Eur Respir J, 1995, 5, 843–848
DOI: 10.1183/09031936.95.08050843
Printed in UK - all rights reserved

European Respiratory Journal
ISSN 0903 - 1936

REVIEW

Can computed tomography quantify pulmonary emphysema?

P.A. Gevenois*, J.C. Yernault**

Can computed tomography quantify pulmonary emphysema? P.A. Gevenois, J.C. Yernault. ©ERS Journals Ltd 1995.

ABSTRACT: In the last decade, several studies have suggested the possible role of computed tomography (CT) in the detection and the quantification of pulmonary emphysema. In order to verify whether this new method is adequately validated, this article gives an overview of these studies.

The review shows that most of the studies used conventional CT and were based on visual scoring. Only a few were based on high resolution CT (HRCT) or concerned objective measurements of computed density. In addition, only a few studies included normal subjects and distinguished centrilobular from panlobular emphysema. The number of scans obtained in each study is extremely variable, whilst the minimum number necessary to provide accurate results remains unknown.

Recently, automatic objective procedures which are truly quantitative and are applicable to HRCT have been made available. They should take the place of subjective scoring methods but further studies, based on macroscopic as well as on microscopic comparisons, are needed to validate and to standardize these techniques. *Eur Respir J., 1995, 5, 843–848.*

Depts of *Radiology and **Chest Medicine, Hôpital Erasme, Université Libre de Bruxelles, Belgium.

Correspondence: P.A. Gevenois
Dept of Radiology
Hôpital Erasme
Route de Lennik 808
1070 Brussels
Belgium

Keywords: Computed tomography
diagnosis of emphysema
emphysema

Received: September 7 1994
Accepted after revision January 16 1995

Chronic obstructive pulmonary disease (COPD), including emphysema, remains a major medical and social problem. As recently emphasized by SNIDER [1], "in many ways, emphysema is to the pulmonologist of the last half of the twentieth century what tuberculosis was to the pulmonologist of the first half of the twentieth century". Epidemiological studies have clearly identified tobacco smoking, socioeconomic status and occupational pollutant exposure as main risk factors for morbidity and mortality from COPD, but these studies have not usually differentiated emphysema from the other components of COPD. As opposed to chronic bronchitis and asthma, the definition of emphysema is based on pathology as a "condition of the lung characterized by abnormal, permanent enlargement of airspaces distal to the terminal bronchioles, accompanied by destruction of their walls, without obvious fibrosis" [2]. Consequently, the diagnosis of emphysema during life, without the availability of lung tissue, is always indirect. The accuracy of the clinical diagnosis is very low, conventional chest radiography is of proven but limited value [3], and the insensitivity of pulmonary function tests to diagnose mild degrees of emphysema is well-documented [4]. So far, clinical, pathophysiological and epidemiological studies would be greatly helped by noninvasive but accurate *in vivo* assessments of emphysema in which computed tomography (CT) could play a role.

In the last decade, several studies have shown correlations between visual grading, as well as objective measurements of attenuation values and various pathological data. On the other hand, high resolution computed tomography (HRCT) has been shown to be superior to conventional CT in evaluating chronic interstitial lung disorders [5], and recently, in several pathophysiological studies, pathology assessment of emphysema has been replaced by HRCT data [6–8]. Nevertheless, before replacing pathology by HRCT, its validity must be proved. In order to verify whether this new method is adequately validated and to suggest possible directions for further studies, this article provides an overview of the previously published studies that were based on quite different methods (Table 1).

In 1982, GODDARD *et al.* [9] compared normal volunteers with patients who had irreversible chronic airflow limitation. They assessed the emphysema by a visual CT scoring method as well as by calculating the mean lung density, but they found a poor correlation (r=0.34) between these two measurements. Nevertheless, the lowest mean density was found to be significantly lower in patients than in normal volunteers. In addition, dividing the study population into two groups according to the CT visual score, they found a significant impairment of forced expiratory volume in one second (FEV_1), FEV_1/vital capacity(VC), transfer factor of the lung for carbon monoxide ($T_{L,CO}$) and $T_{L,CO}$/alveolar volume (V_A) in the group with a CT score greater than 30. Whilst no pathological definition of emphysema was taken into account, the results of this first study suggested a possible role for CT in diagnosis and quantification of emphysema.

