Lung Density and Lung Mass in Emphysema*

Hervé Guenard, M.D.; Mamadou H. H. Diallo, M.D.; François Laurent, M.D.; and Jean Vergeret, M.D.

Mean lung density (dm) and radiologic (VLx) lung volume can be calculated using CT scan data. As many emphysematous patients are overdistended, the analysis of dm alone could be meaningless. However, lung mass (m) can be calculated as the product of dm and VLx. Twenty-four patients suspected of mild or severe emphysema as judged by roentgenographic and physiologic examinations as well as 16 healthy subjects were included in the protocol. They all underwent both a CT scan of the whole lung and functional tests from which the following were derived: airway resistance, forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), total lung capacity (TLC), CO transfer capacity, quasistatic compliance at functional residual capacity (FRC), and blood gases. All CT scans were performed at the FRC of each patient. The dm was lower in emphysema patients than in healthy subjects, as m was greater in patients than in healthy subjects; 1,303 ± 398 g and 997 ± 133 g, respectively. Although dm values were significantly correlated to FEV1, FEV1/FVC, and TLC, m values were not correlated to any of these functional indices. Unexpectedly, these results show that most patients (22/24) with emphysema have a normal or increased lung mass. Normal or above normal m values might be due to overrecruitment in some patients. Nevertheless, the synthesis of new tissue due to chronic inflammation is the most likely explanation that could account for this finding.

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Emphysema is defined as an enlargement of air spaces distal to the terminal bronchiole, accompanied by destructive changes of alveolar walls without obvious fibrosis.1 The first statement in the above sentence, ie, “enlargement of air spaces,” suggests an overdistention of the lungs. In fact, the increase in the total lung capacity (TLC) is considered to be a good index of emphysema even in its mildest forms.2

The second statement, ie, “destructive changes of alveolar walls,” has been the subject of numerous investigations on excised lungs or lobes.1,2,6 These destructive changes have also been assessed from alterations in lung function both in vitro and in vivo, although there is less agreement on their significance. Static lung pressure-volume (P-V) curves, maximal expiratory flow rates, CO transfer capacity (TLCO) have all been used as indices of emphysema. TLCO,7 elastic recoil on excised lung, or in vivo P-V curves6 have all been reported to detect mild forms of emphysema (pathologic grade 5 or less). The decrease in TLCO is not, however, specific for emphysema,3 although it may give a good estimate of its severity.7 Airflow limitation is not constant in mild emphysema,2 although the decrease in the forced expired volume in 1 s (FEV1) is correlated with the estimate of destruction from either pathologic or tomodensitometric (TDM) examinations.8,9,10

There is still disagreement about the in vivo diagnosis of diffuse emphysema,4 although many studies have demonstrated the excellent agreement between TDM findings and pathologic scores. A further problem lies in the interpretation of the definition. Does “destructive changes of the alveolar walls” mean disappearance or restructure of alveolar walls? In the former case, the disappearance would mean loss of lung mass. In the latter case, restructuring might even lead to an increase in lung mass.

Both lung density11 and lung volume can be determined by TDM, giving a quantitative estimate of lung mass. However, lung density depends on the state of inflation of the lung. Overdistention or inflation would reduce lung density, while underinflation would tend to increase it.

The third statement of the definition, ie, “without obvious fibrosis,” rejects the diagnosis of emphysema when destructive changes of alveolar walls are accompanied by interstitial lung diseases or scars. However, centrilobular emphysema is secondary to an inflammatory process that might include some fibrosis, and panlobular emphysema is likely to be complicated by similar processes. Fibrosis increases lung mass, and thus could outweigh the decrease in mass caused by the destructive process.

As a whole, the above definition of emphysema suggests a loss of parenchyma without any significant compensation in weight. As no work seemed to have studied this specific problem, our aims were as follows:

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(1) to describe a method for estimation of lung mass using TDM in patients with mild or severe emphysema; and (2) to find out whether emphysema is accompanied by loss of lung mass, and whether lung density and lung mass are correlated with functional parameters.

