importance of acquiring precise quantitative information, moderate radiation doses (<10 mSv) are probably acceptable. However, as CT detector technology and image reconstruction methods evolve, in combination with improvements in quantitative CT, it is likely that the required CT dose will further decrease. Several large multicenter studies (4,47–50) have used a range of settings for key scan acquisition parameters, and these are summarized in the Table. Expiratory CT may be performed with lower radiation exposure (tube current ≤50 mAs) because it is primarily used to quantify air trapping (51). Iterative reconstruction techniques are not currently recommended because the effects on quantitative and visual evaluation are uncertain at the time of writing (37,52).

**CT Techniques Used for Visual and Quantitative Evaluation of COPD**

| Parameter | Value |
|---|---|
| Detector configuration | ≥16 detectors |
| Pitch | 1–1.4 |
| Acquisition collimation (mm) | ≤1 |
| Kilovolt peak | 120 |
| Effective milliampere second | 40–200 |
| Reconstruction algorithms | Smooth and sharp |
| Reconstruction section thickness (mm) | 0.625–1 |
| Reconstruction interval (mm) | 0.5–0.9 |
| Reconstruction field of view | Lungs only |

## Quantitative CT Image Analysis

The goals of quantitative CT in COPD are to quantify the presence and percentage of emphysema-like lung (low-attenuation areas), the lobar and zonal distribution of the low-attenuation regions, changes in airway walls and luminal caliber, and the severity of gas trapping at expiratory CT. A number of analysis platforms are available as commercial software and in academic institutions (36,53–55). A detailed discussion of quantitative CT methodology is beyond the scope of this article, but further details are available in recent review articles (54,56–58). Although quantitative CT provides useful information regarding emphysema, airways, and air trapping and provides a means of objectively characterizing and following these pathologic processes, visual assessment of CT scans remains important to describe patterns of altered lung structure in COPD and provides distinct phenotypes not currently identified with quantitative CT.

## Visually Defined Subtypes of COPD

Figure 1 lists the visually defined phenotypes of emphysematous destruction as well as the airway changes seen in COPD. Figure 2 illustrates the gross abnormality and micro-CT features of the primary lesions of each of the major emphysematous phenotypes of COPD.

**Figure 1**

**Emphysema***

1. **Centrilobular Emphysema:** the dominant pattern should be scored
   a. **Trace Centrilobular Emphysema (CLE):** minimal centrilobular lucencies, occupying < 0.5% of a lung zone.
   b. **Mild CLE:** scattered centrilobular lucencies, usually separated by large regions of normal lung, involving an estimated 0.5-5% of a lung zone.
   c. **Moderate CLE:** many well-defined centrilobular lucencies, occupying more than 5% of any lung zone.
   d. **Confluent CLE:** coalescent centrilobular or lobular lucencies, including multiple regions of lucencies that span several secondary pulmonary lobules, but not involving extensive hyperexpansion of secondary pulmonary lobules or distortion of pulmonary architecture.
   e. **Advanced Destructive Emphysema (ADE):** panlobular lucencies, with hyperexpansion of secondary pulmonary lobules and distortion of pulmonary architecture.
2. **Panlobular Emphysema**
   Associated with A1AT Deficiency: most commonly, a lower lobe predominant pattern involving generalized destruction of all acini more or less equally.
3. **Paraseptal Emphysema**
   a. **Mild Paraseptal Emphysema (PSE):** small ( ≤1 cm), well-demarcated rounded juxtapleural lucencies, aligned in a row along a pleural margin, sometimes including along an interlobar fissure, and sometimes including a few small rounded lucencies immedi ately central to the juxtapleural lucencies.
   b. **Substantial Paraseptal Emphysema:** mainly large (>1 cm diameter) juxtapleural cyst-like lucencies or bullae, involving more than the lung apices, aligned in a row along a pleural margin, and sometimes including adjacent to an interlobar fissure.

**Airway Disease**

*Airway disease is commonly found with all forms of emphysema, but also commonly occurs in the absence of emphysema as a predominant expression of COPD.*

1. **Bronchial Disease:** Thickening of walls of segmental and subsegmental airways.
2. **Small Airway Disease (SAD):** Inflammatory SAD can be directly identified on CT scan by the presence of peripheral centrilobular micronodular opacities. Obstructive SAD is identified by gas trapping on expiratory CT, or FEV1/FVC ratio < 0.7, in the absence of significant emphysema.

**Associated Features**

1. **Large Airway Disease:** Tracheobronchomalacia, saber sheath trachea, tracheobronchial outpouching/diverticula.
2. **Interstitial Lung Abnormality:** Patchy ground glass abnormality, mild subpleural reticular abnormality.
3. **Pulmonary Arterial Enlargement:** Enlargement of the pulmonary artery, suggesting pulmonary hypertension, occurs in advanced COPD, and a ratio of the pulmonary artery diameter to the aorta diameter >1 has been associated with increased risk of COPD exacerbation.
4. **Bronchiectasis**

**Figure 1:** Visually defined patterns of COPD at CT. * = If there are fewer than four to five small (≤1 cm) juxtapleural circumscribed areas of lucency in the apex of a lung, ignore. *A1AT* = $\alpha_1$-antitrypsin.