In 1984, HAYHURST *et al.* [10] performed the first pathologic-CT comparative study and showed that the cumulative

Table 1. – Methods

First Author [Ref.]	Subject n		Computed tomography						Pathology		
			Scanners	Slice thickness mm	Contrast medium	Slices n	Respiratory level	CT quantification	Macroscopy	Macroscopic quantification	Microscopy
GODDARD [9]	48	COPD	?	10	?	8	Arrested inspiration	Visual scoring, mean density	0	0	0
HAYHURST [10]	11	SPN	EMI 5005	10	?	2	Slightly above FRC	Frequency distribution of EMI numbers	Midsagittal slice	Counting emphysematous spaces	0
FOSTER [11]	25	PM	GE T-8800	10	No	Apex-diaphragm	?	Visual scoring	Horizontal slices	Point-counting	0
BERGIN [12]	32	SPN	Picker Syner-view 600	10	Yes	Apex-diaphragm	TLC	Visual scoring	Midsagittal slice	Grading	0
HRUBAN [13]	20	PM	Siemens DR3	2	No	5	*in vitro*	Visual scoring	Horizontal slices	Grading	0
MILLER [14]	38	SPN	GE 9800	1.5 & 10	Yes	1	Deep inspiration	Grid	Horizontal slice	Point-counting and grading	0
KUWANO [15]	42	SPN	Toshiba	1 & 5	Yes	5	?	Visual scoring slices	Horizontal	Grading	DI
MÜLLER [16]	28	SPN	GE 9800	10	Yes	1	Deep inspiration	Density mask	Horizontal slice	Grading	0
GOULD [17]	28	SPN	EMI 5005	13	No	2	Within 500 ml of TLC	Lowest 5th centile of pixel distribution	Midsagittal slice	Calc area of emphysematous space	AWUV
SPOUGE [18]	15	SPN & LT	GE 9800	1.5 & 10	?	?	?	Visual scoring	Horizontal slices	Grading	0

PM: postmortem; COPD: chronic obstructive pulmonary disease; SPN: surgery for solitary pulmonary nodule; GE: General Electric® ;FRC: functional residual capacity; TLC: total lung capacity; DI: destructive index; AWUV: surface area of the walls of distal airspaces per unit of lung volume ; LT: lung transplantation. calc: calculated.

frequency distribution curve of EMI units within the lung fields of a group of six patients with mild centrilobular emphysema differed significantly from those of a group of five patients without emphysema, more pixels being in the EMI range -450 to -500 in the emphysematous group. In this study, CT attenuation values were expressed in EMI units that can be easily transformed into Hounsfield units (HU), both scales representing radiographic attenuation of tissue relative to that of water, scaled by a factor of either 500 (EMI) or 1,000 (Hounsfield). In these 11 subjects, the cumulative frequency distribution of attenuation numbers in the lung fields was measured on only two horizontal slices through the upper zone of the lungs, 1 and 6 cm below the sternal notch. After resection, the lobes or the lungs were fixed in inflation with formol saline, sliced sagittally, and examined macroscopically by counting the number of centrilobular emphysematous spaces >0.75 mm in diameter in the upper third of the slice of the upper lobe. It was assumed that two CT scans were sufficient for comparison with one vertical slice. This second study reinforced the possible role of CT, but during subsequent years, this method based on attenuation values was not developed until recently, when automatic evaluation procedures were made available; meanwhile, many studies remained based on visual scoring.

Visual scoring of CT needs a definition of the value of the signs used. In 1986, FOSTER *et al.* [11] evaluated the following signs: nonperipheral low-attenuation areas, peripheral low-attenuation areas, pulmonary vascular pruning, pulmonary vascular distortion, and visual density gradient. These authors compared CT visual scoring of each sign with the extent of centrilobular emphysema measured by point counting; the diagnosis of centrilobular emphysema being based on nonuniform lung destruction assessed on gross lung sections. The sign that correlated best with the presence and the severity of centrilobular emphysema was the nonperipheral low-attenuation area, with a sensitivity and a specificity calculated at 87 and 80%, respectively. Using this sign, emphysematous lungs were consistently distinguishable from normal lungs, except in a mild-pathology subgroup.

In 1987, BERGIN *et al.* [12] compared visual CT scores with midsagittal sections of the lung, graded using a modification of the picture-grading system of THURLBECK *et al*. [19] and PARÉ *et al*. [20]. Contiguous 10 mm thick CT slices were assessed individually, and the right and the left lungs were graded separately according to the percentage area that demonstrated changes suggestive of emphysema [12]. A total CT score was calculated for both lungs, as well as for the individual lobe that had to be resected. Immediately after surgery, the resected lobe was inflated with fixative at a distending pressure of 25–30 cm water. Midsagittal sections of the lung were graded using the picture grading system and compared with CT scores. On the basis of significant correlations between macroscopic emphysema grades and CT visual scores, the authors concluded that CT is a useful adjunct in assessing the presence and severity of emphysema.

