

## High-Resolution CT Diagnosis of Emphysema in Symptomatic Patients with Normal Chest Radiographs and Isolated Low Diffusing Capacity<sup>1</sup>

To determine the prevalence of "nonobstructive" (impairment of gas transfer) emphysema in a select population of smokers with dyspnea, a retrospective study of patients with emphysema evident at high-resolution computed tomography (HRCT) was undertaken. Four hundred seventy HRCT studies were reviewed. In 47 cases, centrilobular emphysema was the dominant or sole parenchymal abnormality. Concomitant chest radiographs were available in 41 of these cases; 16 of the 41 lacked radiographic findings of emphysema. Among these 16 patients, pulmonary function testing revealed 10 to have normal flow rates (ratio of forced expiratory volume in 1 second to forced vital capacity and forced expiratory volume in 1 second greater than 80% predicted) and impaired gas transfer (single-breath carbon monoxide diffusing capacity [ $DL_{CO}SB$ ] less than 80% predicted). With the exclusion of one patient with congestive heart failure from the group of 10, the severity of emphysema at HRCT correlated inversely with  $DL_{CO}SB$  ( $r = -.643$ ). These results indicate that HRCT allows detection of emphysema in symptomatic patients when chest radiographs and pulmonary function tests are nondiagnostic.

**Index terms:** Computed tomography (CT), high-resolution, 60.1211 • Emphysema, pulmonary, 60.751 • Lung, CT, 60.1211 • Lung, diseases, 60.751

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EMPHYSEMA is a pathologic diagnosis. The diagnosis of emphysema during life is based on a combination of clinical, functional, and radiographic findings, but this combination is insensitive to mild emphysema (1). The functional hallmarks of emphysema are decreased airflow at spirometry and decreased carbon monoxide diffusing capacity ( $DL_{CO}$ ) due to parenchymal destruction, but patients may have up to 30% of their lung involved with emphysema and have no evidence of functional impairment (2). Evidence of impairment in gas transfer as assessed with  $DL_{CO}$  is more sensitive than abnormal spirometry for diagnosis of emphysema, but it is nonspecific. Gas transfer is also decreased in infiltrative parenchymal processes and pulmonary vascular disease. Chest radiographs are accurate for making a diagnosis of moderate to severe emphysema, but may not allow detection of mild disease (3). High-resolution computed tomography (HRCT) has shown high sensitivity and specificity in demonstrating emphysema (4).

At our institutions, HRCT is often used in dyspneic patients who have normal chest radiographs, abnormal  $DL_{CO}$ , and normal flow rates at pulmonary function testing, in an attempt to detect minimal interstitial disease. We have also encountered a number of patients with this combination of findings who have typical HRCT abnormalities of centrilobular emphysema. To emphasize the value of HRCT for detecting "nonobstructive" emphysema and to determine the prevalence of nonobstructive emphysema (and its clinical correlates) in a population of patients that underwent HRCT of the lungs, we performed a retrospective study of pa-

tients with predominant or sole emphysema seen with HRCT.

### PATIENTS AND METHODS

The subjects included in this study were identified by using computer-generated lists of all thoracic HRCT studies performed at two institutions from June 1987 to March 1991. All HRCT studies were performed with the same scanners (9800; GE Medical Systems, Milwaukee). Most were obtained without concomitant conventional CT examinations.

HRCT was performed in a slightly different fashion at the two institutions participating in this study. At one institution, scans were obtained at 4-cm intervals through the thorax, beginning at a level 2 cm above the aortic arch and proceeding caudally through the lung bases. The technical factors were 1.5-mm collimation, 140 kVp, 170 mA, 2.0-second scanning time, a large field of view, and a high-frequency reconstruction algorithm (bone algorithm). Images were photographed by using a six-on-one format and were displayed at window widths of 350 HU (soft tissue), 1,000 HU (lung), and 2,000 HU (lung-pleural interface). At the other institution, HRCT scans were obtained at the level of the top of the aortic arch, at or just inferior to the tracheal carina, and near the top of the right hemidiaphragm. The technical factors used were 1.5-mm collimation, 120 kVp, 170-200 mA, 2-3-second scanning time, and a high-frequency reconstruction algorithm. Images were photographed by using a 12-on-one format at 350 HU (mediastinal) and 1,500 HU (lung) window widths. At both institutions, all scans were obtained with the patient in the supine position and suspending respiration at end inspiration.