## CLE

McLean in Australia (59–62) and Leopold and Gough in the United Kingdom (63) provided the first pathologic descriptions of CLE and showed that the primary lesion is produced by dilation and destruction of respiratory bronchioles within a single acinus. Furthermore, they both demonstrated that the centrilobular lesions are formed by coalescence of several primary lesions. Subsequently, the destruction spreads to the entire lung lobule and fuses many destroyed lobules together to produce a pattern of coalescent destruction that sometimes disintegrates to form large bullous lesions. By performing three-dimensional reconstructions of serial histologic sections of 90 individual centrilobular spaces, Leopold and Gough (63) showed that all CLE lesions had a supplying bronchiole lined with abnormal epithelium that was associated with varying degrees of airway wall thickening and lumen narrowing. In addition, they also described widespread evidence of bronchiolitis ranging from active cellular infiltration to fibrosis. In a subsequent study, they used fine particulate lead dust bronchograms to confirm that some centrilobular spaces filled easily from the conducting airways and suggested that the pathways between the mainstem bronchus and the centrilobular spaces were shorter in those with emphysema than in normal airways (64). Others used this same technique to visualize CLE, showing that the areas of CLE are hypercompliant and reach their maximum volume at very low transpulmonary pressures and that the resistance to collateral ventilation falls to very low levels

