Pulmonary Emphysema: Objective Quantification at Multi–Detector Row CT—Comparison with Macroscopic and Microscopic Morphometry[1]

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Purpose: To prospectively compare pulmonary function tests and helical computed tomographic (CT) indexes for quantifying pulmonary emphysema with macroscopic and microscopic morphometry.

Materials and Methods: The investigation was approved by the local ethics committee, and written informed consent was obtained from patients. Multi–detector row CT of the thorax was performed with simultaneous acquisition of four 1-mm sections in 80 patients (57 men, 23 women; age range, 38–79 years) referred for surgical resection of lung cancer. From the raw data, 1.25-mm-thick sections were reconstructed at 10-mm intervals. Relative areas of lung with attenuation coefficients lower than nine thresholds and eight percentiles of the distribution of attenuation coefficients were calculated. Relative areas and percentiles were compared with areas found macroscopically to have emphysema and with two microscopic indexes assessed on resected specimens. Pulmonary function tests were measured 24–48 hours before surgery. Spearman correlation coefficients were calculated between each set of CT data obtained with the nine tested thresholds and eight percentiles with macroscopic and microscopic measurements.

Results: For relative lung areas, the strongest correlation with macroscopy was observed with a threshold of −970 HU ($r = 0.543$, $P < .001$) and that with microscopy was observed at −960 and −970 HU, depending on the index considered ($r = 0.592$, $P < .001$ and $r = -0.546$, $P < .001$, respectively). For percentiles, 1st percentile showed the strongest correlation with both macroscopy ($r = -0.463$, $P < .001$) and microscopy ($r = -0.573$, $P < .001$; and $r = 0.523$, $P < .001$ for each microscopic measurement). Forced expiratory volume in 1 second and vital capacity ratio, diffusing capacity of lung for carbon monoxide, and each of the three CT indexes were complementary to predict microscopic indexes.

Conclusion: Relative lung areas with attenuation coefficients lower than −960 or −970 HU and 1st percentile are valid indexes to quantify pulmonary emphysema on multi–detector row CT scans.

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Quantification of pulmonary emphysema in vivo is important for several reasons (1). First, accurate detection of lung destruction when it appears and careful mapping of its progression are required to understand the natural history of emphysema. Second, the treatment and the prediction of outcome of advanced disease with lung volume reduction surgery require knowledge of the location of the lesions and objective methods of assessing surgical results (2–5). Third, computed tomography (CT) could be a way of quantifying the progression of emphysema by helping determine the efficacy of replacement therapy in patients with α_1-antitrypsin deficiency (6–8). Fourth, study findings suggesting that alveolar number and surface-to-volume ratio can be restored in rats with elastase-induced emphysema by using other therapeutic measures imply a future need for measurements that can accurately help assess the effectiveness of such therapeutic interventions (9,10). Fifth, the detection of early emphysema may prevent the occurrence of obstructive ventilatory impairment with smoking cessation or medical intervention.

On CT scans, emphysema is characterized by areas of lung with reduced attenuation coefficients. Authors of several studies have investigated CT indexes derived from the frequency distribution curve of attenuation coefficients (11–16), such techniques being more accurate and more reproducible than visual methods (17). An additional advantage of CT is that it helps identify the specific location of emphysema within the lung, enabling one to target therapeutic intervention (2,18). Recently recommended by a workshop on quantitative CT in longitudinal studies of emphysema, CT is more appropriate to determine the rate of progression of emphysema in the follow-up of intervention trials than is the decline of forced expiratory volume in 1 second (FEV_1) (6).

Indexes used in incremental CT were based on the analysis of individual cross sections and consisted of measurement of the area of these sections occupied by attenuation coefficients lower than the predetermined thresholds (eg, −910, −950, or −960 HU) (13,15,19) or on arbitrarily fixed percentiles of the distribution of attenuation coefficients (eg, 5th, 12th, or 15th percentile) (7,8,14). Incremental CT scanning creates a single visual section, whereas helical CT—owing to continuous table motion—produces a more complete visual image (20). Although differences between incremental and helical CT are minimal, no study has determined which index(es) derived from helical CT would be appropriate to quantify pulmonary emphysema.

