Comparison of Computed Density and Macroscopic Morphometry in Pulmonary Emphysema

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High-resolution computed tomography (HRCT) scans were obtained at 1 cm intervals in 63 subjects referred for surgical resection of a cancer or for transplantation to find out whether the relative area of lung occupied by attenuation values lower than a threshold would be a measurement of macroscopic emphysema. Using a semiautomatic procedure, the relative areas occupied by attenuation values lower than eight thresholds ranging from −900 to −970 HU were calculated on the set of scans obtained through the lobe or the lung to be resected. The extent of emphysema was quantified by a computer-assisted method on horizontal paper-mounted lung sections obtained every 1 to 2 cm. The only level for which no statistically significant difference was found between the HRCT and the morphometric data was −950 HU. To determine the number of scans sufficient for an accurate quantification, we recalculated the relative area occupied by attenuation values lower than −950 HU on progressively fewer numbers of scans and investigated the departure from the results obtained with 1 cm intervals. Because of wide variations in this departure from patient to patient, a standard cannot be recommended as the optimal distance between scans. Gevenois PA, de Maertelaer V, De Vuyst P, Zanen J, Yernault J-C. Comparison of computed density and macroscopic morphometry in pulmonary emphysema.

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With a spatial resolution of the same order of magnitude as that obtained by the unaided human eye, modern computed tomography (CT) scanners could become the standard test for the *in vivo* quantification of pulmonary emphysema (1). Since visual inspection and grading of CT slices were proposed, there have been two technological advances that may further increase the accuracy of CT: high-resolution CT (HRCT), which is definitely superior to conventional CT in evaluating interstitial lung diseases (2), and programs analyzing attenuation values that have opened the way to quantification of the disease processes (3, 4). In the lung, the CT pixel density is determined by the relative amounts of blood, tissue, and air contained in the slice thickness. In emphysema, the proportion of pixels of lowest attenuation values increases as a result of the relative reduction in blood and tissue accompanied by a subsequent relative increase in air (1). Consequently, the relative area (RA) of lung occupied by attenuation values lower than a threshold should be an index of emphysema.

The first purpose of the present study was to determine the most appropriate CT threshold by comparing the relative areas of low attenuation values obtained *in vivo* at various thresholds to the relative area macroscopically occupied by emphysema on paper-mounted lung sections obtained from the same lung specimen. To reduce the radiation dose and the examination time in a further use, the second purpose was to determine the maximum interval distance between scans providing results similar to those obtained from scans performed with a 1 cm interval distance.

METHODS

Patients

This prospective study included 89 consecutive patients referred between October 1991 and September 1992 to the department of thoracic surgery for surgical resection of a lung cancer or for lung transplantation because of emphysema. Patients with previous lung surgery (n = 1), microscopic evidence of interstitial lung disease in the nontumoral parenchyma (n = 1), pleural disease (n = 1), and pneumonia or collapse (n = 9) or who underwent segmentectomy (n = 1) were excluded. Another 13 patients were not surgically treated because of lymph node involvement detected during mediastinoscopy. A total of 63 patients, 52 males and 11 females, with ages ranging from 36 to 77 yr (mean age ± standard deviation, 62 ± 9 yr) were thus included in the present study: 59 patients underwent lobe or whole-lung resection for cancer, and 4 patients underwent lung transplantation. The investigation was approved by the local ethics committee, and informed consent was obtained from the patients.

Computed Tomography

HRCT scans were performed on a Siemens Somatom Plus® (Siemens, Erlangen, Germany) scanner during breath holding at full inspiration. No patients received intravenous contrast medium. The 1 mm collimation scans were performed from the lung apices to the bases, at 1 cm intervals (137 kVp, 255 mA, scanning time 1 s). The "Pulmo® CT" option from Siemens was used to calculate on each scan the total lung area

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and the lung area occupied by attenuation values lower than prefixed thresholds. This program automatically recognizes the lungs, traces the lung contours, determines histograms of attenuation values, and calculates the lung area occupied by pixels included in the predetermined range of attenuation values (3). After calculation separately obtained from each scan, the program provides total results based on the entire scanned volume. In the present study, the relative areas of lung (expressed as percentages) occupied by attenuation values lower than eight different thresholds ranging from −900 Hounsfield units (HU) to −970 HU were calculated for the lobe or the lung to be resected. Based on the threshold of attenuation values that correspond to emphysema, the percentage area of lung occupied by attenuation values lower than this threshold was calculated for both lungs.