**METHODS**

**Subjects**

Twenty-four patients with ages ranging from 30 to 77 years suspected of having pulmonary emphysema on historic, radiologic, and physiologic grounds were selected for the study. The diagnosis was confirmed by examining thin TDM slices (1 mm). The exact diagnosis of the type of emphysema, panacinar, centrilobular, or both, was beyond the possibilities of our system, and can be made only using high-resolution CT scan imaging. Patients who had a history of increasing dyspnea without sputum were referred to as group D (11/24). Those with cough and sputum were group C (10/24), and three patients with big bullae (1 cm or more) without apparent destruction of the remaining lung, on roentgenogram, were distinguished from the other patients, and became group B. Only one of the D patients was homozygote ZZ with a clear-cut antiprotease deficiency (0.3 g/L). Eighteen of the 24 patients were smokers.

Sixteen healthy subjects with ages ranging from 20 to 65 years served as controls. They were subjected to an identical procedure as the patients.

**Lung Density and Lung Mass Determinations with TDM**

The TDM examinations were carried out using a scanner (Siemens CT scanner, Somatom DRH) on 8-mm-thick slices with 1 × 1-mm pixel reconstruction. Acquisition of one slice took 5 s. Slices were taken of the whole lung at functional residual capacity (FRC). Three of the 16 control subjects were asked to breathe in up to TLC prior to the scan acquisition in order to widen the range of the lung volume. Data were analyzed by computer using purpose-designed software that did the following: (1) automatically rejected extrapulmonary tissue by excluding all pixels outside the range −999 to −350 Hounsfield index (HI), the main pulmonary arteries were also excluded; (2) calculated the frequency distribution of HI in both lungs; and (3) calculated lung volumes and mean HI (HIm) within the slices. Mean HI in the right and left lungs, as well as over both lungs, were computed. The overall measured mean HI, referred to as HIm, is the volume weighted average of all HI values:

$$Hlm = \sum_{i=1}^{n} HI_i \cdot (V_i/V_L)$$

*Equation 1*

Where n is the number of slices, Vl and HI are the volume and the HI value in the exposant slice respectively. VLx is the total lung volume. Negative values of HI were not taken into account in the equations.

Mean measured density is: $dm = 1 - Hlm/1000$. Lung mass (m) is the product $dm \cdot VLx$. The validation of the technique was made by comparing the masses of animal lungs or lobes measured gravimetrically and with the TDM method. The TDM method appeared accurate and sensitive (see Appendix and ref 12).

**Lung Function Tests**

TLC and FRC, RV/TLC, maximal flow-rates during expiration, bronchial resistance during panting (Raw), quasistatic compliance at FRC (Cqs) were measured in a home-made plethysmograph, and analyzed using a computer (HP 8200). Esophageal pressure was measured with a balloon connected to a transducer (Schlumberger) (±100 kPa) following the usual techniques. PV curves were obtained during a slow controlled exhalation, and were filtered using a moving average method. Their slopes were calculated using a linear correlation between FRC and FRC + 0.5 L. Results from some patients were discarded due to errors induced by esophageal contractions or for lack of reproducibility. Single-breath measurement of TLco was carried out using a specific system (Hewlett-Packard 47404 A). The TLco maneuver involved breath-holding for 8 s. However, some patients could not achieve this apnea, and since a shorter breath-holding time underestimates the figures,13 the...

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**Table 1 — Functional Tests in the Two Groups**

<table>
<thead>
<tr>
<th>Test</th>
<th>Healthy</th>
<th>Emphysema</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw, kPa 1's</td>
<td>0.15 ± 0.06</td>
<td>0.31 ± 0.20</td>
<td>0.003</td>
</tr>
<tr>
<td>FEV1, % pred</td>
<td>97 ± 11</td>
<td>54 ± 23</td>
<td>0.001</td>
</tr>
<tr>
<td>FEV1/FVC, % pred</td>
<td>100 ± 8</td>
<td>64 ± 17</td>
<td>0.01</td>
</tr>
<tr>
<td>TLC, % pred</td>
<td>101 ± 12</td>
<td>116 ± 19</td>
<td>0.01</td>
</tr>
<tr>
<td>RV/TLC, % pred</td>
<td>90 ± 22</td>
<td>139 ± 42</td>
<td>0.001</td>
</tr>
<tr>
<td>TLco2, % pred</td>
<td>107 ± 23</td>
<td>63 ± 29*</td>
<td>0.01</td>
</tr>
<tr>
<td>Cqs, kPa</td>
<td>2.86 ± 1.31</td>
<td>4.37 ± 2.50*</td>
<td>0.05</td>
</tr>
<tr>
<td>PaO2, kPa</td>
<td>11.96 ± 1.10</td>
<td>9.85 ± 1.50</td>
<td>0.001</td>
</tr>
<tr>
<td>PaCO2, kPa</td>
<td>4.93 ± 0.59</td>
<td>4.74 ± 1.10</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Sixteen of 24 patients performed the measurements.
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**Figure 1.** Plot of HIm data as a function of inflation coefficient. White circle—healthy subjects. Black circle—patients with emphysema. Data were fitted with hyperbolic regression equations. The upwards curve and equation are for the patients.
Table 2—Measured Densities, dm, and Lung Masses in the Two Groups