**Figure 2**

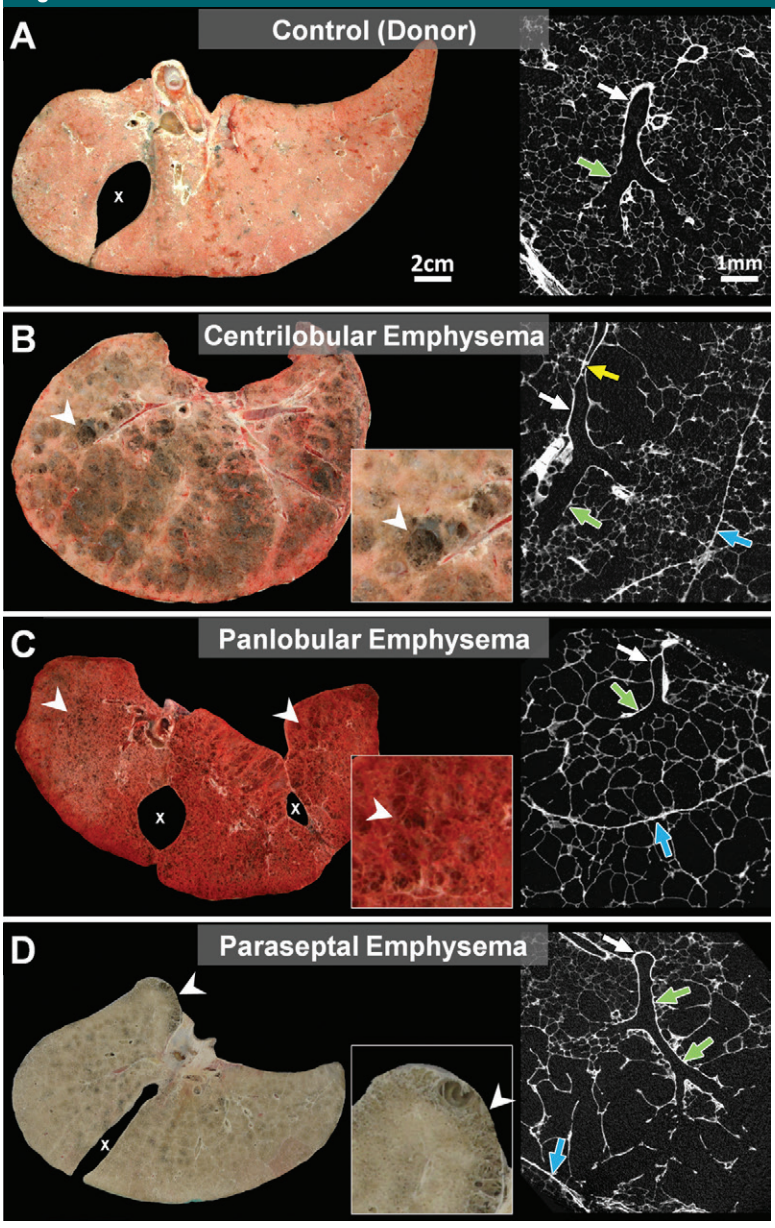



**Figure 2:** Comparison of frozen lung slices and micro-CT images from, *A*, donor (control) lung to lungs affected by, *B*, centrilobular, *C*, panlobular, or, *D*, paraseptal phenotypes of emphysematous destruction. *A*, Micro-CT image of control lung shows a terminal bronchiole (white arrow) connecting to respiratory bronchiole (green arrow) supplying alveoli of normal size. *B*, Extensive centrilobular destruction (arrowheads) is seen in lung slice, and micro-CT scan of primary lesion shows dilatation and destruction of proximal respiratory bronchioles (green arrow), with sparing of alveoli near lobular septa (blue arrow). Moreover, terminal bronchiole leading into centrilobular lesion is narrowed (yellow arrow) and then opens up again (white arrow), a feature that can be better appreciated in video associated with the article by McDonough et al (7). *C*, In contrast, the panlobular phenotype of emphysema in this case of $\alpha_1$-antitrypsin deficiency shows relatively mild destruction of gross specimen (arrowheads), and micro-CT scan shows uniform destruction of alveoli extending right up to lobular septa (blue arrow). Terminal bronchiole (white arrow) and respiratory bronchiole (green arrow) are normal. *D*, Paraseptal phenotype of emphysema shows typical lesions (arrowheads) beneath pleural surface on gross specimen, and micro-CT scan shows that alveoli adjacent to lobular septa are dilated and destroyed, with sparing of center of lobule. Terminal bronchiole (white arrow) and respiratory bronchiole (green arrow) are normal. Images from control lung and lung affected by PSE came from organ donors and were released for research when judged to be unsuitable for transplantation, whereas lungs affected by CLE and panacinar emphysema were donated by patients treated by means of lung transplantation. The protocol for the preparation of the specimens is fully described in reference 7. *x* on *A*, *C*, and *D* indicates interlobar fissure(s).

in regions of emphysematous destruction (65). More recent studies based on micro-CT confirmed earlier observations that the supplying bronchioles often follow a tortuous pathway to reach the centrilobular space (7) (see video in article by McDonough et al [7]). More importantly, they also showed a remarkable reduction in the total number of terminal bronchioles per lung, from 22 300 ± 3900 per adult human lung in control subjects to 2400 ± 600 per lung when CLE was present. This study provided histologic evidence that it was surviving airways with thickened walls (see figure 4 in the article by Klein et al [5]) that supplied the terminal bronchioles. Most importantly, micro-CT measurements showed that the reduction in terminal bronchioles occurred before the onset of emphysematous destruction. Collectively, these data support the hypothesis that bronchiolitis is the earliest lesion in COPD and suggest that CLE is formed distal to surviving bronchioles, supported by collateral ventilation of acini within the same lobule that lost terminal bronchioles (7).

At CT, CLE is characterized by small well-defined or poorly defined areas of low attenuation surrounded by normal lung. Centrilobular pulmonary arteries or arterioles, which are often seen traversing the hypoattenuated areas, mark the center of each lobule (9). This pattern of emphysema correlates well with pathologically demonstrated CLE (59,66–68) and with micro-CT measurements of the primary lesions (Fig 2, *B*). This is the most common type of smoking-related emphysema and is usually upper lung predominant (Figs 3, 4). The low-attenuation areas may range

**Figure 3**

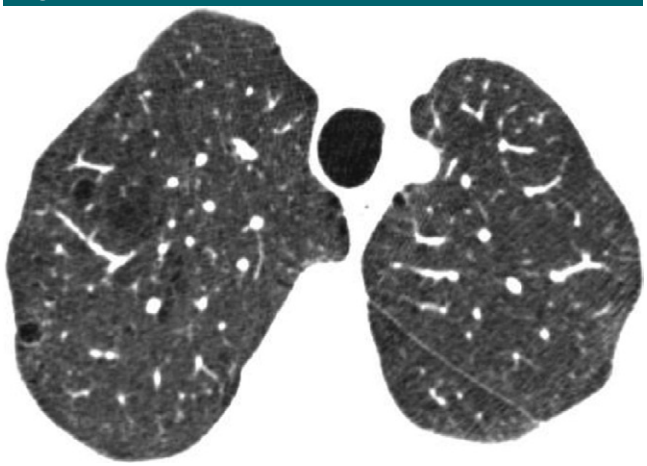


**Figure 3:** Mild CLE. CT scan in patient with GOLD stage I COPD shows scattered centrilobular lucencies, separated by large regions of normal lung, involving an estimated 0.5% of upper lung zone.

**Figure 4**

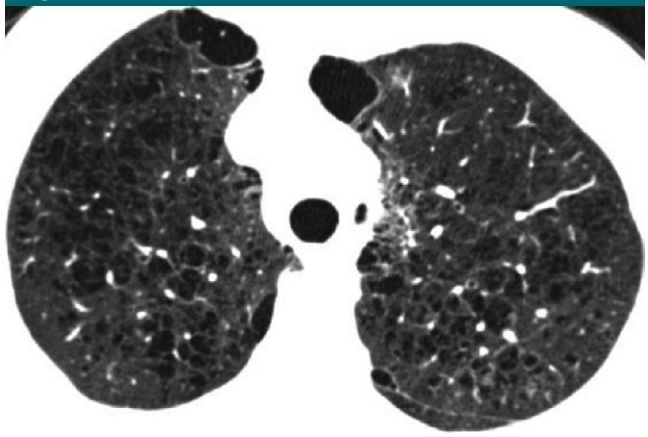


**Figure 4:** Moderate CLE. CT scan in patient with GOLD stage I COPD shows many well-defined centrilobular lucencies that occupy more than 5% of upper lung zone. PSE is seen in antero-medial right and left lungs.