The reports of 470 HRCT studies were reviewed. Ninety-two studies originally interpreted as showing emphysema were obtained for reinterpretation. Centrilobular or panacinar emphysema, defined as well-demarcated areas of decreased attenuation in comparison with contiguous

**Abbreviations:**  $DL_{CO}$  = carbon monoxide diffusing capacity,  $DL_{CO}SB$  = single-breath carbon monoxide diffusing capacity,  $FEV_1$  = forced expiratory volume in 1 second, FVC = forced vital capacity, HRCT = high-resolution CT.

normal lung and margined by a very thin (less than 1-mm-diameter) or indefinable wall, was confirmed in all 92 cases.

The HRCT studies showing emphysema were then evaluated for concomitant additional nonemphysematous parenchymal lung disease. Three levels of each HRCT study (1 = at or just cephalic to the aortic arch, 2 = at the tracheal carina, 3 = at the apex of the right hemidiaphragm) were viewed and scored for interstitial, alveolar, and/or airways disease. At each of the three levels scanned, each lung was evaluated individually; thus, six lung sections were evaluated in each subject. Significant nonemphysematous disease was defined as a parenchymal abnormality involving at least 25% of the cross-sectional area of at least two of the six lung sections. Of the 92 patients with HRCT findings of emphysema, 45 also showed evidence of significant nonemphysematous lung disease and were excluded from further study. The remaining 47 patients had either less than 25% involvement of up to two lung sections (predominant emphysema) or no nonemphysematous disease (sole emphysema).

Chest radiographs obtained in 41 of the 47 patients with predominant or sole emphysema were available for review. The radiographs obtained closest to the date of the HRCT study were selected and scored independently for emphysema by two chest radiologists, on the basis of diagnostic criteria proposed by Pratt (2). Findings of emphysema on the posteroanterior view were (a) decreased opacity of the lungs and (b) depression and flattening of the diaphragm with blunting of the costophrenic angles, with the actual level of the diaphragm being more important than the contour and with the body build of the patient taken into account. On the lateral view, evidence of emphysema included (a) abnormal retrosternal space, defined as decreased opacity and a distance of more than 2.5 cm from the retrosternal stripe to the anterior margin of the ascending aorta, and (b) flattening or concavity of the diaphragmatic contour, best defined as a sternodiaphragmatic angle of 90° or greater (2). When there was disagreement in the scoring between the two radiologists, the higher score was chosen. Emphysema was considered radiographically evident if at least two of the four criteria were met. Radiographs were interpreted without knowledge of HRCT findings.

The medical records of the patients with sole or dominant emphysema at HRCT and with chest radiographs available were reviewed for initial pulmonary symptoms and results of pulmonary function testing. Pulmonary function tests included assessment of lung volumes by means of closed-circuit helium dilution technique and spirometry with measurement of forced expiratory volume in 1 second (FEV<sub>1</sub>) and ratio of FEV<sub>1</sub> to forced vital capacity (FVC), both expressed as a percentage predicted by using the equations of Crapo et al (5). Diffusing capacity was measured by use of single-breath carbon monoxide diffusing capacity (DL<sub>CO</sub>SB) and the predic-

tion equations of Miller et al (6). Abnormal flow rates indicating airflow obstruction and diminished diffusing capacity were defined as a value less than 80% of predicted.

Since the HRCT diagnosis of emphysema was considered definitive and no patients with emphysema had clinical evidence of pulmonary vascular disease, none of the 47 patients with predominant or sole emphysema underwent ventilation and perfusion lung scanning or pulmonary angiography.

Finally, in patients with emphysema and normal expiratory flow rates and diminished DL<sub>CO</sub> at pulmonary function testing (nonobstructive emphysema), the HRCT scan was scored for overall severity of emphysema by using the direct observational method of Sakai et al (7). Each of the six lung sections evaluated in each patient was scored for severity of emphysema by using a four-point scale, where 0 = no emphysema; 1 = low-attenuation areas less than 5 mm in diameter; 2 = circumscribed low-attenuation areas more than 5 mm in diameter and in addition to those less than 5 mm in diameter; and 3 = diffuse low-attenuation areas without intervening normal lung or large, confluent low-attenuation areas. The extent of emphysema was then scored for each section by using a four-point scale, where 1 = less than 25% cross-sectional area involvement, 2 = 25%–50% involvement, 3 = 50%–75% involvement, and 4 = greater than 75% involvement. The extent multiplied by the severity was summed for the six sections, with a maximal possible score of 72 for each patient.

