Imaging Studies in Emphysema

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Definitions of types of emphysema within the framework of chronic obstructive pulmonary disease are given. The classic findings on the chest radiograph are described, and the advances in sensitivity and specificity achieved with computed tomography (CT) scanning are noted. The “density mask” and the “percentile point” measurements rely on the densitometric property of X-rays, but the scan also shows the severity and distribution of low-attenuation regions that usually represent pathologic emphysema. The alteration of absolute density with changes in lung inflation, CT slice thickness, collimation, and reconstruction algorithm make comparison between CT scans and across studies more difficult. Nevertheless, quantitative CT has superseded subjective scoring of scan appearance by readers as a sensitive way to measure emphysema.

Keywords: radiology; emphysema; COPD; quantitative CT

DEFINITION OF THE KINDS OF EMPHYSEMA UNDER STUDY

Pathologists have distinguished different kinds of emphysema for at least a generation, mostly on the basis of Gough whole-lung paper-mounted sections. This is duplicated well by high resolution computed tomography (CT) scanning. Histologic analysis allows further discrimination, although severe emphysema does not lend itself to microscopic examination because one cannot take a section of a hole.

Centriacinar (commonly called “centrilobular”) emphysema is recognized as focal breakdown of alveolar walls in the central portion of the acini, initially sparing the peripheral parts of the acinus and lobule. Centrilobular emphysema is usually more marked in the upper lung zones. There is usually no wall of tissue around the hole. With increasing severity, the distinction from panlobular emphysema is lost (Figure 1).

Panlobular emphysema is defined as destruction involving all portions of the lobule out to the periphery (Figures 2 and 3). It is generally more severe in the lower lung zone. The prototypical example is α_1 protease deficiency, which characteristically involves the lower lobes. Review of CT scans of a number of cases shows that it is not as uniformly distributed as one might expect from chest films. Scans of paraseptal emphysema usually show well-demarcated spaces from tissue destruction exclusively in the periphery of the lobule, hence their delineation by interlobular septa or the pleura. However, the term may also be used for focal destruction not confined to a lobule: a bulla. In both cases there is often visible tissue surrounding the emphy-

sematous space, some of which is fibrosis. Paraseptal emphysema may be seen independently of “airflow limitation” or obstruction (e.g., chronic obstructive pulmonary disease [COPD]) or may be a minor feature of centriacinar and panlobular emphysema.

It has been known for many years that emphysema is often accompanied by some degree of airway disease, manifest by airflow limitation, which is the *sine qua non* of COPD. This is also caused by emphysema, but assessing the amount of airway disease is not further discussed in this review. This review focuses on estimating the type and severity of emphysema.

RADIOGRAPHIC STUDIES

Detection of emphysema on the chest radiograph (CXR) has been a subject of interest for more than 50 years. The most reliable finding is a flat but horizontal diaphragm, best demonstrated on the lateral view of the chest. The diaphragm is usually lower than normal, consistent with enlargement of the lungs. The individual muscular slips of the costal insertions of the diaphragm may be thrown into prominence by the low position of the diaphragm, giving the appearance of “scalloping” of the costophrenic angles. The antero-posterior diameter of the chest is also usually increased with emphysema, with an enlarged retrosternal space (>2.5 cm) in front of the ascending aorta on the lateral view, but there are some emphysematous individuals who retain a normal antero-posterior diameter, particularly women. A secondary observation is an increase in the normally acute angle between the diaphragm and the anterior chest wall, becoming greater than a right angle (1, 2).

More directly in keeping with the pathology of emphysema, vascular attenuation or oligemia in lung radiographs of emphysematous patients has been noted by many observers. Not all patients have large enough emphysematous spaces to be appreciated on the CXR, with or without the findings described previously. Patients with oligemia evident on a properly exposed CXR, however, are likely to have significant emphysema (3). In other cases, diseases such as pulmonary embolism, advanced primary or cardiogenic pulmonary hypertension, and bronchial plugging with air trapping or rarities such as bronchial stenosis (congenital or acquired) may cause perceptibly avascular regions on the chest film. These should and usually can be distinguished from emphysema because of the lack of emphysematous changes in lung size and shape.