**Figure 5**

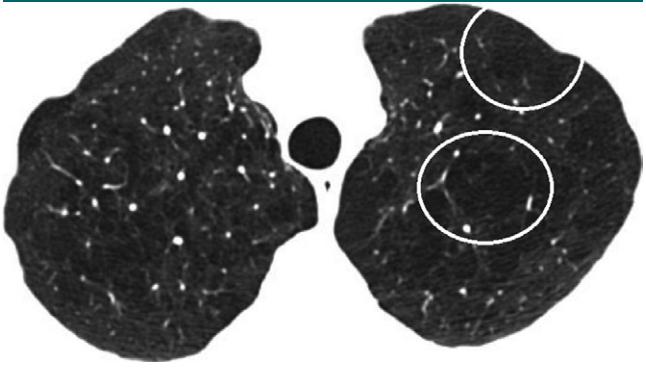


**Figure 5:** Confluent CLE. CT scan in patient with GOLD stage I COPD shows multiple lucencies that span several secondary pulmonary lobules (circled in left lung) but are not associated with extensive hyperexpansion of secondary pulmonary lobules or distortion of pulmonary architecture.

**Figure 6**

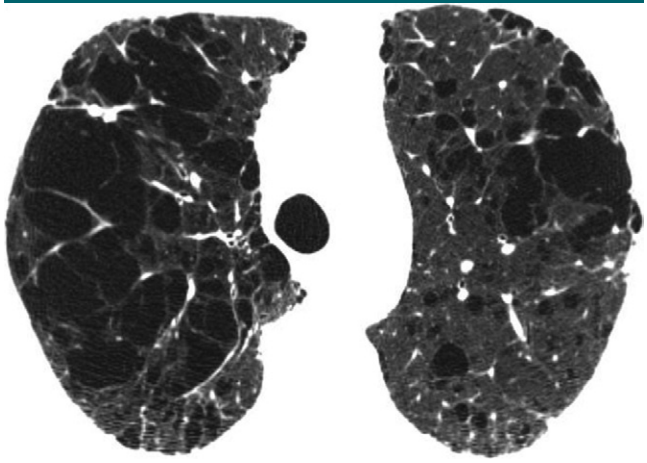


**Figure 6:** Advanced destructive emphysema. CT scan in patient with GOLD stage I COPD shows hyperexpansion of secondary pulmonary lobules with distortion of pulmonary architecture.

from less than 1 mm to more than 3 cm in diameter.

### Severe Emphysema

*Confluent emphysema.*—As CLE becomes more severe, the areas of low attenuation become confluent (Fig 5) and the centrilobular distribution becomes less apparent. In most cases, the areas of low attenuation have no visible walls; however, very thin walls may be seen—particularly when the areas of emphysema are extensive. The apparent walls in such cases probably represent atelectasis or interlobular septa adjacent to the emphysematous spaces. Confluent emphysema may be differentiated from advanced destructive emphysema by the presence of a preserved rim of normal lung attenuation intervening between areas of lung destruction, and by the absence of lobular hyperexpansion, architectural distortion, or splaying or decreased caliber of vessels.

*Advanced destructive emphysema.*—Advanced destructive emphysema is manifested as a generalized decrease of attenuation of the lung without focal hypoattenuation (Fig 6) and represents an advanced stage of CLE. Interlobular septa are often preserved and splayed, facilitating the identification of pulmonary lobular hyperexpansion. In addition, the more central pulmonary vessels are often distorted, splayed, and narrowed with decreased branching (architectural distortion). Although this pattern may be indistinguishable at CT from the panlobular pattern described

**Figure 7**

**Figure 7:** PLE related to $\alpha_1$-antitrypsin deficiency. CT scan through lower lungs shows widespread confluent areas of hyperlucency spanning one or several lobules. Some lobules, outlined by intact interlobular septa, appear hyperexpanded (arrowheads).

below, and the term *panlobular* has been previously used to describe this entity (4,69), we prefer to use the term *advanced destructive emphysema* because it may not represent histologic panlobular emphysema (PLE).

## PLE

PLE specifically refers to diffuse emphysematous destruction across the lobule (Fig 2, *C*). Wyatt et al (70) first described this pattern, which was subsequently linked to low circulating levels of $\alpha_1$-antitrypsin (71). It is now known that low levels of $\alpha_1$-antitrypsin are produced by a genetic defect in the $\alpha_1$-antitrypsin gene that causes the protein to misfold after it is produced, causing it to accumulate in liver cells, where it stimulates inflammation and subsequent cirrhosis without being secreted into the circulating blood (72). In general, the extent and severity of alveolar destruction in PLE is milder than that in CLE, but it affects all of the acini within a lung lobule more or less equally (see the gross pathology and micro-CT images of the primary lesion in Fig 2, *C*).

PLE has also been reported in the absence of $\alpha_1$-antitrypsin deficiency (73), including in intravenous drug abuse (74). In cigarette smokers, mixtures of PLE and CLE can be found within the same lungs (69). Under these conditions, Kim et al (69) have suggested that PLE is less likely to be associated with small airway obstruction than CLE. However, micro-CT studies of $\alpha_1$-antitrypsin deficiency indicate that both CLE and PLE are associated with narrowing and destruction of the terminal bronchioles in end-stage COPD (7).