## RESULTS

There were 47 patients with sole or dominant emphysema demonstrated on HRCT scans. Twenty-eight were men and 19 were women. The mean age was 60 years (range, 34–78 years). All had predominantly centrilobular emphysema (Fig 1). Thirty-five had emphysema as the sole finding, whereas 12 patients had insignificant concomitant interstitial disease. Of the 41 patients with emphysema and concomitant chest radiographs, 40 had posteroanterior and lateral radiographs available and one patient had only a frontal radiograph available. The mean interval between performance of HRCT and chest radiography was 11.2 days (range, 0–31 days). Sixteen patients had chest radiographic emphysema scores less than 2, and thus were not considered to have evidence of emphysema; one of these had a score of 1 on the basis of a frontal radiograph alone. One patient without radiographic evidence of emphysema demonstrated cardiomegaly, pulmonary venous hypertension, and interstitial pulmonary edema indica-

tive of congestive heart failure.

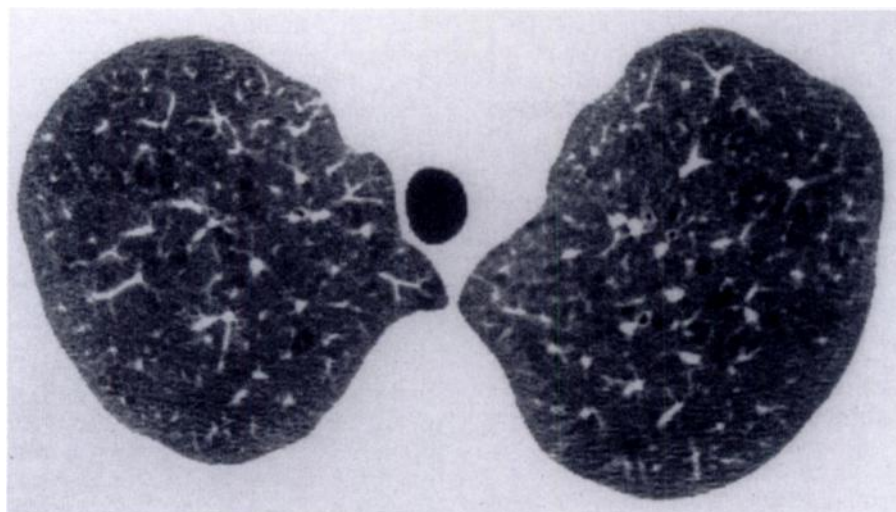
History obtained from the medical records indicated that at the time of HRCT evaluation, all 41 patients had shortness of breath during exertion or at rest. Ten of the 16 patients with an emphysema score less than 2 had normal flow rates and diminished DL<sub>CO</sub> at pulmonary function testing performed a mean of 10.0 days (range, 0–22 days) after the HRCT study (Table). For these 10 patients, the mean FEV<sub>1</sub> ( $\pm 1$  standard deviation) was 96.1%  $\pm$  16.4 predicted (range, 80%–132% predicted), mean FEV<sub>1</sub>:FVC (available in nine of the 10 patients) was 92.7%  $\pm$  3.5 predicted (range, 82%–116% predicted), and mean DL<sub>CO</sub>SB was 55.2%  $\pm$  13.6 predicted (range, 29%–72% predicted).

The HRCT-determined emphysema scores for the 10 patients with HRCT-determined emphysema, negative chest radiographs, and isolated low DL<sub>CO</sub> at pulmonary function testing are shown in the Table. The mean emphysema score was 20.2  $\pm$  10.7. With the exclusion of the patient with congestive heart failure, who had a relatively high DL<sub>CO</sub>SB, the severity of emphysema at HRCT was inversely correlated with DL<sub>CO</sub>SB in this group of patients ( $r = -.643$ ) (Fig 2).

Four of the 47 patients with dominant or sole HRCT-determined emphysema had undergone upper lobe resection for neoplasm and had lung specimens available for review. All four showed centrilobular emphysema; the Thurlbeck emphysema scores (0–100) for these specimens were 5, 5, 25, and 35 (8). All four patients had evidence of airways obstruction at pulmonary function testing. The corresponding diffusing capacities in these four patients were 67%, 16%, 58%, and 61% predicted, respectively.