Macroscopic Quantification of Emphysema

Immediately after surgery, the resected lobes and lungs were inflated with 10% buffered formalin at a distending pressure of 25 to 30 cm water for 12 h. Using a modified Gough-Wentworth technique, horizontal whole-lung sections were obtained every 1 to 2 cm (5, 6). The mean number of sections available for surgical specimens was 11 and ranged from 5 to 20, depending on whether the specimen was from a lobe or an entire lung. The mean diameter of the tumor on the fixed specimen was 3.1 cm. In 53 cases, the specimen was from a lobectomy or a bilobectomy. In the remaining 6 patients, a pneumonectomy was carried out, and in these cases, we used the tumor-free lobe for quantifications. They were performed on the entire lung in the 4 transplanted patients.

The area macroscopically occupied by emphysema was measured on the paper-mounted lung sections using a computer-assisted method that was previously validated (7). Lung sections were divided into fields of 7 × 7 cm, digitalized, and stored on a microcomputer. The image thresholding was selected by the operator so that highest gray levels correspond to emphysematous spaces, contrasting with the lower gray levels corresponding to the lung structures. Before calculation, the vessels and bronchi were erased. The number of pixels in the digitalized image of the paper-mounted lung section that corresponds to low densitometry readings and to the total lung area, respectively, were counted separately by the computer. The results obtained per field were added, and the overall relative area (expressed as a percentage) occupied by the low densitometry reading was calculated for the entire surgical specimen and corresponds to the pathologic extent of macroscopic emphysema in this specimen.

Data Analysis

As a first step, we tried to determine a threshold of attenuation values that accurately corresponds to the morphometric data of emphysema. Therefore, we considered eight thresholds and compared each of the sets of CT data with the corresponding set of morphometric data. We made this comparison for the whole group and separately for moderately emphysematous specimens, that is, with a percentage area of macroscopic emphysema not exceeding 20%. We rejected the thresholds that yielded values statistically different from the morphometric data. The statistical tests concerned the mean (Student's *t* test for paired samples) and the median (Wilcoxon matched-pairs signed-ranks test).

As a second step, we tried to find a maximum interval distance between HRCT scans providing valid results. We recalculated the relative area of lung occupied by attenuation values lower than the appropriate threshold by successively considering one scan of two, one of three, one of four, and so on, and investigated the progressive departure from the results obtained with 1 cm intervals. For this purpose, the individual (intrapatient) variations in the set of CT data were investigated while progressively increasing the interval distance through the evolution of the coefficient of variation (square root of the variance divided by the mean). This coefficient of variation was submitted to an analysis of variance procedure with repeated measurements corresponding to the results obtained for different interval distances, and we looked for any trend in the evolution of the coefficient of variation when increasing the interval distance.

RESULTS

The distribution of macroscopic data is illustrated in Figure 1. The mean percentage area of lung macroscopically occupied by emphysema was 9.18% and ranged from 0.13 to 50.81%. The distribution of the CT results obtained for each threshold was compared with the distribution of the morphometric data with a Wilcoxon matched-pairs test. The only threshold for which there was no statistically significant shift in the distributions ($p = 0.224$) was −950 HU (Figure 2). Similarly, the parametric Stu-

Figure 1. Relative area of lung macroscopically occupied by emphysema.