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>dm</th>
<th>mass (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy subjects</td>
<td>16</td>
<td>0.288*</td>
<td>997</td>
</tr>
<tr>
<td>Patients</td>
<td>24</td>
<td>±0.064</td>
<td>±31</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.0004</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*Some healthy subjects were asked to inflate their lungs fully since measurements on the patients were all performed at TLC.

RESULTS

HIm and dm data for healthy subjects and patients were plotted (Fig 1) against an inflation coefficient, VLx/(FRC0 + Vtiss), which is the ratio of the actual radiologic lung volume to the sum of the tissular volume (Vtiss) and the normal value for FRC (FRC0) (see appendix). It can be seen that both HIm and dm depended on this ratio. Data were fitted with hyperbolic regression equations for both the healthy subjects and the patients. The curve for the patients was shifted upwards slightly.

The average lung mass was significantly greater in the patients (+26 percent) than in the healthy subjects (Table 2); however, the values were more scattered in the patient group (2.3 to 0.64 kg). Twelve patients (group 4) had lung masses above the confidence interval of healthy subjects (group 1) as only two had lung masses below this confidence interval (group 2); the remaining ten patients had normal lung masses (group 2) (Fig 2).

Functional indices and their correlations with dm and m are listed in Table 3 for the patients. Values of dm in patients were correlated with FEV1, FEV/FVC, and TLC, but neither TLCO nor Cqs were correlated to dm. None of those functional parameters were correlated to m. In healthy subjects, m was correlated to quasistatic compliance.

DISCUSSION

Lung Density in Healthy Subjects

The hyperbolic curve fitting HIm, or 1/dm as a function of the inflation coefficient, shows the effect of lung inflation on the recovered values of HIm or dm (Fig 1). This is in agreement with the theoretical hyperbolic relationship between HIm and VLx (see Appendix).

It could be argued that it would be more accurate to measure HIm at TLC rather than at FRC, as FRC may change more than TLC from one acquisition to another. However, this method has two drawbacks: (1) in a normal individual, HIm at TLC can increase to a value of about 850 (air = 1,000), and so the relative sensitivity of the measurement of HIm decreases with increasing lung volume; (2) at least 20 scans are needed for the whole lung, and so making the TDM acquisitions at TLC would require 20 successive vital capacities and breath-holds, which would be too tiring for patients with severe pulmonary disease.

The mean dm in our healthy subjects, ie, 0.288, is in agreement with values from TDM or from positron emitting tomodensitometry (PET) reported in the literature. The value reported in the early study of Rosenblum et al is slightly lower, 0.266, although this figure was obtained during quiet breathing, ie, at a lung volume above FRC. As in our study, these authors did not find any change in lung density with age, suggesting that there was no decrease in lung mass with age, and that alterations in pulmonary function with age are due to alterations in structure of the parenchyma rather than to tissue destruction. The mean lung density value reported by Brudin et al using PET (0.28 ± 0.03 g/dm3) is in close agreement with our value.