At CT, advanced PLE in association with $\alpha_1$-antitrypsin deficiency often occurs in a lower lobe–predominant distribution (Fig 7) (75,76). (CLE may also be found in cigarette smokers with $\alpha_1$-antitrypsin deficiency.) Earlier stages of PLE are quite difficult to identify at CT, and quantitative CT may be preferred.

## Paraseptal Emphysema

Heard (77) used the term *paraseptal emphysema* (PSE) to describe emphysematous lesions caused by selective destruction of the distal acinus (Fig 2, *D*), and subsequent reports have used it to describe lesions located near the pleural surface close to the chest wall and in the interlobar fissures. In some cases, multiple destroyed acini coalesce to form striking lesions just under the pleural surface on CT scans. Its relative frequency in radiology-based studies like COPDGene suggest that it has been underappreciated in studies of postmortem and surgically resected lungs, perhaps because these specimens are rarely properly inflated before being examined. However, PSE is often not associated with significant symptoms or physiologic impairment (4).

PSE is characterized at CT by subpleural and peribronchovascular foci of low attenuation separated by intact interlobular septa thickened by associated mild fibrosis (78) (Figs 8, 9). PSE has a special predilection for peripheral subpleural lobules along the mediastinal and peripheral pleura and fissures, usually most marked in the middle and upper lungs and along the mediastinum. CT shows subpleural areas of low attenuation with a well-defined wall. Rows of PSE may mimic honeycombing, but the size of the cysts is larger than that of honeycomb cysts and architectural distortion and other signs of fibrosis are not present. In our experience, PSE is commonly associated with marked thickening of the walls of proximal bronchi and bronchioles, suggesting a significant airway inflammatory component. PSE occurs across the entire spectrum of minimal involvement to severe parenchymal obstruction and can be progressive. Because minimal subpleural emphysematous abnormality is quite common even in nonsmokers (79,80), it is reasonable to ignore or discount the presence of up to four or five small cysts (≤1 cm) at the lung apices.

Bullae (avascular low-attenuation areas >1 cm in diameter, with a thin but perceptible wall) are found in all types of emphysema (81) but are most commonly associated with PSE. Bullae are often located in the upper lobes in both CLE and PSE but are more evenly distributed in the lungs of patients with advanced destructive emphysema (76). Bullae may be large enough to cause reduced expansion of the adjacent lung parenchyma, which may sometimes result in sufficient atelectasis to appear as a masslike opacity (82). The term *giant bullous emphysema* has been used to describe the presence of bullae occupying at least one-third of a hemithorax (83).

**Figure 8**

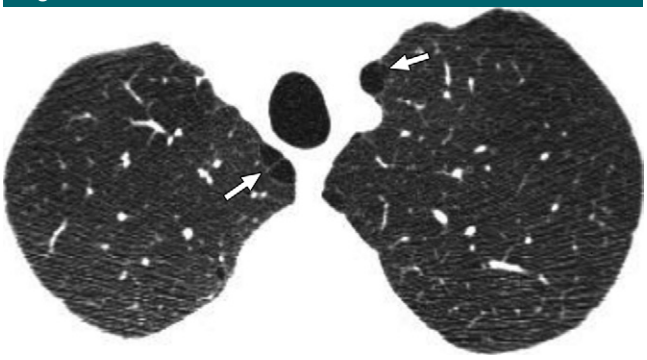


**Figure 8:** Mild PSE. CT scan in smoker without COPD shows subpleural foci of low attenuation separated by intact interlobular septa along the mediastinum (arrows), measuring less than 1 cm.

**Figure 9**

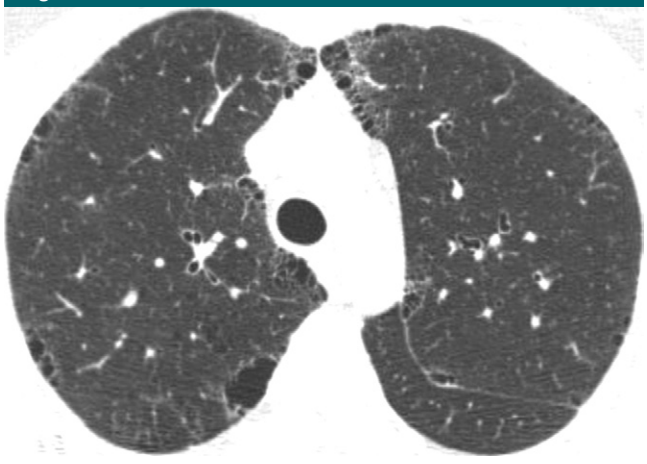


**Figure 9:** Substantial PSE. CT scan in patient with GOLD stage I COPD shows numerous well-demarcated areas of subpleural emphysema along chest wall and mediastinal pleural margins.