## DISCUSSION

Emphysema is defined histologically as an abnormal, permanent enlargement of air spaces distal to the terminal bronchiole, accompanied by destruction of the air space walls and without obvious fibrosis (1). Various pathologic grading systems that provide a measurement of overall severity of emphysema in whole lung specimens have been developed by Thurlbeck et al (8). Even though emphysema is defined pathologically, lung specimens are rarely available for making a diagnosis of emphysema during life. Therefore, diagnosis has been based on clinical, functional, and radiographic criteria.



**Figure 1.** HRCT scan obtained above the aortic arch in a 63-year-old male smoker (patient 2 in the Table) with progressive dyspnea during exertion. Scattered areas of centrilobular emphysema are seen throughout both upper lobes. The HRCT-determined emphysema score was 24. The corresponding frontal chest radiograph (not shown) demonstrated subtle areas of decreased opacity in the upper lobes (chest radiographic emphysema score of 1). Airflow rates were the following: FEV<sub>1</sub>, 92% of predicted; FEV<sub>1</sub>/FVC, 88% of predicted. The DL<sub>CO</sub>SB was 43% of predicted.

**Demographic Information, Emphysema Scores, and Pulmonary Function Test Results in 10 Patients with Sole or Dominant HRCT-determined Emphysema, Negative Chest Radiographs, and Isolated Low DL<sub>CO</sub>**

Patient No.	Age (y)/Sex	Emphysema Score*		FEV <sub>1</sub> †	FEV <sub>1</sub> /FVC†	DL <sub>CO</sub> SB†
		Chest Radiography	HRCT			
1	67/F	1	23	113	95	52
2	63/M	1‡	24	92	88	43
3	64/M	0	18	83	90	72
4	55/F	1	41	84	87	29
5	53/F	0	24	104	80	45
6	54/M	0	8	100	104	55
7	72/F	1	32	80	82	72
8	45/F	1	19	85	92	57
9	61/M	0	9	132	116	63
10	34/F	0	4	88	NA	64
Mean ± SD	56.8 ± 11.2	0.5	20.2 ± 11.31	96.1 ± 16.4	92.7 ± 11.3	55.2 ± 13.6

Note.—NA = not available, SD = standard deviation.

\* Possible emphysema scores were 0–4 for chest radiography and 0–72 for HRCT.

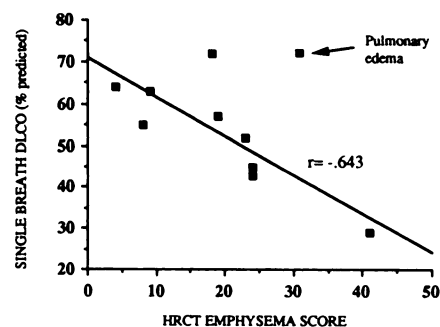
† Values are percentages predicted.

‡ Posteroanterior view only.

The physiologic hallmarks of emphysema are expiratory airflow obstruction and decreased DL<sub>CO</sub>. Airflow obstruction, as commonly measured by means of spirometric determination of FEV<sub>1</sub> and FEV<sub>1</sub>/FVC, is secondary to increased airways resistance and decreased driving pressure (elastic recoil) (9). In patients with moderate to severe emphysema, the predominant factor limiting expiratory airflow is the decreased elastic recoil that results from parenchymal destruction. Increase in airways resistance from intrinsic airways abnormality may be absent in patients with pure emphysema, unless forced expi-

ration leads to dynamic compression of large airways (9).

Airflow obstruction, however, is not invariably present in patients with mild emphysema. In a study of 14 patients who underwent pulmonary function testing prior to thoracotomy and lobectomy or pneumonectomy, Gelb et al (10) compared measures of airways obstruction with pathologic confirmation of emphysema in the resected specimens. All seven patients demonstrating morphologic emphysema had a DL<sub>CO</sub> of less than 70% predicted, yet all had normal FEV<sub>1</sub>:FVC percentages predicted and five of seven had normal FEV<sub>1</sub> percentages



**Figure 2.** Correlation of DL<sub>CO</sub>SB with severity of emphysema in nine of 10 patients without evidence of airways obstruction.

predicted. In another study, Petty et al (11) measured total lung capacity, elastic recoil, FEV<sub>1</sub> percentage predicted, and small airways disease in 21 excised human lungs judged to be mildly emphysematous morphologically and compared findings with those in 18 normal lungs (11). There was a significant difference in total lung capacity and elastic recoil between the two groups, but pathologic evidence of small airways disease and FEV<sub>1</sub> percentage predicted did not differ significantly.