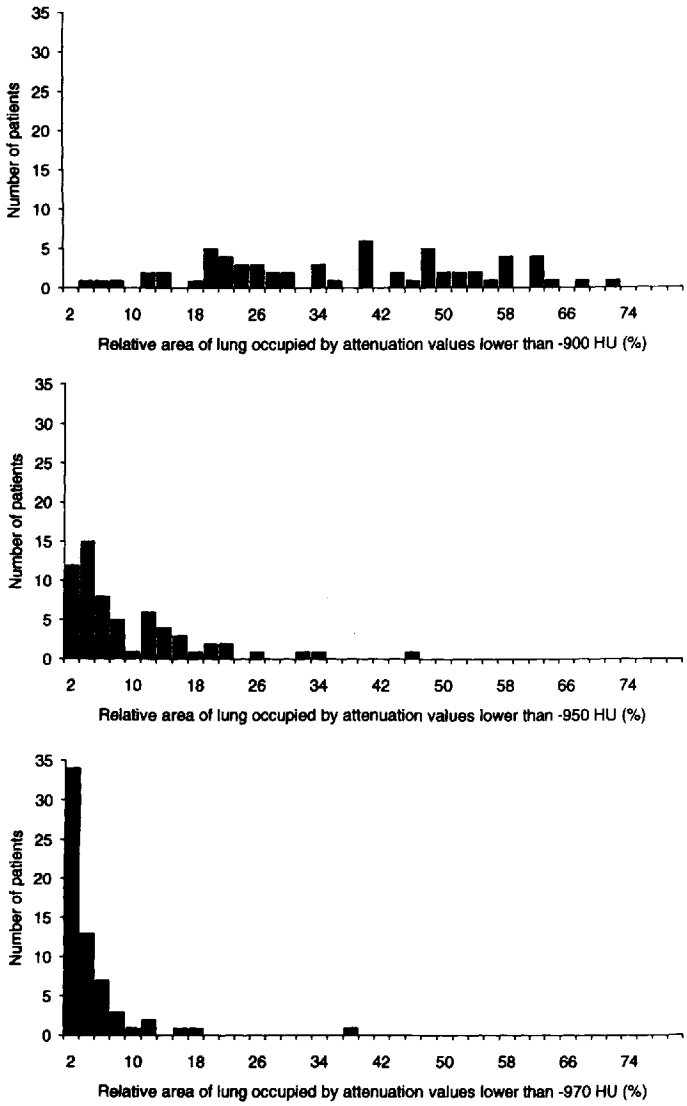

Figure 2. Relative area of lung occupied by CT attenuation values lower than −900 (*top*), −950 (*middle*), and −970 HU (*bottom*).

TABLE 1

MEAN, STANDARD ERROR OF THE MEAN, AND 95% CONFIDENCE INTERVAL ON THE DIFFERENCES BETWEEN THE RELATIVE AREA OBTAINED WITH VARIOUS THRESHOLDS AND MACROSCOPIC MORPHOMETRY (ALL PATIENTS)

Threshold (*HU*)	Mean	SEM	95% Confidence Interval
−900	−27.1	1.9	−30.9, −23.3
−910	−20.5	1.7	−24.0, −17.0
−920	−14.1	1.5	−17.1, −11.0
−930	−8.2	1.3	−10.7, −5.6
−940	−3.1	1	−5.2, −1.1
−950	0.7	0.9	−1.0, 2.4
−960	3.7	0.8	2.1, 5.3
−970	5.8	0.8	4.1, 7.4

Definition of abbreviations: HU = Hounsfield units; SEM = standard error of the mean.

dent's *t* test showed that the only threshold for which there was no significant difference between the means of the CT and the morphometric data was also −950 HU ($p = 0.384$). In other words, the distribution of the macroscopic measurements does not overlap the distribution of the CT measurements except for the −950 HU threshold. Thresholds lower than −950 HU underestimate emphysema, and thresholds above −950 HU overestimate emphysema compared with morphometric data. The mean, the standard error of the mean, and the 95% confidence interval on the differences between the relative area obtained with various thresholds and macroscopic morphometry for all patients are shown in Table 1, the corresponding values for patients with a pathologic extent of macroscopic emphysema up to 20% are shown in Table 2.