Because emphysema is defined with histopathologic criteria—an abnormal permanent enlargement of the air spaces distal to the terminal bronchioles, accompanied by destruction of the alveolar walls, and without obvious fibrosis—any new method of quantification should be validated against histopathologic references (21). The purpose of the present study was, therefore, to prospectively compare pulmonary function tests and helical CT indexes for quantifying pulmonary emphysema with macroscopic and microscopic morphometry.

Materials and Methods

Patients

This investigation was approved by the local ethics committee, and written informed consent was obtained from patients.

This prospective study included 121 consecutive patients referred between September 2001 and June 2003 to the Department of Thoracic Surgery (Hôpital Erasme) for surgical resection of a lung tumor. Thirty-one patients were not included in our research protocol because they had pneumonia ($n = 4$), pulmonary atelectasis ($n = 4$), or interstitial lung disease ($n = 3$) at admission or because they were referred for tumorectomy ($n = 20$). In addition, four patients were excluded after multi–detector row CT owing to breathing artifacts ($n = 3$) or evidence of interstitial lung disease in nontumoral parenchyma ($n = 1$). Six patients were excluded after thoracic surgery because they underwent segmentectomy, a procedure that would prevent us from fixing the lung specimen in an appropriate way for morphometric measurements.

Eighty patients (57 men, 23 women) with an age range of 38–79 years (mean, 62 years ± 10 [standard deviation]) were included in the present study. The mean interval from CT to surgery was 3 days (range, 1–7 days). The mean interval from CT to pulmonary function testing was 2 days (range, 1–6 days). Seventy-two patients underwent lobe resection and eight underwent lung resection. Eleven were nonsmokers, 19 were ex-smokers, and 50 were current smokers. On average, the current smokers smoked 39 pack-years ± 20 (range, 10–100 pack-years).

CT Examination

CT scans were obtained by using a commercially available multi–detector row scanner (Somatom Volume Zoom; Siemens Medical Systems, Forchheim, Germany) with simultaneous acquisition of four 1-mm sections. The scale of attenuation coefficients in this CT scanner ranges from −1024 to 3072 HU. The CT scanner had been calibrated periodically and after major maintenance

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Abbreviations:
D_{LCO} = diffusing capacity of lung for carbon monoxide
FEV_1 = forced expiratory volume in 1 second
RA_{970} = relative surface area with attenuation less than −970 HU
RA_{960} = relative surface area with attenuation less than −960 HU
V_A = effective alveolar volume
VC = vital capacity

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work. Patients were scanned craniocaudally during a full-inspiration breath hold. No spirometrically controlled lung volume was used because this procedure has not been shown to significantly improve the repeatability of quantitative CT in assessing the amount of emphysema (3). No patient received intravenous contrast medium. A 1-mm collimation was used at a table feed of 6 mm per 0.75-second rotation (8 mm/sec) at constant 140 kV and 80 mAs. These parameters result in a pitch of 1.5:1; the pitch was defined by Silverman et al (22) as the ratio between the table feed per rotation and the x-ray beam width. From the raw data, 1.25-mm-thick sections were reconstructed with a soft-tissue kernel (20S; Siemens Medical Systems) at 10-mm intervals. We used this interval because it has been widely used in CT studies investigating diffusely distributed lung disease.

By using the Pulmo CT program (Siemens Medical Systems), which automatically recognizes the lung and traces the lung contours, attenuation coefficients of each lung CT section were measured by a radiologist (A.M.) with 11 years of experience. From these coefficients, the relative areas of lung (expressed as percentage) with attenuation coefficients lower than thresholds ranging from −900 to −980 HU (−900, −910, −920, −930, −940, −950, −960, −970, and −980 HU) and 1st–18th percentiles (1st, 3rd, 5th, 7th, 10th, 12th, 15th, and 18th percentiles) were calculated for the lobe or the lung to be resected.

In addition, we investigated the possible influence that an associated disease such as coal worker pneumoconiosis could increase lung attenuation and therefore influence the CT quantification of pulmonary emphysema (23). In such a disease, nodules and masses tend to shift the distribution of the attenuation coefficients toward less negative coefficients, while coexistent pulmonary emphysema tends to shift this distribution toward more negative coefficients. Therefore, we used the lung tumor as a model to investigate the possible influence such diseases could have in influencing the distribution of attenuation coefficients in opposite directions. We thus compared CT indexes that were measured while the lung tumor was either included or excluded from a single CT scan containing the largest section of the tumor.