**Figure 10**

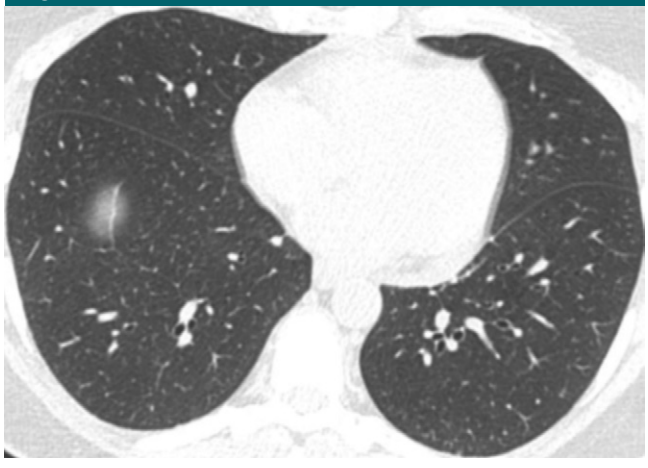


**Figure 10:** Normal bronchial walls. CT scan in asymptomatic nonsmoker with normal spirometric findings demonstrates normal airways.

**Figure 11**

**Figure 11:** Bronchial wall thickening. CT scan in cigarette smoker demonstrates marked thickening of segmental and subsegmental airways but no emphysema.

### Bronchial Wall Thickening

Bronchial wall thickening is commonly observed in heavy cigarette smokers (84), particularly those with chronic bronchitis, presumably because of bronchial inflammation and remodeling. It may be visually identified at CT by a relative increase in bronchial wall thickness compared with the bronchial lumen and with the diameter of adjacent pulmonary arteries (85); however, this CT feature is subjective and associated with substantial interobserver variation (80,86). It is probably best assessed by comparison with visual standards obtained from subjects with normal (Fig 10) and abnormal (Fig 11) findings (27).

Quantitative CT of airway dimensions is less subjective than visual evaluation. Quantitative CT of subsegmental airway dimensions can provide an estimate of small airway remodeling (87), probably because the same pathophysiologic process that causes small airway obstruction also takes place in large airways.

Increased thickness of airway walls is associated with the presence of COPD (88), with reversibility of airway obstruction (89), and with symptoms of chronic bronchitis (90). In patients with COPD, bronchial wall thickening is an important independent predictor of $FEV_1$ (91,92) and of the risk of acute exacerbation (13).

### Small Airways Disease

Cigarette smoking has distinct effects on the small airways that may be visible both pathologically and at CT. Niewoehner et al (93) showed that a characteristic form

**Figure 12**

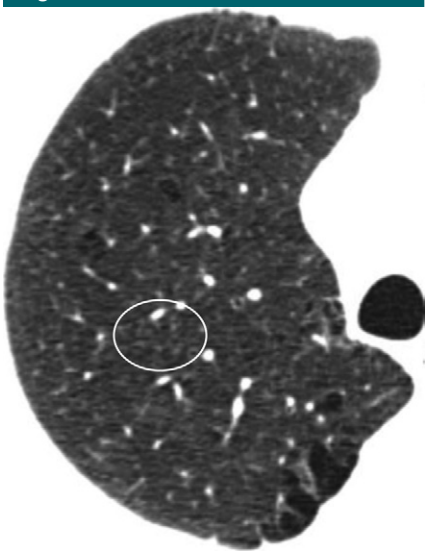


**Figure 12:** Widespread small centrilobular nodules. Centrilobular nodules (circled) in cigarette smoker are suggestive of respiratory bronchiolitis. Mild CLE and PSE are also present.

of respiratory bronchiolitis was present in the lungs of young persons who died suddenly outside the hospital. Although most of these lesions were observed in smokers, they were also found in nonsmokers. The authors postulated that this form of bronchiolitis was a precursor to CLE. Myers et al (94) reported a similar but more severe form of respiratory bronchiolitis as the only finding at lung biopsies performed in six patients with clinical and radiologic evidence of interstitial lung disease. That was confirmed by other authors (95). Respiratory bronchiolitis is dominated by infiltrating mononuclear cells containing large numbers of macrophages with brown to black "smokers" inclusion bodies that stain positively with periodic acid Schiff and iron stains. These inclusions are thought to be based on abnormal lysosomal function of macrophages in smokers (96). Respiratory bronchiolitis is also commonly found in lung specimens removed as a treatment for lung cancer (97). The decrease in $FEV_1$ in COPD has also been related to a persistent infiltration of inflammatory immune cells into the walls of purely conducting airways, with a tendency to form tertiary lymphoid organs in the later stages of COPD (98). A decrease in $FEV_1$ has also been associated with a reduction in terminal bronchiolar number and thickening of the walls of the bronchi that survive (7). Collectively, these data suggest that the region of the lung where the smaller purely conducting airways transition into respiratory bronchioles, alveolar ducts, and sacs is susceptible to the inhalation of a variety of toxic particles and gases, primarily but not exclusively derived from tobacco smoking.

Small airway disease is often an important major component of both emphysema-predominant disease and airway-predominant disease involving larger airways (bronchi). Isolated small airway disease can also occur as a primary expression of COPD. Physiologic identification of small airway disease is difficult. CT can be helpful in identifying signs of inflammatory small airway disease and small airway obstruction.