In the following, the area occupied by attenuation values lower than −950 HU related to the total lung area is abbreviated RA_{950} and is expressed as a percentage. The mean RA_{950} calculated on the lobe or the lung to be resected was 8.6% and ranged from 0.3 to 45.4%. The mean RA_{950} calculated on both lungs was 8.7% and ranged from 0.5 to 30.5%. A significant correlation was found between the RA_{950} calculated on the lobe or the lung to be resected and both lungs ($r = 0.926$, $p < 0.001$).

The case-by-case comparisons between the relative area occupied by attenuation values lower than the different thresholds and the relative area of lung macroscopically occupied by emphysema are summarized in Figure 3. The proportions of emphysematous surfaces measured by both techniques were not identical in every patient: the mean of the absolute values of the differences between the RA_{950} and the relative area of lung macroscopically occupied by emphysema was 4.9 ± 4.6% and ranged from 0.1 to 19.9%.

When increasing the interval distance between HRCT scans by successively considering one scan of two, one of three, one

TABLE 2

MEAN, STANDARD ERROR OF THE MEAN, AND 95% CONFIDENCE INTERVAL ON THE DIFFERENCES BETWEEN THE RELATIVE AREA OBTAINED WITH VARIOUS THRESHOLDS AND MACROSCOPIC MORPHOMETRY (PATIENTS WITH MACRO UP TO 20%)

Threshold (*HU*)	Mean	SEM	95% Confidence Interval
−900	−27	2.1	−31.1, −22.9
−910	−20.3	1.9	−24.1, −16.6
−920	−14	1.7	−17.3, −10.7
−930	−8.2	1.4	−11.0, −5.5
−940	−3.5	1.1	−5.7, −1.3
−950	0.06	0.9	−1.8, 1.9
−960	2.7	0.8	1.2, 4.3
−970	4.4	0.7	3, 5.9