With an increased spatial resolution, HRCT is definitely superior to conventional CT in evaluating lung parenchymal disorders, such as diffuse interstitial disease [5]. In 1987, HRUBAN *et al.* [13] used HRCT in the field of emphysema, and compared CT data to post-mortem lung specimens fixed by a method that allows direct one-to-one pathologic-radiologic correlations [21]. Each lung was scanned at five levels, and the degree of centrilobular emphysema was scored on each scan by comparing the destructive changes to the grading panel of parasagittal standards established by THURLBECK *et al.* [19]. After fixation, the cut surface of the lung sectioned along the plane of the HRCT scan was assessed pathologically by scoring against the same grading panel. In this visual-scoring based study, the panel of standards established on parasagittal sections was used on horizontal CT sections and on transverse lung. This problem was said to be overcome by mentally averaging and reconstructing each set of CT images and each set of cut sections into a three-dimensional image of the lung. The authors claimed that, in this manner, they were able to apply their axial images and cross-sections to the parasagittal panel of THURLBECK *et al*. [19]. However, no study has validated the comparison of horizontal slices, obtained either by CT or by section of the fixed lung specimen, against the parasagittal sections of the panel. Nevertheless, this study suggested that HRCT is able to distinguish normal lungs from emphysematous lungs, to detect even the mildest degrees of centrilobular emphysema, and by using visual scores to grade accurately the degree of centrilobular emphysema [13].

On the other hand, in a one-to-one pathologic-CT comparative study, MILLER *et al.* [14] found CT to be insensitive in detecting the earliest lesions of emphysema because most lesions less than 0.5 cm in diameter were missed. These authors compared: 1) grid and panel-grading methods for the purpose of CT-pathological correlation; and 2) 10 and 1.5 mm collimation images with corresponding slices of pathological specimens cut in the same plane. The diagnosis of emphysema on CT was based on the presence of areas of low attenuation. Extent of emphysema on CT was assessed by superimposing a grid with squares corresponding to 1 cm^2 on the CT images and determining the percentage of squares containing emphysema. Severity of emphysema was assessed by estimating the average relative area of destruction of each abnormal 1 cm square. The CT score was obtained by multiplying extent by the average severity grade. For pathological assessment, the lungs were inflated with Bouin's fixative transpleurally using a large-bore syringe, and sectioned transversely in the orientation of the CT scans. As mentioned for the study of HRUBAN *et al.* [13], mental adjustments were required to apply the grading panel to horizontal images [19]. A good correlation was found between the CT score and the pathological score (r=0.81) with the grading panel, but a lower correlation (r=0.70) with the grid system. The CT-pathological correlation was 0.81 with the use of 10 mm collimation scans, and 0.85 with the use of 1.5 mm collimation scans. Nevertheless, the lesions of emphysema less than 0.5 cm in diameter were missed, and close comparison of CT scores and pathological grid scores showed that CT consistently underestimated mild and moderate emphysema. Consequently, these authors concluded that CT is insensitive in detecting the earliest stage of the disease [14].

In a population of mildly emphysematous patients, KUWANO *et al.* [15] used HRCT for comparisons with pathology. HRCT scans were examined for destructive changes, characterized by low-attenuation areas and disruption of the vascular pattern, and individually assessed using the grading panel of THURLBECK *et al.* [19]. The mean score for five HRCT scans was determined, and the composite mean of three observers' scores was calculated. Immediately after surgery, the resected lobe was inflated at a distending pressure of 25 cm water for 24 h, and sectioned in the same plane as the CT scans. Each section of the lobe was impregnated with barium sulphate and graded for emphysema by three independent observers. The mean of the pathology scores for the five sections was individually determined, and the composite mean of the three observers' scores was calculated. As in other previous studies, the authors have modified the grading panel so that transversally-oriented specimens could be compared with sagittally-oriented standards. KUWANO *et al.* [15] reported a significant correlation between the mean CT score and the mean pathology score (r=0.68). In addition, they quantified emphysema microscopically by using the destructive index (DI) proposed by SAETTA *et al.* [22], and found significant correlation (r=0.62) between CT score and DI. Nevertheless, as recently pointed out by MÜLLER [23], this study "did not include normal controls", and it "cannot be used to claim a high sensitivity of CT in the detection of mild emphysema".