Table 3—Values of p for the Correlations between dm or m and Fractional Indices

<table>
<thead>
<tr>
<th></th>
<th>dm</th>
<th>m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>FEV1</td>
<td>0.0001</td>
<td>NS</td>
</tr>
<tr>
<td>FEV/FVC</td>
<td>0.006</td>
<td>NS</td>
</tr>
<tr>
<td>TLC</td>
<td>0.02</td>
<td>NS</td>
</tr>
<tr>
<td>TV/TLC</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>TLCO</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Cqs</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Lung Density and Mass in Emphysema (Guenard et al)
Lung Mass in Patients

The 12 patients in group 4 had high lung mass, two of them were of B type. One of these B type patients had numerous bullae (1 to 2 cm in diameter) partly filled with infected secretions. Despite antibiotic treatment, he had a permanent cough with sputum. After resection of his lungs for lung-heart transplant, pathologic examination confirmed the presence of secretions and diffuse inflammation throughout the lung. In this case, the high lung density was due, at least in part, to oversecretion. The other B type patient had had a pneumothorax, but no history of recurrent pulmonary infection. These two B patients had the highest lung densities. The ten others were C (five cases) and D type (five cases), their lung overweights were slight, but, in the D patients, at least, could not be attributed to oversecretion. When present, oversecretion is mainly confined to the bronchial tree, whose volume is around 150 ml. Even if this volume was filled with secretions, it could not account for the observed increases in lung mass.

The two group 2 patients had low lung mass. They were of D type. Interestingly, the patient with the lowest lung density, 22 percent below the lower limit of normal, was a 77-year-old man with a normal static lung compliance (2.05 L/kPa). The association of these two findings indicated that the remaining parenchyma of this patient had a lower than normal specific compliance.

The ten group 3 patients had normal lung mass (5C, 1B, 4D). This normal lung mass could be the result of (1) compensation of loss of alveolar weight with inflammatory materials, (2) the synthesis of new tissue in compensation of the destruction of the alveolar walls, or (3) the negligible mass of alveolar walls compared with the remaining parenchyma. In this case, the method would not be able to detect a peripheral parenchymal loss. This latter possibility will be discussed first.

From peripheral samples of the lung, Gehr et al estimated that the volume of parenchymal tissue in normal lungs was 298 ± 36 cm³ with a total capillary volume of 213 ± 31 cm³. Therefore, the total mass of the parenchyma excluding large vessels and bronchi is around 500 g, which represents about half the mass of normal lungs determined with TDM (Table 2). In normal subjects, the confidence interval of m (2 SD/mean) is 27 percent. Hence, assuming that emphysema affects only the peripheral parenchyma, a 54 percent change in the mass of this peripheral parenchyma is needed to obtain a significant change in total lung mass. Nevertheless, five of the ten patients in group 3 were at the upper limit of the confidence interval. Therefore, in these patients, as in most of the patients in group 4, the mass of parenchyma due to the destructive process is likely to be compensated for by a gain of inflammatory materials or new tissue. Mucous edema, fibrosis of the airways, hyperplasia of the bronchiolar and alveolar walls, mucus hypersecretion, and muscular hyperplasia are common in any chronic disease of the airways. A more speculative possibility is a remodeling of the parenchyma, i.e., a rearrangement of the structure of the parenchyma after a destructive process, which has been indicated in animal experiments. In the hamster, instillation of pancreatic elastase is rapidly followed by a decrease in lung elastin content. At this time, there was a clear-cut loss of lung material, although 21 days later, lung elastin content had returned to normal. However, air spaces were greatly enlarged with a complete rearrangement of their components. Aging, which is accompanied by an increase in mean linear-intercept of alveolar walls, is not followed by a decrease in lung density.

These indirect arguments lend support to the idea that the increase in alveolar spaces, which is suspected to decrease lung density, is often accompanied by a compensative increase in the mass of parenchyma.