*Inflammatory small airway disease.*—Inflammation in and around the small airways in patients with COPD can cause the airways to become visible at CT as poorly defined centrilobular nodules of ground-glass attenuation (Fig 12) (99–101). Pathologically, this process commonly corresponds with respiratory bronchiolitis (24). CLE and bronchial wall thickening are frequent associated findings. The centrilobular nodules of respiratory bronchiolitis may progress to CLE (102). Unless it is severe, centrilobular nodularity is a subjective visual finding and the boundary between normal and abnormal may be difficult to set. For this reason, substantial observer variation has been found in the assessment of centrilobular nodularity (73). The small centrilobular nodules of respiratory bronchiolitis are sometimes associated with patchy areas of ground-glass opacity that reflect respiratory bronchiolitis–interstitial lung disease or desquamative interstitial pneumonia (100).

*Obstructive small airway disease.*—Obstructive small airway disease, in the absence of significant emphysema (defined in this analysis as quantitative CT extent of low-attenuation area <6%) may be identified by finding gas trapping at expiratory CT and/or by identifying physiologic obstruction (low $FEV_1$ with low $FEV_1$/FVC consistent with GOLD grades II, III, and IV).

At expiratory CT in healthy subjects, the lung attenuation usually increases in a homogeneous fashion. Air trapping, recognized as patchy or diffuse preservation of lung attenuation at expiratory CT (Fig 13), is common in cigarette smokers (12,103–106). Mechanisms of air trapping identified at CT may include prolonged lung emptying because of bronchiolar narrowing and dropout (7) and/or emphysematous destruction with loss of the elastic recoil force required to drive air out of the lungs (17,107).

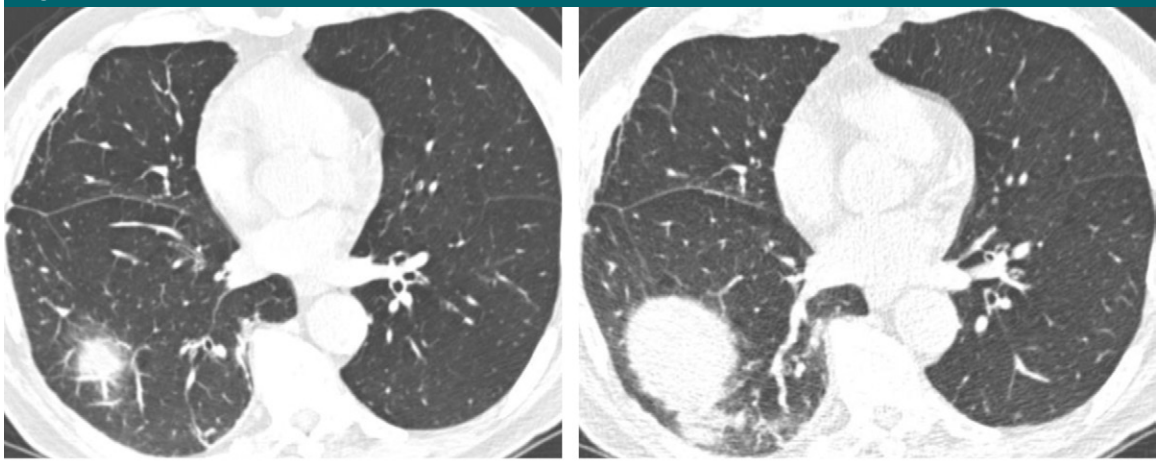
The resistance in the small conducting airways smaller than 2 mm in diameter accounts for only 10%–20% of total lower airway resistance in healthy subjects (108–110). In lungs affected by COPD, however, small airway resistance increases substantially (109,110)—particularly in subjects with COPD who have minimal emphysematous destruction (110). Micro-CT has shown that the number of terminal bronchioles is reduced to as little as 10% of control values in the end stage of the CLE phenotype of COPD and to 25% of control values in the end stage of the PLE phenotype of COPD (7). This degree of reduction in numbers of terminal bronchioles probably makes a very important contribution to the increase in small airways resistance in COPD.

## Other Important CT Features in Cigarette Smokers and in COPD

### Interstitial Lung Abnormalities

In addition to centrilobular nodules, CT scans obtained in cigarette smokers may show abnormalities compatible with infiltrative lung disease, including ground-glass and reticular abnormalities. In a study of 2416 COPDGene participants who were cigarette smokers, an interstitial lung abnormality was found in 194 subjects (8%) (111). The prevalence of an interstitial abnormality increased with age, tobacco exposure, and current smoking. Although the interstitial abnormalities were usually asymptomatic, subjects with an interstitial

**Figure 13**



a. b.

**Figure 13:** Gas trapping at expiratory CT. **(a)** Inspiratory and **(b)** expiratory CT scans in patient with severe airway obstruction (GOLD stage III) but only minimal emphysema. Lung attenuation fails to increase on expiratory scan, which is indicative of diffuse gas trapping owing to small airway obstruction.

abnormality were more likely to have a restrictive lung deficit and were less likely to meet the GOLD criteria for COPD. Similar changes were also seen in 2563 cigarette smokers in the MESA Lung Study and in the National Lung Screening Trial (112,113). Although detailed pathologic correlation is not available, these interstitial abnormalities likely correspond to variable combinations of respiratory bronchiolitis, airspace enlargement with fibrosis, and smoking-related interstitial fibrosis (114–116).