To avoid subjectivity and subsequent within-observer and between-observer discrepancies in the reading of CT scans, MÜLLER *et al.* [16] have used a CT programme that highlights voxels within a given density range and automatically gives the area occupied by the highlighted pixels. In their study, a single representative CT image, obtained with 1 cm collimation and after injection of contrast material, was compared to the corresponding macroscopic section of fixed lung cut in the same plane as the CT. As previously detailed, the pathological scores were obtained using a modification of the panel of standards. A significant correlation was observed between the extent of emphysema assessed by the CT programme and the pathological grades. With this programme, the highest correlation was observed by highlighting voxels with attenuation $\leq$-910 HU. However, correlation coefficients indicate only that CT and pathology results are linked, not that percentage areas obtained by CT quantifications are equal to those obtained from pathological measurements. In the studies published by BERGIN *et al.* [12] and MÜLLER *et al.* [16], a percentage of lung area occupied by the lowest attenuation values was compared to the grading panel, but the scores provided by this ranking method do not represent the extent of lung involved by emphysema [19].

In most of the studies, quantification of emphysema was assessed by comparison of horizontal CT scans and/or cut sections of the fixed lungs against the grading panel

of THURLBECK *et al.* [19], originally established on parasagittal lung sections, this particular use requiring mental adjustment [13, 15, 16]. More importantly, grading systems are only semiquantitative. In order to overcome these problems, we have recently developed and validated an image analysis-based method that allows a quantitative measurement of the area macroscopically occupied by emphysema [24]. By using this computed method, the area of emphysema can be easily measured on paper-mounted sections obtained through a lung specimen and expressed as a percentage of the whole lung section area. These data can be compared to quantitative CT data, also expressed as percentage area [16, 25].

The minimum number of CT scans necessary to measure the extent of emphysema remains unknown, most CT studies being based on a few CT sections. Using point-counting, TURNER and WHIMSTER [26] have demonstrated that an adequate assessment of pulmonary emphysema cannot be made from one lung slice alone but, as recently pointed out by MORGAN [27], "cost and radiation exposure are likely to favour sampling techniques rather than whole lung measurements". Depending on the presence of emphysema and on its spatial distribution, the minimum number of scans providing accurate results could change from patient to patient.

All the above studies but one [15] were based on macroscopic comparisons. Recently, MCLEAN *et al.* [28] suggested that if emphysema is to be histopathologically quantified, it should be measured microscopically. In addition, GOULD and co-workers [29] showed that, in patients with bullae, the major determinant of respiratory function is the severity of the emphysema in non-bullous lung, and that the extent of the bullae has less functional importance, suggesting that the macroscopic quantification of emphysema in the parenchyma between the bullae is more important that the measurement of the extent of these bullae. Nevertheless, although emphysema is defined as abnormal, permanent enlargement of distal airspaces accompanied by destruction of their walls, there is no consensus as to what exactly is meant by "abnormal enlargement" and by "destruction". Several criteria have been suggested, including loss of alveolar surface area, mean linear intercept, fenestrae and destructive index, implying that no pathologic method is universally accepted. Consequently, it may be difficult to assess how accurate CT is in the diagnosis of emphysema if different pathologists use different microscopic criteria. Using the alveolar surface area, GOULD and co-workers [17] measured microscopically the airspace size in randomly selected, plastic-embedded histological sections taken from the inflation-fixed resected lobes or lungs, and compared these microscopic data with the EMI unit that defined the lowest fifth percentile of the frequency histogram of CT numbers calculated on pre-operative conventional CT scans obtained at 6 and 10 cm below the sternal notch. The EMI unit defining the lowest fifth percentile was correlated with the mean value of the surface area of the walls of distal airspaces per unit lung volume (AWUV) in the five 1 × 1 mm microscopic fields with the lowest AWUV values. Despite several limitations in the CT method, these authors concluded that the CT scan can quantify mild-to-moderate emphysema. Using 13 mm thick slices, small emphysematous lesions are superimposed with lung structures and, because of volume averaging, are undetectable [5]. In addition, the time needed for each scan slice was 17 s. During such a long scanning time, motion artefacts could impair the image quality and, subsequently, the attenuation numbers. Moreover, the EMI units that define the lowest fifth percentile are not only determined by emphysema but also by the relative amounts of higher densities. This number is, therefore, potentially influenced by associated disorders. As shown by RIENMÜLLER *et al.* [30] and more recently by HARTLEY *et al.* [31], the histogram of frequencies is modified and displaced to the right in the presence of infiltrative disorders. Consequently, if an associated disease coexists with emphysema (*i.e.* pneumoconiosis), the lowest fifth percentile will be modified and emphysema subsequently underestimated. To overcome this limitation, the relative area occupied by the range of the most significant lowest attenuation values should be given [16].