Bullae are the ultimate in vascular attenuation because there are no vessels visible and there is a line of demarcation between the enlarged airspace and the rest of the parenchyma. Although bullae are commonly found in emphysema, they may occur as independent, unrelated lesions with no other sign of emphysema. Blebs, often confused with bullae, are small intrapleural air cysts and are rarely seen by radiologists on CXR or CT scans (4, 5). Ancillary findings include “saber-sheath” trachea, which was first described in 1905 but was firmly connected to obstructive lung disease in 1978 (6). Even though the mechanism may be bronchitic weakening of cartilage, it is usually found with emphysema, possibly because of the chronic effect of positive intrapleural pressure during expiration with severe airflow limitation.

(Received in original form August 16, 2007; accepted in final form September 25, 2007)

The National Emphysema Treatment Trial (NETT) is supported by contracts with the National Heart, Lung, and Blood Institute (N01HR76101, N01HR76102, N01HR76103, N01HR76104, N01HR76105, N01HR76106, N01HR76107, N01HR76108, N01HR76109, N01HR76110, N01HR76111, N01HR76112, N01HR76113, N01HR76114, N01HR76115, N01HR76116, N01HR76118, and N01HR76119), the Centers for Medicare and Medicaid Services (CMS), and the Agency for Healthcare Research and Quality (AHRQ).

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Proc Am Thorac Soc Vol 5, pp 494–500, 2008

DOI: 10.1513/pats.200708-128ET

Internet address: www.atsjournals.org

Figure 1. Upper lobe 5-mm slice of lung showing centriacinar emphysema. (A) Conventional windowing. (B) Narrow windowing, with center adjusted upward to optimize appearance. The emphysematous spaces are much easier to recognize on this high contrast scan, although vessels are thickened.

“Increased markings” include tramline shadows and ring shadows and are an accentuation of bronchovascular shadows. They are usually seen in the lower lobes and are commonly seen in emphysema with secondary pulmonary hypertension, associated with the chronic bronchitic or “blue bloater” clinical phenotype of COPD. These shadows probably represent bronchial wall thickening, mainly due to peribronchial inflammatory changes, with or without mild bronchiectasis. Increased markings are related to the associated bronchitis and its vascular changes and not directly to the emphysema. Fraser (7) emphasized that the success, however limited, of the CXR in detecting emphysema depended on recognizing the increased markings and arterial deficiency patterns.

Moderate to severe centriacinar emphysema characteristically affects the upper lobes, whereas panlobular (or panacinar) emphysema, notably in α_1 antiprotease deficiency, classically affects the lower part of the lung. Both are visible on CXR. However, a recent observation reported by the National Emphysema Treatment Trial (NETT) using CT imaging to determine suitability for lung volume reduction surgery found that half of a small cohort of α_1 -deficient individuals had upper lobe predominance of their emphysema (8). Mild centriacinar or

Figure 2. Lower lobe showing pan lobular emphysema anteriorly, especially in the right middle lobe. (A) Collimation 7.5 mm. (B) Collimation 1.25 mm. Note the centriacinar emphysema posteriorly, seen much better on this high-resolution scan than in A.

panacinar emphysema is rarely detectable radiographically. Enlargement of the central pulmonary arteries, with exaggerated tapering to the periphery, is characteristic of emphysema, but is seen with pulmonary hypertension of other etiologies as well. The bronchitis of COPD that often accompanies emphysema is usually invisible on the chest film but may appear as increased markings. When COPD proceeds to the point of right-sided heart failure in a “blue bloater,” the chest film shows cardiomegaly, vascular engorgement, and pleural fluid (9).