### Pulmonary Vascular Disease

Pulmonary hypertension can be a complication of advanced COPD and may be due to hypoxic vasoconstriction, pulmonary vascular obliteration, sleep apnea, or left heart abnormality. This important comorbidity is an important predictor of hospitalization and death in COPD (117). Pulmonary hypertension can be identified at CT with the ratio of the diameters of the pulmonary artery and aorta (118,119). Enlargement of the pulmonary artery as determined by a pulmonary artery–aorta ratio of more than 1 was recently shown to be an independent risk factor for exacerbations in patients with COPD (120).

### Abnormalities of the Trachea and Central Bronchi

Tracheobronchomalacia, defined as a reduction in the tracheal luminal cross-sectional area by more than 80% at dynamic expiratory imaging, is found in about 20% of patients with COPD but is not correlated with physiologic impairment (39). Indeed, the degree of tracheal collapse at end expiration in patients with COPD does not appear to be significantly different from that of control subjects (121). However, narrowing of the trachea in the coronal plane (saber-sheath trachea) is associated with COPD—particularly with more advanced stages of COPD (121–123). Diverticula or outpouching from the central airways may also be present; although the prevalence of bronchial diverticula is not different in patients with COPD than in control subjects (124), an increased number of diverticula is associated with a history of cigarette smoking (125) and with symptoms of cough (126).

### Bronchiectasis

Bronchiectasis is defined at CT as a dilated bronchial lumen relative to the adjacent pulmonary artery, lack of bronchial tapering, or identification of bronchi within 1 cm of the pleural surface (81). The reported prevalence of bronchiectasis at CT in subjects with COPD ranges from 27% (127,128) to 58% (129). Differences in prevalence may relate to differing populations and the variation in criteria for the diagnosis of bronchiectasis. Bronchiectasis is most commonly cylindrical in character (129). The presence of bronchiectasis is associated with more severe airflow obstruction and with hospital admission for exacerbation (129).

## Summary

Integration of visual characterization of emphysema and airway abnormalities with physiologic and quantitative CT assessment permits categorization of COPD into distinct structurally and functionally defined subtypes. These include identification of patients with five different patterns of emphysema-predominant subtypes and two patterns of airway-predominant subtypes (Fig 14). In addition, quantitative CT analysis is important to determine the severity of emphysema and the magnitude of expiratory gas trapping. The subjectivity of visual determinations of emphysema severity and gas trapping suggests that the combination of visual scoring and

**Figure 14**

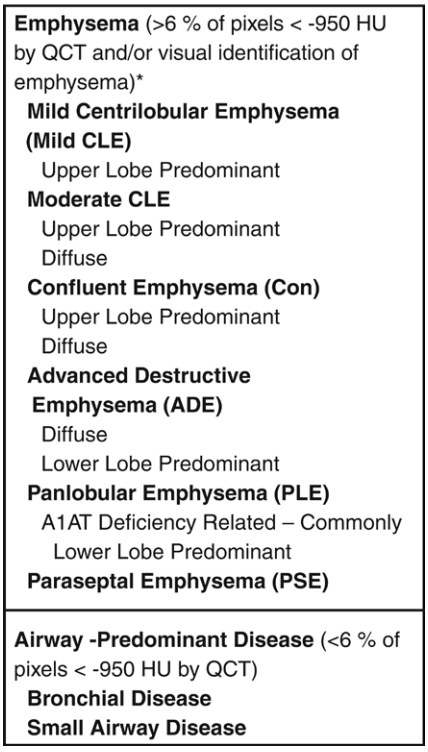



**Figure 14:** CT-defined subtypes of COPD. Most subjects with emphysema have significant airway disease. Airway-predominant disease represents subjects with minimal or no emphysema as defined at quantitative CT (*QCT*). * =There is a group of subjects without visually defined emphysema who have more than 6% of pixels less than −950 HU at quantitative CT. Further work is needed to understand the importance of this finding, and these individuals cannot currently be classified. *A1AT* = $\alpha_1$-antitrypsin.

quantitative CT is essential to define these structure- and/or function-based COPD subtypes. Visual and quantitative CT evaluation will identify a substantial amount of disease in subjects with mild or absent physiologic evidence of airway obstruction. Use of consistent CT technique is required to characterize and quantify COPD subtypes in a manner that can help determine the progression of specific patterns of disease over time.

Clearly, this classification must be regarded as a work in progress, and a number of areas can be identified for future research, including observer variation of the visual classification system, outcomes of the CT-defined phenotypes, histologic correlations of CT patterns, effect of aging on visual and quantitative features in the lung, CT phenotyping of nonsmoking-related COPD (eg, COPD related to biomass fuel), and clinical importance of increased quantitative measures of emphysema in subjects without visual emphysema.

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