Pulmonary Function Tests

Pulmonary function tests were performed with the patient seated. Vital capacity (VC) and FEV_1 were measured with a Lilly-type pneumotachograph (Jaeger, Höchberg, Germany), while functional residual capacity was measured by using a constant-volume body plethysmograph (Zan; Oberthulba, Würzburg, Germany). Total lung capacity and residual volume were calculated by using the values of functional residual capacity and the subdivisions of VC. The effective alveolar volume (V_A) and the diffusing capacity of lung for carbon monoxide (D_{LCO}) were measured by using the single-breath method (Zan; Oberthulba, Würzburg, Germany). The measured values were then compared with the predicted values established by the European Respiratory Society (24,25). Pulmonary function tests were performed 24–48 hours before surgery.

Macroscopic Quantification of Emphysema

Immediately after surgery, the resected lobes and lungs were inflated with 10% buffered formalin at a constant distending pressure of 25 cm of water for 12 hours and were immersed in the same solution of formalin for an additional 24 hours. By using a modified Gough-Wentworth technique, two 1-mm-thick vertical whole-lung sections were obtained from the fixed specimen (26). The sections were cut by pathologists who were blinded to the quantitative CT results about the remaining nontumoral lung parenchyma and were mounted (A.M.) between two transparency films for plain paper copiers (3M, St Paul, Minn), digitized (Hewlett Packard Scan Jet 6100C/T, Palo Alto, Calif), and stored on a personal computer by a physicist (J.Z.) with more than 10 years of experience regarding lung pathology measurements and who was blinded to the quantitative CT results. The area macroscopically occupied by emphysema was measured on these sections by using a computer-assisted method that had been previously validated (26). For both lung sections, the number of pixels that corresponded to low densitometry readings and to the total lung area were counted separately with use of an image analyzer system (KS400; Carl Zeiss Vision, Hallbergmaas, Germany). The image threshold was selected by the operator so that the highest gray levels corresponded to emphysematous spaces and lower gray levels corresponded to the lung structures. The relative area (expressed as a percentage) occupied by low densitometry reading corresponded to the pathologic extent of macroscopic emphysema. Since this part of our study started in November 2001, only 69 of 80 specimens were investigated.

Microscopic Quantification of Emphysema

Material for microscopic quantification consisted of 18 samples obtained from the nontumoral lung parenchyma by using a 2.5 × 2 cm template. To obtain representative samples of the lung specimen, two tissue samples were obtained by our pathologists from each of the nine regions selected in the lung specimen by dividing the specimen along the cephalocaudal direction in upper, middle, and lower zones and along the horizontal direction in central, middle, and peripheral zones. After dehydration, the blocks were then embedded in paraffin before being cut into 5-μm-thick sections and stained with Masson trichrome. The perimeter of alveoli and alveolar ducts was measured with an image analyzer system (KS400; Carl Zeiss Vision). Lung sections were observed at ×25 magnification by using a microscope connected to a high-resolution video camera. From each lung section, two microscopic fields were digitized, displayed on a color monitor (512 × 512 pixels), and stored on a personal computer by a physicist (J.Z.). With the optical system used, each field measured 4.293 mm^2. If bronchus was present in a field, another field was considered. After establishing the image threshold, the total perimeter of alveoli

and alveolar ducts in the field was measured with a computer.

As a second step, distances between intersections of alveolar and duct walls and seven horizontal lines arbitrarily drawn by the computer were automatically measured with the image analyzer. These "interwall" distance values reflect the diameter of the alveoli and of the alveolar ducts. Perimeters and interwall distances were measured on 36 fields; 35 having been recommended by Gould et al (14). From the measurements obtained from one lung specimen, the mean perimeter per field and the mean interwall distance were calculated. These results originally expressed in pixels were converted to micrometers (with the optical system used, one pixel corresponded to 3.205 μm).