Only few studies have distinguished centrilobular from panlobular emphysema. MILLER *et al.* [14] compared HRCT with corresponding sections of pathological specimens cut in the same plane. Using a grid system numerically expressing extent and severity of emphysema, they found very poor correlation in four cases of panlobular emphysema. More recently, SPOUGE *et al.* [18] have evaluated the ability to assess the presence and the extent of panlobular emphysema with CT. These authors visually assessed the severity of panlobular emphysema on CT and on inflated pathological specimens cut in the transverse plane at the same level as the CT scan. On CT, panlobular emphysema was identified by the presence of decreased parenchymal attenuation and diminished vascularity, and the extent was assessed on a scale from 0 to 100% of involvement. On the pathological sections, the severity was assessed by using a modification of the grading panel of THURLBECK *et al.* [19]. Significant correlations were found between the pathological grade and the extent assessed on conventional CT ($r=0.90$; $p<0.01$) as well as on HRCT ($r=0.96$; $p<0.01$). However, because of the uniform involvement of the lung in panlobular emphysema, the presence and the extent of the disease were underestimated by both CT techniques, and mild-to-moderate forms were missed.

Finally, only two studies have included normal subjects, but none of them have considered the ageing of the lung [14, 16]. GILLOOLY and LAMB [32] have shown that there is a normal linear increase in airspace size associated with advancing age in adult lungs of lifelong nonsmokers, and they have proposed that only lungs with a mean airspace size, expressed as AWUV, below the 95% prediction limit of the regression line should be considered as having emphysema. More recently, preliminary data from MOUDGIL *et al.* [33] showed that CT lung density decreases with age, suggesting that normal CT values must be established.

In summary, this review suggests the possible role of CT in the diagnosis and quantification of emphysema, but reveals that: 1) the vast majority of the published

studies have attempted to measure macroscopic emphysema and have shown that a visual scoring system on CT scan correlates with a visual scoring system for macroscopic emphysema; 2) most of these studies have concerned centrilobular emphysema and only few have distinguished centrilobular from panlobular emphysema; 3) no study was based on objective CT quantification of emphysema applied to HRCT; 4) no study was based on a sufficient number of CT scans performed *in vivo* in a predetermined volume of lung and secondarily compared with the pathological extent of emphysema established on a set of sections obtained from the same lung specimen; 5) no study has defined the minimum number of scans necessary to provide accurate results; 6) no study has taken into account the ageing of the normal lung; and 7) no study has defined, in terms of the best descriptor of emphysema, the lung volume at which CT scan has to be performed. Recently, an approach to reproducible measurement of lung attenuation by means of respiratory-gated CT has been developed [34]. Using this technique, LAMERS *et al.* [35] have suggested that a spirometrically-controlled CT technique should be required for accurate assessment of COPD *in vivo*, and that the change between densitometric data obtained at 90% vital capacity and at 10% vital capacity could be used in the differential diagnosis of emphysema and chronic bronchitis.

In the immediate future, the use of HRCT and objective quantitative techniques should take the place of subjective visual scoring methods [25, 36], but further studies, based on macroscopic as well as microscopic comparisons, should evaluate the capability of these procedures to detect and to quantify the disease. In addition, potential pitfalls have to be evaluated. Using conventional CT, ZERHOUNI *et al.* [37] have shown that the density of a pulmonary nodule is influenced by patient size, location and environment of the area being assessed, type of CT scanner, kilovoltage and the reconstruction algorithm. On the other hand, using 1.5 mm thick sections and studying the fine structure of the lung, MURATA *et al.* [38] have shown that the reconstruction algorithm has no significant influence on the CT attenuation value of the lung. In conclusion, if these objective CT procedures prove to be valid, their standardization must be established.