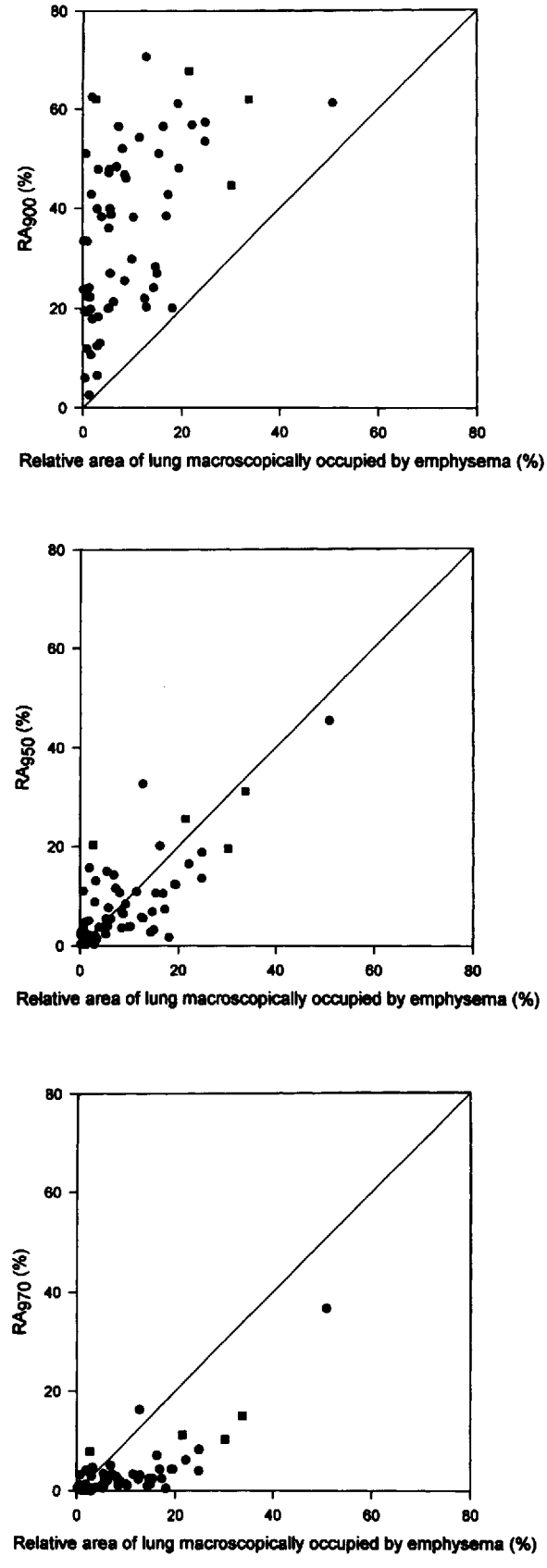

Figure 3. Relative area of lung occupied by CT attenuation values lower than −900 (*top*), −950 (*middle*), and −970 HU (*bottom*) (RA_{900}, RA_{950}, and RA_{970}, respectively) against the relative area of lung macroscopically occupied by emphysema. The diagonal represents the line of identity. Circles represent lungs resected for tumor, and squares represent lungs resected before transplantation.

of four, and so on, the individual variability in the RA_{950} (expressed as the coefficient of variation) was very heterogeneous from patient to patient. In some, the coefficient of variation increased; in others it decreased or remained stable. Nevertheless, the linear decrease when reducing the interval distance was statistically significant ($p = 0.002$), but quadratic and higher order equations were not significant. In other words, there is no bend in the relationship linking the coefficient of variation of R_{950} and the interval distance. Consequently, no particular interval distance can be proposed as an optimal standard.

DISCUSSION

In the past decade, several CT studies based on visual grading of pulmonary emphysema have shown promising results. Bergin and colleagues applied the panel grading method (8) to 10 mm collimation CT scans obtained at 10 mm intervals from the apex to the diaphragm in 32 patients undergoing lung resection (9). Significant correlation ($r \geq 0.63$, $p < 0.001$) was found between the preoperative CT score and the pathologic grade on resected lung specimens. Hruban and colleagues applied HRCT to 20 postmortem lung specimens fixed by a method that allows direct one-to-one pathologic-radiographic correlation (10). The cut surface of the lung and the corresponding HRCT scan image were assessed by scoring against the same panel of standards (8). A significant correlation ($r = 0.91$, $p < 0.005$) was found between the pathologic grade and the *in vitro* CT score. Miller and colleagues obtained 10 and 1.5 mm collimation CT scans in 27 patients undergoing lung resection (11). The 10 mm collimation scans were performed from the lung apices to the bases, and two 1.5 mm collimation scans were obtained at the level of the upper margin of the aortic arch and tracheal carina. In each patient a single CT level was compared with the corresponding pathologic slice determined by assessment of bronchial anatomy and distance from the tumor. There was good correlation between the 10 mm CT scan-scored emphysema and the pathologic score using the panel of standards ($r = 0.81$, $p < 0.001$) that improved slightly with the 1.5 mm CT scan ($r = 0.85$, $p < 0.001$). However, CT consistently underestimated mild and moderate emphysema because lesions less than 0.5 cm in diameter were missed. Kuwano and coworkers compared five HRCT scans with five corresponding cut surfaces of the fixed lung impregnated with barium sulfate and obtained at the same anatomic level in 42 patients with mild emphysema (12). Applying the grading panel to scans and to pathologic sections, they found a significant correlation ($r = 0.68$, $p < 0.001$).

In all these studies, both the CT images and the cut sections of fixed lungs represented axial cross sections, whereas the sections used in the panel of standards of Thurlbeck and coworkers are parasagittal, extending from the apex to the base of the lung (8). Comparison of these two types of images required mental adjustments (10, 11) or modifications of the panel (12). In addition, the panel of standards is designed for Gough-Wentworth paper-mounted lung sections, not for the cut surface of lung specimens. More importantly, the grading system is not really quantitative but is a method of ranking emphysema according to several categories of severity (8). To overcome these limitations, we applied to horizontal paper-mounted lung sections a quantitative computer-assisted method yielding results on a continuous scale, thus more informative than a ranking technique (7).