The mean perimeter per field and the mean interwall distance calculated from the histologic slides must be corrected for shrinkage and distortion produced by processing and cutting tissue, mainly due to dehydration (27). The shrinkage factor is determined by measuring the size of the blocks of tissue prior to processing and then measuring the size of the cut sections after processing. Final measurements of the shrunken tissue section can be made by dividing the mean area of stained tissue (length × width, expressed in square centimeters) by the total area of the template (5 cm^2) and then by calculating the square root of this ratio. Mean interwall distance and mean perimeter per field were corrected for shrinkage by dividing the values by the geometric mean of the 18 shrinkage factors from each patient.

Statistical Analysis

Relative areas of lung with attenuation coefficients lower than each considered threshold and each percentile were compared with macroscopic and microscopic quantitative indexes.

We calculated Spearman correlation coefficients between each set of CT data obtained with the nine tested thresholds and eight percentiles with mean interwall distance and mean perimeter per field—the higher this coefficient (for a given set of data), the more accurate the threshold in quantifying emphysema. Statistical significance was defined as a *P* value of less than .05. Statistical software (SPSS for Windows, release 12.0; SPSS, Chicago, Ill) was used.

In a second step, and to determine the performance of multi–detector row CT in quantifying early pulmonary emphysema, we restricted our study sample to a subset of patients with less than 5% of the surface area of the macroscopic lung section involved by emphysema.

We evaluated the potential added value of the most accurate threshold and the most accurate percentile and pulmonary function test in predicting microscopic indexes. Two sets of stepwise multiple regressions (with mean perimeter per field as dependent variables) were performed: first with all pulmonary function test measurements and the relative area of lung with attenuation coefficients lower than the most accurate threshold and then with all pulmonary function test measurements and the most accurate percentile as explicative variables. The same analysis was also performed with the mean interwall distance as dependent variable.

Table 1

Spearman Correlation Coefficients between Relative Areas of Lung with Attenuation Coefficients Lower than Various Thresholds and Microscopic and Macroscopic Measurements

Threshold (HU)	MIWD		MP		Macroscopic Measurement	
	r Value	*P* Value	*r* Value	*P* Value	*r* Value	*P* Value
−900	0.398	<.001	−0.354	<.001	0.175	<.151
−910	0.435	<.001	−0.385	<.001	0.215	<.076
−920	0.481	<.001	−0.425	<.001	0.263	<.029
−930	0.516	<.001	−0.457	<.001	0.325	<.006
−940	0.564	<.001	−0.503	<.001	0.397	<.001
−950	0.584	<.001	−0.527	<.001	0.450	<.001
−960	0.592	<.001	−0.543	<.001	0.465	<.001
−970	0.584	<.001	−0.546	<.001	0.543	<.001
−980	0.582	<.001	−0.543	<.001	0.495	<.001

Note.—MIWD = mean interwall distance, MP = mean perimeter per field.

Results

The mean percentage area of lung macroscopically occupied by emphysema was 7.05% ± 7.94 (range, 0.17%–30.94%). The mean interwall distance was 204 μm ± 51 (range, 146–407 μm). The mean perimeter per field was 20 μm/mm^2 ± 4 (range, 10–29 μm/mm^2). Spearman correlation coefficients between the macroscopic extent and the microscopic indexes were 0.625 and −0.662, respectively, for mean interwall distance and mean perimeter per field, which were significant correlations ($P <$ .001). The Spearman correlation coefficient between the two microscopic indexes was −0.947, which also was significant ($P <$ .001).

Thresholds

Spearman correlation coefficients between the relative areas of lung with attenuation coefficients lower than the nine tested thresholds and histopathologic measurements are listed in Table 1. Depending on the macroscopic or microscopic measurements, the highest correlation coefficients were obtained for −970 and −960 HU. The relationship between relative surface area with attenuation less than −970 HU (RA_{970}) and macroscopic measurement is illustrated in Figure 1. The relationship between relative surface area with attenuation less than −960 HU (RA_{960}) and mean interwall distance is illustrated in Figure 2.