CT

Our ability to detect emphysema changed dramatically in the early 1980s when CT was first exploited to demonstrate subtle parenchymal patterns and to produce objective lung density measurements in Hounsfield units (HU) (10–12). The widespread adoption of high-resolution scanning has put into everyone’s hands the tool to identify anatomic emphysema before there are any clinical manifestations. “Early” disease, not necessarily all disease, can be detected on CT scans; scattered holes in the lung less than 5 mm in size are difficult or impossible to detect, but CT scanning can detect earlier disease than can be detected by airflow obstruction or changes in diffusing capacity (13). A sensitive volumetric sampling technique, called sliding

Figure 3. Upper lobe (in a different case) showing upper lobe pan lobular emphysema. (A) A 7.5-mm thick slice showing unequivocal emphysema from the vascular pattern. (B) A high-resolution, 1.25-mm slice showing emphysema equally well.

thin slab, minimum (or maximum, as originally described) intensity projection, has been tested successfully in the detection of minimal emphysema but has not been adopted widely, probably because of the complexity of the extra steps involved and its failure to detect much more emphysema than thin spiral scans and because of the emphysema-simulating artifacts (14–16). It requires combining thin sections in 3- to 8-mm stacks and selecting the minimum absorption from all slices to form the stack's image. The "sliding" refers to the formation of the slabs by adding one slice on top and removing one from the bottom and recalculating the image density.

Qualitatively, with the individual thin slice, inspiratory narrow windowed scan is the best for routine detection and characterization of emphysema. A representative idea of the disease can be obtained with three or four slices spaced through the lung. Displacement and attenuation of vessels are good supporting findings, but the accuracy of these routine scans is reduced if the images viewed are too dark or blurred by motion. Respiratory motion makes it almost impossible to detect even moderate emphysema. A window width of 800 HU and level centered at –800 HU are much better at showing minimal emphysema than the usual 1,500 HU, –500 HU setting.

The extent of emphysema can be estimated subjectively by visual inspection. In each region, the part of the lung that ap-

pears emphysematous is roughly estimated to be (1) less than 25% of the area, (2) 26% to 50% of the area, (3) 51% to 75% of the area, or (4) 76% to 100% of the area (17, 18). This four-point scale can be expanded to five levels by defining (0) as normal. The region may be one or both lungs on the slice or dorsal and ventral portions of each lung.

It was regional distribution of emphysema that proved most useful in the NETT for predicting outcome after lung volume reduction surgery (LVRS), as had been proposed in prior reports (19). Predominant upper lobe emphysema was found by NETT to be predictive of a favorable outcome of LVRS. Conventionally, scan slices at 20-mm intervals were considered adequate for this determination. Emphysema distribution can be determined adequately using this subjective qualitative method, but variations, such as plotting the amount of emphysema from top to bottom, have helped characterize individuals' degrees of emphysema heterogeneity (20).

The severity of emphysema has been less often quantitated. A scheme used two decades ago (17) was (0) none, (1) low-attenuation areas less than 5 mm, (2) circumscribed low-attenuation areas greater than 5 mm in addition to smaller ones, or (3) diffuse low-attenuation without normal lung or large confluent areas of very low attenuation. This was applied to the whole lung scan but also was applied regionally on the lung scan.

The technology that has been used for quantification of emphysema by many workers is the density mask technique, which allows highlighting of pixels in a selected range of HU (21). The pixels less than a particular value (originally –910 HU) could be highlighted, perhaps in color, and their number compared with the total number of pixels in the lung image. Since the original description, all the parameters that could be checked for relevance have been: inspiration versus expiration, 1.5 mm versus 3 mm or 5 mm or 10 mm collimation or reconstruction, intravenous contrast material versus noncontrast, and wide (1500–2000 HU) versus narrow (800–1000 HU) windows for printing or viewing on a console. The threshold for measuring emphysematous pixels has varied from below –900 HU to below –960 HU by various investigators, with various slice thicknesses and reconstruction algorithms (Figure 4). This technique allows for more precise assessment of pixel density than previously possible. Quantification of the severity and extent of emphysema has been used to assess the suitability of patients for LVRS, to follow the natural history of emphysema, and to look for diminished deterioration with treatment of α -1-antitrypsin deficiency (22).