Relationship between Pulmonary Function and Lung Density

Indices of obstruction (FEV₁/FVC) or distention (TLC, RV/TLC) were correlated with dm but not with m (Table 3). Since the obstruction and distention parameters were related (p<0.05), the correlation of dm with obstructive parameters is meaningless; dm is physically related to distention. As m was not correlated with the obstruction parameters, obstruction is more likely to have been due to an alteration in mechanical properties of the airways rather than to loss of parenchyma. If the obstruction is due, at least in part, to loss of elastic recoil, it may arise from a rearrangement of lung parenchyma. This idea is supported by the fact that quasistatic compliance at FRC was higher in the emphysematous patients than in our healthy subjects. There was no correlation between compliance and either dm or m. This is not in complete agreement with results obtained using different techniques. Pare and coworkers used an exponential analysis of the P-V curves (V = A - Be⁻¹⁵/K) from FRC to TLC using the technique described by Greaves and Colebatch. The coefficient in the equation is related to the steepness of the exponential curve. The emphysema grade was judged on resected lobes using the picture grading system of Thurlbeck. Using these methods, patients with emphysematous grades over 20 were found to have K values above those with mild emphysema (grade under 20) or those without emphysema. However, the K values in these two last groups were not different. Interestingly, five of the other 16 patients with emphysematous scores above 20 had low or normal K values, suggesting that...
the disease-induced rearrangement of the lung parenchyma was not a unitary phenomenon. Compliance measured over 0.5 L above FRC does not have the same significance as values measured from FRC to TLC. In fact, the coefficient K in the exponential regression of the P-V curve is not a true compliance figure, but a descriptive index of the shape of the curve, representing the nonlinear behavior of the lung. In patients with an increase in elastin-derived peptides, McLennan et al. reported a lack of correlation between the concentration of these peptides and Cqs, although there was a correlation between Cqs and K.

The lack of correlation between Cqs and dm is not surprising as dm depends on both individual FRC and the mechanical properties of the restructured parenchyma.

The correlations between TLCO and dm or m were low (Table 3), although higher than with compliance. In the absence of reaction of the lung to destruction, the lung mass index should be correlated with indices of gas exchange such as TLCO. However, if there is productive inflammation, m values are likely to depend on them in an unpredictable manner. This is supported by the findings of McLennan et al. who reported that TLCO was not correlated with the destructive activity of the emphysematous process assessed by blood levels of elastin-derived peptides.

Lung mass is related to age in patients with emphysema. This could suggest that the cumulated effects of inflammatory episodes are greater in older patients and/or that the younger patients have more destruction. In this respect, a longitudinal study of emphysematous patients would help to identify relationships between emphysema and biological indices of inflammation, destruction, or remodeling.

In conclusion, lung mass is not an index of the extent of emphysema, at least in most patients, but rather an index of the reaction of the lung to the emphysematous process.

**Appendix**

(1) m, VLX, dm being lung mass, total lung volume, and mean lung density, respectively:

\[ m = VLX \cdot dm \]

Assuming the density of lung tissue close to that of water the lung mass (m) expressed in g is equal to the tissular volume (Vtiss) expressed in ml.

The absolute value of the Hounsfield index being 1,000 for air whose density will be neglected, and 0 for water, density and HI are directly related.

\[ HI = (H - 1) \cdot 1000 \quad \text{or} \quad d = 1 - (HI/1000) \]

The total lung volume measured with TDM is the sum of tissular volume (Vtiss) and gas volume. If acquisitions are made at FRC:

\[ VLX = FR C + Vtiss \]

FR C being the theoretical FRC of a given subject or patient given by standard morphometrics equations, dc and Hi, the mean lung density and HI for this lung volume, respectively:

\[ m = dc \cdot (FR C + Vtiss) = dm \cdot VLX \]

\[ dc = dm \cdot [VLX/(FR C + Vtiss)] \]

and \[ HIc = 1,000 - [VLX/(FR C + Vtiss)](1,000 - HIm) \]

The ratio in brackets is referred to as the inflation correction coefficient (in the text this is shortened to inflation coefficient).

From the above equation:

\[ HIc = 1,000 - (1,000 - HIc)([FR C + Vtiss]/VLX) \]

For a given individual, HIc, FR C, and Vtiss are constants.

Increasing VLX increases HIc in a hyperbolic relationship.

(2) In order to validate the method, 11 animal lungs or lobes (five sheep, three cows, three pigs) were weighed and thereafter examined with the CT scan procedure described in the text. Each lung or lobe was examined twice, deflated, and inflated with a 10 cm H2O pressure. The mean weight was 950 g with the balance, 904 and 911 g with the CT scan in the deflated and inflated lung, respectively. The mean paired differences were significant (p = 0.05 and 0.015), but slight, \(-3.76 \pm 2.53\) and \(-3.38 \pm 2.65\) percent of the gravimetric weight deflated and inflated, respectively. These slight differences were attributed to the automated rejection by the CT software program of all regions of interest the HI of which were above \(-350\). As the differences between the balance and the CT methods were slight, systematic and readily explained, the CT method for the determination of lung mass was considered to be a reliable technique.

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