In patients with less than 5% of macroscopic emphysema (n = 39), the

mean percentage of lung macroscopically occupied by emphysema was 2.14% ± 1.37 (range, 0.17%–4.71%). Correlation coefficients between RA_{960} and either mean interwall distance or mean perimeter per field calculated for the lobe or the lung to be resected were both significant ($r = 0.397$, $P = .012$ for mean interwall distance; $r = -0.365$, $P = .023$ for mean perimeter per field). Correlation coefficients between RA_{970} and either mean interwall distance or mean perimeter per field calculated for the lobe or the lung to be resected were both significant ($r = 0.388$, $P = .015$ for mean interwall distance; $r = -0.380$, $P = .017$ for mean perimeter per field).

Percentiles

Spearman correlation coefficients between the eight tested percentiles and the macroscopic and microscopic measurements (Table 2) showed that the highest coefficient was obtained for the 1st percentile ($r = -0.463$, $P < .001$ for macroscopic measurements; $r = -0.573$, $P < .001$ and $r = 0.523$, $P < .001$ for mean interwall distance and mean perimeter per field, respectively). The mean 1st percentile was −965 HU ± 27 (range, −1019 to −896 HU). The relationship between the 1st percentile and macroscopic measurements of emphysema is illustrated in Figure 3. The relationship between the 1st percentile and mean interwall distance is illustrated in Figure 4.

When the study sample was restricted to patients with less than 5% of macroscopic emphysema, Spearman correlation coefficients between the 1st percentile and either mean interwall distance or mean perimeter per field were significant ($r = -0.372$, $P = .02$; $r = 0.331$, $P = .04$).

Influence of Positive Attenuation Coefficients on CT Pulmonary Indexes

The mean percentage area of lung occupied by the tumor on the CT lung section was 11% ± 9 (range, 0.71%–38.64%). Mean values and statistical significance of the differences in RA_{960}, RA_{970}, and 1st percentile calculated with and without the tumor are summarized in Table 3.

Figure 1

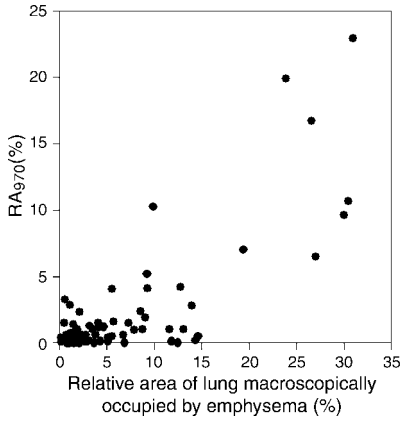

Figure 1: Graph illustrates correlation between RA_{970} and macroscopic emphysema, which was the strongest correlation ($r = 0.543$, $P < .001$).

Figure 2

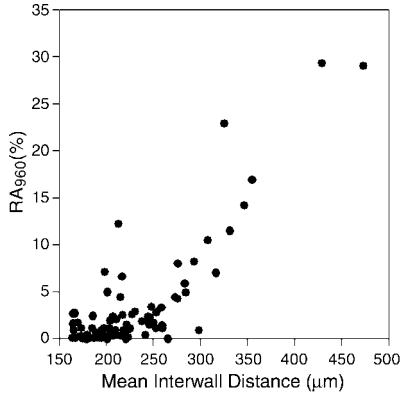

Figure 2: Graph illustrates correlation between RA_{960} and mean interwall distance, which was the strongest correlation ($r = 0.592$, $P < .001$).

Table 2

Spearman Correlation Coefficients between Percentiles and Microscopic and Macroscopic Measurements

	MIWD		MP		Macroscopic Measurement	
Percentile	*r* Value	*P* Value	*r* Value	*P* Value	*r* Value	*P* Value
1st	−0.573	<.001	0.523	<.001	−0.463	<.001
3rd	−0.567	<.001	0.502	<.001	−0.412	<.001
5th	−0.559	<.001	0.492	<.001	−0.394	<.001
7th	−0.551	<.001	0.482	<.001	−0.373	<.002
10th	−0.527	<.001	0.458	<.001	−0.344	<.004
12th	−0.513	<.001	0.444	<.001	−0.318	<.008
15th	−0.498	<.001	0.430	<.001	−0.299	<.013
18th	−0.479	<.001	0.405	<.001	−0.277	<.021

Note.—MIWD = mean interwall distance, MP = mean perimeter per field.