QUANTITATIVE DENSITOMETRY

Quantitative densitometry of the lung was first done by measuring the mean value of pixel density in a region of interest drawn on each scan. Figure 4 shows examples of histograms of the density values of pixels or voxels in a case of emphysema. Because normal lung at full inspiration has a mean density between –750 and –850 HU (on 10-mm slices) and emphysema has been defined to be more than 2 SD below the normal average density, this gave a value close to –900 HU as the threshold for calling an area emphysematous (23). The standard deviation argument fell apart in many other studies, however, with differences in reconstruction algorithm, use of contrast, or collimation; nevertheless, until recently –910 HU had been the most frequently used cutoff value for defining emphysema. This is a fairly arbitrary value, as indicated by the use of –950 HU as a cutoff by recent investigators using equipment with thinner collimation or image-sharpening reconstruction algorithms. The percentage of pixels below this value seemed to correlate better

Figure 4. Histogram of density of pixels or voxels in the whole lung in an emphysematous individual (same as Figure 2). The proportion of the area under the curve to the left of the vertical line at -950 Hounsfield units (HU) is a common measure of emphysema. (A) Inspiratory scan histogram made with standard algorithm, 7.5 mm collimation; 18.0% of pixels/voxels less than -950 HU. Total lung volume (at -600 HU threshold) 5,875 mL; mean density -889 HU; SD 74.9 HU. (B) Expiratory scan showing only 5.7% of pixels/voxels less than -950 HU; volume of 4,115 mL; mean density -849 HU; SD 80.9 HU. (C)

with pulmonary function studies in scans done with relatively thick sections of lung, as with helical scanning, whereas a more negative number was called for with thin sections, as in high-resolution selective slice scans. Emphysema is considered to be present when more than 10% of pixels fall below the cutoff of -910 HU or -920 HU, depending on slice thickness and reconstruction algorithm.

Quantitative measures combine information about severity and extent of emphysema in one number, which offers the simplicity of a measure that can be tested statistically, although some descriptive information is lost. Regional assessment requires division of the lungs into four or six regions or into lobes. Another approach to assessment of regional involvement is to measure density in the core versus the periphery, or "rind," of the lung (24). Lobar segmentation by computer also has been accomplished (25). Separation of regions as upper and lower is simpler and may be sufficient for applications such as LVRS.

Measuring the pixel density frequency accurately on each slice, whether at 3 or 4 representative levels or all the way through the lungs, is tedious. Volumetric sampling of data, using helical scanning, has offered another option for quantifying lung densities. Calculations now measure the density of voxels rather than pixels, to be more precise, because the spiral slices are assembled into a three-dimensional structure in which the picture element is now a volume element. There is not much to distinguish quantitatively between these methods (26, 27). Both require a preliminary separation of the lung from the chest wall and the diaphragm, using a technique called segmentation (28). Computer programs do this automatically after the process is "seeded" by the operator indicating the lung, but the different methods result in different amounts of pleura in the lung periphery, size of vessels retained in the lung volume, or retention of the trachea and main bronchi, and therefore the quantitative measures of mean density and lung volume vary. Few authors detail how they do this initial segmentation of the lungs or indicate the threshold for identifying lung parenchyma, relying on standard computer programs.

Dirksen (22) studied the density of the 5% to 15% lowest attenuation pixels or voxels and showed that the variance of their density was substantially less than the variance of the pulmonary function measures that had been used to date to estimate clinical severity of α -1-antitrypsin deficiency emphysema. These measures, called here the "percentile point," vary somewhat less than the density mask and remain a popular alternative, particularly in Europe. The coefficient of variation, which is the standard deviation of density divided by (or normalized by) the mean density, is a good measure of global severity, as are ratios such as the percent voxels less than -940 HU divided by the percent less than -910 HU (personal observations). The correlations of these measures with other radiologic measures and with pulmonary function tests will be described elsewhere.