Measurement of DL<sub>CO</sub> with a single breath-hold technique allows assessment of the integrity and surface area of the alveolar-capillary membrane within the lung (12). If it is the result of emphysema, decreased DL<sub>CO</sub>SB correlates well with the severity of the emphysema at examination of post-mortem specimens (13). Patients with normal lung volumes and airways resistance can have significantly reduced DL<sub>CO</sub>SB that correlates with emphysema as seen in lobectomy specimens, but some patients with mild to moderate morphologic emphysema can also have a normal DL<sub>CO</sub>SB (14). Indeed, Symonds et al, in comparing the severity of emphysema at evaluation of postmortem specimens with pre-mortem measurements of DL<sub>CO</sub> in 34 patients, found only one patient with mild emphysema and a clearly abnormal DL<sub>CO</sub>SB (corrected for alveolar volume) (13).

Not only is the DL<sub>CO</sub>SB normal in some patients with proved emphysema, but an abnormal DL<sub>CO</sub>SB is entirely nonspecific and can be seen in a variety of pulmonary disorders, of which emphysema is but one. Since diffusion of carbon monoxide depends predominantly on the surface area available for gas diffusion and the number and hemoglobin content of red blood cells within the pulmonary capillaries, any process affecting these factors can alter the measure-

ment of  $DL_{CO}SB$ . For example, any disease that diminishes the volume of pulmonary capillaries available for gas diffusion (ie, pulmonary embolism) or that leads to airway obstruction, thereby diminishing the gas-exchanging air spaces (ie, cystic fibrosis), can decrease  $DL_{CO}SB$ .

Frontal and lateral chest radiographs are usually the initial radiographic examinations in patients with suspected emphysema. While it is clear that widespread, extensive emphysema may be accurately diagnosed with chest radiographs, mild disease is often not evident radiographically. In the seminal study comparing the clinical, functional, and radiographic diagnosis of emphysema with morphologic emphysema seen in whole lung specimens, Thurlbeck et al (3) used four radiographic criteria to determine the presence or absence of emphysema in 61 patients (3). Radiographs were assessed for overinflation, increase or decrease in pulmonary vascular markings, pulmonary arterial hypertension, and right-sided heart enlargement; emphysema was diagnosed when there were findings of hyperinflation and vascular changes. The radiographic diagnosis in all patients with moderately severe and severe emphysema morphologically was correct, but radiographic diagnoses were correct in only 61% of patients with mild to moderate emphysema and in only 40% of patients with the mildest degrees of emphysema. Similarly, Sutinen et al (15), who employed a four-point scoring system based on hyperinflation and irregular radiolucency of the lungs, detected 13 cases of asymptomatic emphysema but did not demonstrate six cases of emphysema (15). The authors stated that "it is clear that, even with this method, some cases in which structural emphysema is present would be missed by a roentgenographic survey."

Thurlbeck and Simon, using arterial deficiency as the primary radiographic finding for emphysema, correctly diagnosed emphysema in only 41% of patients with moderately severe or severe emphysema (16). In their study, additional objective measurements of hyperinflation, such as lung length and width, heart size, diaphragm position, or depth of the retrosternal air space, did not improve the ability to recognize emphysema radiographically beyond the subjective evaluation of arterial deficiency. Nicklaus et al (17), in a study that used the same chest radiographic criteria as Sutinen et al (15), with the

additional finding of a reduction in the number and caliber of the peripheral branches in the outer half of the lung, found that one-third of patients with mild and possibly asymptomatic emphysema will be missed.

In 1987, Pratt published a review of the literature regarding the use of chest radiographs in the diagnosis of emphysema (2). He noted a wide discrepancy among reports of the value of chest radiographs in the diagnosis of emphysema and attributed these differences to differing criteria in the scoring of chest radiographs among various studies, differing uses of given criteria in diagnosis or exclusion of emphysema, and differing intended goals of each study. The author states that the presence of two or more of four criteria for hyperinflation on frontal and lateral chest radiographs is an accurate indicator of the presence or absence of emphysema.