Comparisons with Pulmonary Function Test

Since the pulmonary function test allows investigation of both lungs, RA_{960}, RA_{970}, and 1st percentile were recalculated and measured for both lungs together. On average for both lungs, RA_{960} was calculated to be 3.51% ± 5.37 (range, 0.04–32.09%), RA_{970} was calculated to be 2.14% ± 3.87 (range, 0.02%–24.50%), and 1st percentile was −968 HU ± 23 (range, −1019 to −909 HU). Significant correlations between CT indexes calculated for the lobe or the lung to be resected and for both lungs together were obtained for RA_{960} ($r = 0.897$, $P < .001$), RA_{970} ($r = 0.905$, $P < .001$), and 1st percentile ($r = 0.917$, $P < .001$). Correlation coefficients between the pulmonary function test and macroscopic and microscopic measurements are listed in Table 4.

To determine whether CT provides any added value over that of a pulmonary function test, we first considered the mean interwall distance as the measurement of reference. Stepwise multiple regressions showed that RA_{960} was the most highly correlated variable ($r = 0.766$), with DLCO/VA yielding a small but significant additional contribution (multiple $r = 0.850$). The correspond-

ing relationship can be described as follows: mean interwall distance equals 272 + 6.44(RA_{960}) − 1.07(DLCO/VA).

For the most accurate percentile, stepwise multiple regressions showed that DLCO/VA was the most highly correlated variable (r = 0.629), and 1st percentile (and then FEV_1/VC) yielded small but significant additional contributions (multiple r = 0.711 and 0.758). The corresponding relationship can be described as follows: mean interwall distance equals −276 − 1.01(DLCO/VA) − 0.67(1st percentile) − 0.8(FEV_1/VC).

Second, we then considered mean perimeter per field as the measurement of reference. Stepwise multiple regressions showed that DLCO/VA was the most highly correlated variable (r = 0.650), with RA_{970} (and then FEV_1) yielding small but significant additional contributions (multiple r = 0.735 and 0.759). The corresponding relationship can be described as follows: mean perimeter per field equals 11.27 + 0.10(DLCO/VA) − 0.32(RA_{970}) + 0.04(FEV_1).

For the 1st percentile (the most accurate percentile), stepwise multiple regressions showed that DLCO/VA was the most highly correlated variable (r = 0.665), with FEV_1/VC yielding a small but significant additional contribution (multiple r = 0.729); the 1st percentile, however, did not yield significant contribution. The corresponding relationship can be described as follows: mean perimeter per field equals 5.94 + 0.10 DLCO/VA + 0.79 FEV_1/VC.

Discussion

Findings of this study show that *(a)* RA_{960}, RA_{970}, and the 1st percentile best reflect the extent of pulmonary emphysema on 1.25-mm-thick CT sections, although other cutoffs, except the percentage area with attenuation lower than −910 and −900 HU, also showed significant correlations with pathologic reference standards; *(b)* even if significant, an associated disease that might shift the distribution of attenuation coefficients toward less negative values does not substantially flaw these measurements; and *(c)* CT and a pulmonary

Figure 3

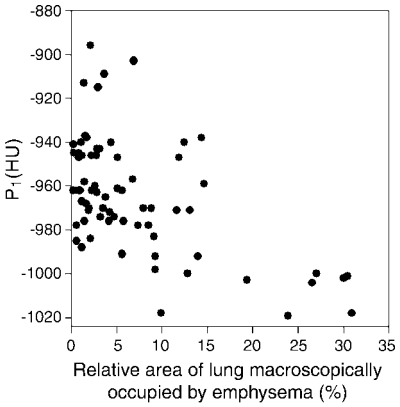

Figure 3: Graph illustrates correlation between the 1st percentile (P_1) of the distribution of attenuation coefficients that had the strongest correlation with macroscopic emphysema (r = −0.463, P < .001).