MORE TECHNICAL PARAMETERS

Whether the entire lung or selected regions are scanned, attention must be paid to the effects of slice thickness, or scanner collimation, and reconstruction algorithm (29). This information is incomplete in many reports. As scan technology pro-

Inspiratory scan with edge-enhancing (bone) algorithm, also slightly thinner collimation (same raw data as A). The curve is broader and much less peaked, with 21.3% of pixels/voxels less than -950 HU in density. Total lung volume measured as 5,851 mL; mean density -888 HU; SD 80.8 HU. Compare the appearance of the curve with A. Note also the changed scale of the vertical axis.

gresses, thinner collimation can be used, resulting in greater sensitivity to small regions of emphysema. However, this changes the criterion for emphysema on the Hounsfield scale; for example, -910 HU with 10 mm collimation is closely equivalent to -920 HU with 2.5 mm collimation (personal observations). Similarly, many physicians like to look at scans with an edge-enhancing algorithm (e.g., "bone" or "lung" or "detail" or some proprietary code number). The more edge enhancement, the broader the histogram of densities, and the greater the percent pixels less than any chosen number (Figure 4C) (30). For quantitation of emphysema, the standard algorithm should be used without edge enhancement. Different manufacturers perform different proprietary filtering operations so that the equivalence of even "standard" algorithms on different machines is questionable. However, much of the variability of results on different machines is due to patient variables, such as lung volume (31,32).

RADIATION DOSE EFFECTS

Radiation dose reduction is a practical issue in CT quantitation. The effective radiation dose to the chest for a helical CT examination has been estimated to be 8.9 to 10.9 mSv. Conventional examinations are done with a mAs setting of 180 to 240 , but with a kVp of 120 to 140 , doses of 100 mAs are common in chest screening, and 20 to 40 mAs can be used for emphysema quantification, representing a 6- to 10-fold dose reduction (33). The noise level of the image, and hence the variance of the density or the blurriness of the structures, varies with the dose. This may have limited effect on the density mask score, but there is enough difference that some investigators avoid automatic dose reduction, which is available on newer machines. The noise difference affects the CT measurements using density mask or percentile point (32). To reduce the radiation dose to the subject, various investigators use a limited number of selected slices to represent the entire lung, at the risk of measuring unrepresentative levels in the lung. The variation of density in a comparative study using selected slices would be greater than if the whole lung were scanned. On the newer and faster CT machines, the time cost of a whole lung study is reduced, and the temptation is to scan the whole lung, even though the radiation dose is still substantial. One major advantage of doing this is that the lung volume at which the scan was made can be measured.

LUNG VOLUME CONSIDERATIONS

Controlling for lung volume is important for quantitative work, especially on serial studies taken to evaluate an intervention (22). Some workers are convinced that reliable reproducibility of scan volumes requires automatic control of the scanner to have it operate at a preset volume, which is usually taken as 90% of the total lung capacity measured in advance (34). Others believe that constant volume is not assured because residual volume may vary with disease and is not controlled in this process. There is also the expense of purchasing the apparatus to accomplish controlled and measured inspiration and the inconvenience of using it.

How reliable is total lung capacity on the CT table without spirometry? In general, it is good enough and is not improved significantly by spirometric control (35). In our laboratory, measurements on repeated scans, including casual "take a deep breath and hold it" lung cancer screening scans, show a coefficient of variation of 5.5% to 7.7% between scans in various studies over 1 to 2 years. Some of this variation may be due to the slow increase in lung volume that occurs over time with emphysema, which was not demonstrable in the spirometric

data obtained at the same time as the CT scan. Most investigators without special equipment or motivation continue to use unmonitored deep breaths and consider this adequate for clinical studies.