In a recent editorial, however, Burki concluded that the chest radiographic diagnosis of emphysema is not very accurate (15-22). In an addendum to his review of the subject, Pratt does note that emphysematous destruction can be detected by means of computed tomography (CT) in the absence of chest radiographic findings of hyperinflation (2). Because of its cross-sectional nature and high-contrast resolution, CT is ideally suited to the diagnosis of emphysema. In early reports, the use of CT in the diagnosis of emphysema depended on the recognition of large avascular areas or regions with abnormally low attenuation coefficients (18,19). More recently, shorter scanning times, improved detector capabilities, and the ability to obtain thinly collimated sections and reconstruct them with a high-spatial-resolution algorithm (HRCT) have allowed the depiction of mild centrilobular emphysema as well-defined areas of abnormally decreased attenuation that lack definable walls and are situated within the secondary pulmonary lobule adjacent to the central bronchovascular bundle (22-25). Several studies have shown a significant inverse correlation between the CT-determined severity of emphysema and functional markers of emphysema such as airflow obstruction ( $FEV_1$ , FVC, and  $FEV_1:FVC$ ) and  $DL_{CO}$  (7,26,27). CT and HRCT studies including pathologic correlation achieved with postoperative or postmortem lung specimens have demonstrated the ability to quantitate the amount of lung involved by emphysema (27-29). A recent study, however, suggested that while CT

and HRCT findings correlate well with pathologic gradings of emphysema, the very mildest forms of centrilobular emphysema may be missed with these imaging techniques (30).

We have used HRCT as a diagnostic tool in the evaluation of symptomatic patients with nonspecific or normal chest radiographs and abnormal pulmonary function tests. HRCT, with its thin collimation technique and high spatial resolution, can enable detection of mild centrilobular emphysema that may be missed with conventional, 10-mm collimated CT because of partial volume averaging of small emphysematous areas within the thickness of the section (24).

In our review of 470 studies, we found 47 cases of sole or dominant emphysema. Chest radiographs in 16 of 41 patients for whom they were available were initially interpreted as being normal, which was confirmed by two chest radiologists (G.G., W.R.W.) who independently reviewed the chest radiographs obtained in patients with HRCT-demonstrated emphysema and scored them by using Pratt's criteria. The fact that an inordinately high percentage of patients with emphysema in this study had "normal" chest radiographs relates to the design of our study. Those patients with shortness of breath and chest radiographs and pulmonary function tests that are not diagnostic of emphysema are usually selected for HRCT scanning. Thus, patients with minimal disease tend to be selected.

Furthermore, 10 of the 16 patients with HRCT-detected emphysema had pulmonary function tests that showed normal flow rates and an isolated diminished  $DL_{CO}$ . A diminished  $DL_{CO}$  is nonspecific and is found in a wide variety of pulmonary disorders that affect the alveolar-capillary interface, including interstitial lung disease and pulmonary vascular disease. In this group of patients, the recognition of emphysematous changes on HRCT scans provides a specific diagnosis that is not possible to arrive at by other means. This obviates further noninvasive and invasive diagnostic testing and may allow for some therapeutic intervention. Furthermore, the excellent inverse correlation ( $r = -.643$ ) between the HRCT-estimated emphysema score and the diffusing capacity (Fig 2) in nine of our 10 patients with nonobstructive emphysema (the one patient with evidence of congestive heart failure at chest radiography likely had a rela-

tively high  $DL_{CO}SB$  and was therefore excluded from this correlation) suggests that even screening HRCT studies performed at spaced intervals can enable quantitation of the overall severity of mild to moderate centrilobular emphysema.

There are several limitations to this study. The number of patients with HRCT-detected sole or predominant centrilobular emphysema ( $n = 47$ ) is small. Only four patients had lung tissue specimens available for direct pathologic correlation; all of these patients had abnormal flow rates and were not among the group of 10 patients with nonobstructive emphysema. Several studies have shown excellent correlation ( $r = .85-.91$ ) between HRCT demonstration of emphysema and pathologic scoring of emphysema in whole lung specimens (4,28,30). In fact, CT and HRCT may have an advantage over examination of whole lung or lobar specimens in that all regions of both lungs are visualized, making sampling errors less likely, especially since "emphysema in mildest form is characteristically localized" (9).

From results of this retrospective study, we are unable to determine the sensitivity of HRCT relative to plain radiographs and pulmonary function tests for the detection of mild centrilobular emphysema, and we cannot speculate on the overall incidence of nonobstructive emphysema. It is clear from our study, however, that in a significant subgroup of symptomatic patients with nondiagnostic clinical, radiographic, and pulmonary function test findings, HRCT can permit a definitive diagnosis of emphysema. In such patients, further diagnostic evaluation is not usually necessary. HRCT may represent the most sensitive method available for detecting mild emphysema. As therapeutic measures for this disease become available, the detection and quantification of mild emphysema may have considerable import. ■

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