Visual methods used in these previous studies for grading CT scans involve characterization of areas of low attenuation and disruption of the vascular pattern, which probably reflects the size and number of enlarged airspaces. These methods are subjective and require that emphysematous lungs display visible areas of decreased density. In the present study, we replaced visual grading of CT scans by objective quantification using commercially available CT software that calculates the relative area of lung occupied by attenuation values included in a predetermined range (3). In a slice-to-slice comparative study including 28 patients, Müller and coworkers have applied such a computer method to contrast-enhanced conventional 1 cm thick CT scans (13). They have correlated the percentage of lung area occupied by attenuation values lower than three thresholds, −900, −910, and −920 HU, with the visual pathologic grade of emphysema. Using regression analysis, these authors have found the highest correlation coefficient for −910 HU ($r = 0.89$) (13). Their results cannot be compared with ours because they obtained 1 cm thick scans and their patients received contrast material. In addition, correlation coefficients indicate that CT and pathology results are linked but do not indicate that percentage areas obtained by CT quantification are equal to those obtained from pathologic measurements. To complement the method based on the correlation coefficients, we have investigated the possible overlapping between the distributions of the CT and macroscopic quantification through statistical tests focused on the equality of means and on the equality of medians, as recommended by Bland and Altman (14). Moreover, Müller and coworkers compared percentage areas on CT scans with panel grading of macroscopic sections. As pointed out by Thurlbeck, the scores provided by this grading method do not correspond to percentages and do not represent the exact extent of emphysema (8). We had the opportunity to verify this discrepancy by comparing the grading panel with our computed method (7). The methods we used allow a direct comparison between the surface area of emphysema measured macroscopically and the surface area of emphysema measured by quantitative CT, both being expressed as percentages.

As opposed to slice-to-slice studies, the data of the present study were obtained from an entire lobe or lung. The CT and the morphometric quantifications were based on a set of HRCT scans, as well as on a set of macroscopic sections. Slice-to-slice comparisons require that macroscopic slices correspond exactly to CT scans, but perfect concordance is virtually impossible to obtain. In addition, it has been shown that an adequate assessment of emphysema cannot be made from one lung slice alone (15). To overcome these limitations, we considered numerous HRCT scans as well as numerous paper-mounted lung sections, attempting to obtain a quantification reflecting as closely as possible the overall extent of emphysema involving the lung specimen.

Like Müller and colleagues (13), we used an absolute threshold, expressed in HU, instead of the lowest fifth percentile of the histogram of attenuation values proposed by Gould and coworkers (16). The lowest fifth percentile calculated from the histogram depends on the extent of emphysematous spaces but is also influenced by the relative amount of higher attenuation values, which tend to increase the lowest fifth percentile. The high attenuation values correspond to blood vessels, airway walls, and any area of infiltrate or collapse. This has been shown by Rienmüller and colleagues (17) and, more recently, by Hartley and coworkers (18): the histogram of attenuation values is modified and displaced to the right in the presence of infiltrative disorders. Consequently, if an associated disease coexists with emphysema (for example, pneumoconiosis), the lowest fifth percentile is modified and emphysema subsequently underestimated.

Because an adequate assessment of emphysema needs several slices (15) and we had no knowledge of the minimum number of scans providing valid results, we obtained HRCT sections at 1 cm intervals associated with a radiation dose widely accepted in the field of infiltrative lung diseases. To reduce this dose and the examination time in further patients, the number of scans should be decreased. The heterogeneity of the evolution of the coefficient of variation when reducing the interval distance is

related to the heterogeneous spatial distribution of emphysema and prevents us from recommending a maximum interval distance valuable for every subject.

In conclusion, by comparison between pathologic measurements and CT measurements, we have demonstrated that the relative area of lung occupied by attenuation values lower than −950 HU and calculated on HRCT obtained at full inspiration and at 1 cm intervals appears to be a method allowing an objective quantification of macroscopic emphysema *in vivo* and with an acceptable error. However, this threshold could differ from scanner to scanner; this interinstrument variation could probably be reduced by adequate calibration. In the present study, most of the patients were surgically treated for a lung cancer and only a few patients had macroscopically severe emphysema (Figure 1). It is not known whether the correspondence between CT measurements and morphometric data might be strengthened if more patients with severe emphysema could have been included in our sample. This needs to be confirmed by further investigations.

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