Figure 4

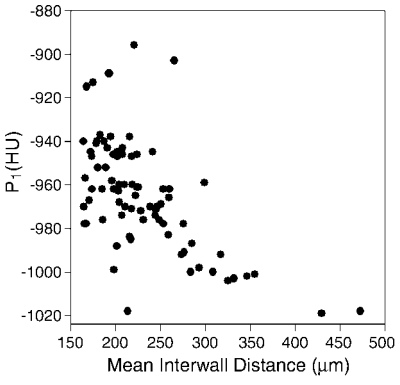

Figure 4: Graph illustrates correlation between the 1st percentile (P_1) of the distribution of attenuation coefficients that had the strongest correlation with the mean interwall distance (r = −0.573, P < .001).

Table 3

Influence of Attenuation Coefficients on CT Indexes

CT Index	Mean with Exclusion of Tumor	Mean with Inclusion of Tumor	Percentage Difference of Mean	*P* Value*
1st percentile (HU)	−975 ± 28	−975 ± 29	0.0	.549
RA_{960} (%)	5.24 ± 6.98	4.74 ± 6.02	0.5	.004
RA_{970} (%)	3.37 ± 5.19	3.05 ± 4.46	0.3	.010

* Wilcoxon test.

Table 4

Summary of Pulmonary Function Data and Correlations with Microscopic and Macroscopic Measurements

Pulmonary Function Data (%)*	Mean ± SD†	MIWD		MP		Lung Area‡	
		r Value	*P* Value	*r* Value	*P* Value	*r* Value	*P* Value
VC	87 ± 15 (56–133)	−0.62	<.591	0.52	<.653	−0.99	<.428
TLC	103 ± 18 (62–195)	0.320	<.004	−0.310	<.006	0.133	<.283
FRC	120 ± 28 (57–198)	0.584	<.001	−0.556	<.001	0.335	<.006
RV	135 ± 37 (63–250)	0.404	<.001	−0.409	<.001	0.223	<.069
FEV_1	79 ± 22 (34–135)	−0.420	<.001	0.426	<.001	−0.465	<.001
FEV_1/VC	95 ± 17 (46–129)	−0.555	<.001	0.588	<.001	−0.606	<.001
DLCO	66 ± 21 (26–119)	−0.600	<.001	0.653	<.001	−0.502	<.001
DLCO/VA	61 ± 19 (25–106)	−0.633	<.001	0.675	<.001	−0.485	<.001

Note.—FRC = functional residual capacity, MIWD = mean interwall distance, MP = mean perimeter per field, RV = residual volume, SD = standard deviation, TLC = total lung capacity.

* Expressed as percentage of predicted values established by the European Respiratory Society (24,25).

† Data in parentheses are the range.

‡ Percentage area of lung macroscopically occupied by emphysema.

function test are complementary to predict microscopic measurements of pulmonary emphysema.

When microscopic measurements are considered as references, −960 and −970 HU yield the strongest correlations with the mean interwall distance and mean perimeter per field, although the correlation coefficients concerning other thresholds are not significantly different. For example, correlations are also significant with −950 HU, a threshold previously proposed by Gevenois et al (15,16) for incremental thin-section CT. Although these authors reported stronger correlations with microscopic measurements than we did, this difference could be explained, at least in part, by several methodological aspects. First, Gevenois et al used parametric correlation tests, whereas we used nonparametric tests on account of the skewed distribution of our data. Second, Gevenois et al used 225 mAs and a high-frequency algorithm, whereas we used 80 mAs and soft-tissue kernel—two differences that could influence the signal-to-noise ratio and the contrast resolution (20). Such differences could also explain why we did not find −910 HU to be significantly correlated with the macroscopic measurement, as did Müller et al (13). Moreover, Müller et al used 1-cm-thick sections after contrast material injection.

Various percentiles have been proposed and were used in previous studies (7,8,14), but only the 5th percentile has been validated through correlation with microscopic measurements reflecting the diameter of distal air spaces (14). In addition to the percentage surface area occupied by attenuation coefficients lower than a particular threshold, we also investigated relationships between percentiles ranging from 1st to 18th and histopathologic measurements. These percentiles were significantly correlated with macroscopic and microscopic measurements. The strongest correlation observed, however, was the 1st percentile that, as a mean, corresponds to −965 HU—a value logically lying between the two most accurate thresholds: −960 HU (determined with mean interwall distance) and −970 HU (determined with macroscopic measurements). Since correlation becomes progressively stronger as percentiles become lower, percentiles lower than the 1st would probably show an even stronger correlation with histopathologic measurements. Nevertheless, we restricted the correlations to the 1st percentile to avoid noninteger percentile values.