Expiratory scans reveal air trapping in patients with small airways obstruction even when inspiratory scans appear normal (36,37). A number of investigators believe that expiratory scans are useful in the quantitation of emphysema and have shown higher correlation coefficients with pulmonary function tests using density masks calculated on expiratory scans (38,39). Correlation coefficients of FEV₁ with voxels less than -950 HU, for example, increased from about 0.5 to nearly 0.7 on going from inspiration to expiration. In recent work, intermediate densities of -900 to -950 had a correlation coefficient as high as -0.86 between the ratio of these pixels on inspiration and expiration and the pulmonary function tests (40). Others have found no advantage in expiratory scans but have demonstrated greater consistency in the volume of scans made at total lung capacity compared with those done at lower volumes (41). They reported macroscopic morphometry to be highly significantly correlated with inspiratory pixels less than -950 HU ($r = 0.55$), although the expiratory pixels less than -910 HU were not significantly correlated. On the other hand, microscopic morphometry correlated significantly with expiratory pixels less than -820 HU ($r = 0.53$) (41).

Those who measure airflow at the mouth to control scan volume on inspiration tend to favor expiratory scanning under spirometric control. One should use a higher density cutoff to measure emphysema on expiration, and the initial segmentation may be more difficult due to basilar atelectasis of the lungs. The particular application determines whether it is worth the extra difficulty in scanning. Figure 4 shows histograms of density of inspiratory and expiratory scans and the effect of using a moderately high-resolution algorithm.

The effect of small changes in volume on measured density have no significant effect on measures of severe disease, which depend on only the lowest density pixels, such as the -950 HU density mask or the fifth percentile point, because their value is changed little by overall differences in density (32).

CALIBRATION

All CT scanners are calibrated for water density, the central level of 0 HU, close to the density of tissue. However, it has been shown that quantitative CT for emphysema is dependent on the accuracy of air calibration at $-1,000$ HU or, in the case of GE scanners, -1024 HU, because that is closer to the level at which emphysema is measured (42). Therefore, for serial studies to measure the rate of progression of emphysema, calibration with an air phantom and a water phantom is recommended.

SUMMARY

Improvements in CT technique have resulted in increasingly subtle levels of emphysema being detected, but there is still a gap between emphysema measurements and severity of COPD (43). Differences between emphysema and chronic airway disease in COPD can be detected (44), but enabling this distinction to be made confidently remains an important challenge, essential for the testing of therapies. A recent paper suggests a novel approach, using the intermediate density voxels (-900 to -950 HU) as a measure of air trapping on expiratory scans compared with inspiratory scans, without the diluting effect of the low-attenuation voxels below -950 HU that are presumed to show fixed emphysema (40). Reviews of the literature on CT in emphysema have recently been reported and may be useful as additional background information (25,45-49).

For clinical purposes, careful inspection of CT images using a narrow window (see Figure 1B) is sufficient to detect emphysema. For scan interpretation, a high-resolution algorithm gives clearer results, the degree depending on the slice thickness and noisiness of the images. For research or to follow a patient over a course of treatment, quantitative CT is necessary. We suggest a whole lung (spiral or helical) scan with a well-calibrated scanner using 2.5 to 5 mm collimation, 140 kVp, 40 mAs if possible (higher mAs for an obese subject), and a "standard" reconstruction algorithm for quantitation with a high-resolution algorithm for scan interpretation. This allows one to calculate lung volume and potentially to make corrections for different lung volumes. Patient cooperation in reaching the correct lung volume is variable but is helped by coaching and practice beforehand; a spirometer is not necessary.

New scanners require a breathhold of much shorter duration for imaging. In addition, reconstructions to 1.25 mm for calculation or interpretation can be made without exposing the patient to additional radiation. In the future, expiratory scans at residual volume may become standard in addition to full-inspiration scans, but this is probably less important in patients with substantial disease. New methods of calculation using expiration/inspiration scans may help distinguish different types of emphysema and quantitate their severity and rate of progression.

Conflict of Interest Statement: P.J.F. has received grant money for work done on the NETT and FORTE studies, supervising and reading CT scans. He has also received funds from David Broide's NIH grant to do CT scans on another group of subjects. He receives regular funding from Broncus Technologies, Mountain View, CA, for reading CT scans on patients to have stents placed in their bronchi and for consulting on radiologic issues. He has been doing this since November 2006 and nets about \$4,000 per month. He will receive a stipend for reading and supervising CT scans on a pharmaceutical study of emphysematous patients from Hoffman La Roche.

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