Percentiles depend, per se, on the proportion of negative attenuation coefficients that are related to the air content of the lungs and positive attenuation coefficients that are related to blood vessels, airway walls, and/or infiltration of the lung parenchyma. As shown by Hartley et al (23) and Rienmüller et al (28), infiltrative lung disorders displace the distribution curve of attenuation coefficients toward positive values. Therefore, we investigated this influence on RA_{960}, RA_{970}, and the 1st percentile by measuring these values while including and excluding the lung tumor within the region of interest. No significant difference was shown for the 1st percentile. However, for RA_{960} and RA_{970}, statistically significant differences were found (0.5% and 0.3%, respectively) but were not clinically relevant.

Since correlations were significant between CT indexes (RA_{960}, RA_{970}, and 1st percentile) and microscopic measurements and between pulmonary function tests and microscopic measurements, it was interesting to investigate the possible complementary roles of these parameters in quantifying pulmonary emphysema. Depending on the microscopic reference considered (mean interwall distance or mean perimeter per field), stepwise multiple regressions suggest that DLCO/VA, RA_{960} or RA_{970}, and FEV_1/VC are complementary. Curiously, the 1st percentile yields a significant additional contribution to predict the mean interwall distance but the mean perimeter per field does not. This could be related to the use of stepwise analysis, which eliminates one variable from the final relationship when two variables are strongly linked. Although not significantly different, the stronger correlation between 1st percentile and mean interwall distance versus 1st percentile and mean perimeter per field ($r = -0.573$ and 0.523, respectively) and the stronger correlation between DLCO/VA and mean perimeter per field versus DLCO/VA and mean interwall distance ($r = 0.675$ and −0.633, respectively) could explain why 1st percentile was eliminated from the final relationship.

Our study had limitations. The first limitation consisted of the fact that in this prospective study, all patients were surgically treated for lung cancer and only few had very severe pulmonary emphysema. It is not known whether the correspondence between CT measurements and morphometric data might have been strengthened if a higher proportion of patients with severe emphysema had been included. Nevertheless, we investigated correlations between CT data and microscopic measurements in patients with a macroscopic extent of emphysema lower than 5%. Even if weaker, correlations were still statistically significant, which suggests that the lower limit for quantification of pulmonary emphysema at multi–detector row CT approximates 5% of the lung surface area.

A second limitation concerns macroscopic sampling. Since it was decided to obtain macroscopic specimens after we had begun the study with microscopic samples, the number of patients with macroscopic measurements was lower than that with microscopic measurements. Moreover, we considered two macroscopic sections that were mainly dependent on the available nontumoral lung parenchyma and could therefore not be perfectly representative of the whole lung parenchyma. However, to consider the cephalocaudal gradient in the distribution of pulmonary emphysema, these sections were obtained vertically (27).

A third limitation was how our CT indexes were selected. However, while the interval of 10 HU between each threshold was chosen arbitrary, all thresholds reported in the literature (13,15,16,19) were taken into account. Likewise, the percentiles were also arbitrarily determined, but all values re-

ported in the literature (7,8,14) were also taken into account for our study.

A fourth limitation could arise from the fact that the multiple regression statistical procedure requires the variables to be normally distributed. Since these constraints are actually not satisfied, this entails that the reported *P* values must be interpreted with caution.

In conclusion, findings of the present study show that RA_{960}, RA_{970}, and the 1st percentile do indeed reflect the extent of pulmonary emphysema on multi–detector row CT scans, although other cutoffs, except the percentage area with attenuation lower than −910 HU and −900 HU, showed also statistically significant correlations with pathologic references. Furthermore, they are complementary to two particular pulmonary function tests, DLCO/VA and FEV_1/VC. Because the 1st percentile corresponds to −965 HU, this threshold could be recommended to quantify the extent of pulmonary emphysema. Finally, associated diseases likely to increase lung attenuation do not appear to influence these parameters.

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