References

1. Snider GL. Emphysema: the first two centuries and beyond. *Am Rev Respir Dis* 1992; 146: 1334–1344.
2. Snider GL, Kleinerman J, Thurlbeck WM, Bengali ZH. The definition of emphysema. Report of a National Heart, Lung and Blood Institute, Division of Lung Diseases Workshop. *Am Rev Respir Dis* 1985; 132: 182–185.
3. Thurlbeck WM, Simon G. Radiographic appearance of the chest in emphysema. *Am J Roentgenol* 1978; 130: 429–440.
4. Thurlbeck WM. Overview of the pathology of pulmonary emphysema in the human. *Clin Chest Med* 1983; 4: 337–350.
5. Leung AN, Staples CA, Müller NL. Chronic diffuse infiltrative lung disease: comparison of diagnostic accuracy of high-resolution and conventional CT. *Am J Roentgenol* 1991; 157: 693–696.
6. Wallaert B, Gressier B, Marquette CH, *et al*. Inactivation of α_1-proteinase inhibitor by alveolar inflammatory cells from smoking patients with or without emphysema. *Am Rev Respir Med* 1993; 147: 1537–1543.
7. Gelb AF, Schein M, Kuei J, *et al*. Limited contribution of emphysema in advanced chronic obstructive pulmonary disease. *Am Rev Respir Med* 1993; 147: 1157–1161.
8. Kinsella M, Müller NL, Vedal S, Staples C, Abboud RT, Chan-Yeung M. Emphysema in silicosis: a comparison of smokers with nonsmokers using pulmonary function testing and computed tomography. *Am Rev Respir Dis* 1990; 141: 1497–1500.
9. Goddard PA, Nicholson EM, Laszlo G, Watt I. Computed tomography in pulmonary emphysema. *Clin Radiol* 1982; 33: 379–387.
10. Hayhurst MD, Flenley DC, McLean A, *et al.* Diagnosis of pulmonary emphysema by computerized tomography. *Lancet* 1984; ii: 320–322.
11. Foster WL Jr, Pratt PC, Roggli VL, Godwin JD, Halvorsen RA Jr, Putman CE. Centrilobular emphysema: CT-pathologic correlation. *Radiology* 1986; 159: 27–32.
12. Bergin C, Müller N, Nichols DM, *et al*. The diagnosis of emphysema: a computed tomographic-pathologic correlation. *Am Rev Respir Dis* 1986; 133: 541–546.
13. Hruban RH, Meziane MA, Zerhouni EA, *et al.* High resolution computed tomography of inflation-fixed lungs. *Am Rev Respir Dis* 1987; 136: 935–940.
14. Miller RR, Müller NL, Vedal S, Morrison NJ, Staples CA. Limitations of computed tomography in the assessment of emphysema. *Am Rev Respir Dis* 1989; 139: 980–983.
15. Kuwano K, Matsuba K, Ikeda T, *et al*. The diagnosis of mild emphysema: Correlation of computed tomography and pathology scores. *Am Rev Respir Dis* 1990; 141: 169–178.
16. Müller NL, Staples CA, Miller RR, Abboud RT. "Density mask": an objective method to quantitate emphysema using computed tomography. *Chest* 1988; 94: 782–787.
17. Gould GA, Macnee W, McLean A, *et al*. CT measurements of lung density in life can quantitate distal airspace enlargement - an essential defining feature of human emphysema. *Am Rev Respir Dis* 1988; 137: 380–392.
18. Spouge D, Mayo JR, Cardoso W, Müller NL. Panlobular emphysema: CT and pathologic findings. *J Comput Assist Tomogr* 1993; 17: 710–713.
19. Thurlbeck WM, Dunnill MS, Hartung W, Heard BE, Heppleston AG, Ryder RC. A comparison of three methods of measuring emphysema. *Hum Pathol* 1970; 1: 215–226.
20. Paré P, Brookes LA, Bates J, *et al*. Exponential analysis of the lung pressure volume curve as a predictor of pulmonary emphysema. *Am Rev Respir Dis* 1982; 126: 54–61.
21. Makarian B, Dailey ET. Preparation of inflated lung specimen. *In*: Heitzman ER, ed. The Lung: Radiologic-Pathologic Correlations. 2nd edn, St. Louis, CV Mosby, 1984; pp. 4–12.
22. Saetta M, Shiner RJ, Angus GE, *et al*. Destructive index: a measurement of lung parenchymal destruction in smokers. *Am Rev Respir Dis* 1985; 131: 764–769.
23. Müller NL. CT diagnosis of emphysema. It may be accurate, but is it relevant? *Chest* 1993; 103: 329–330.
24. Gevenois PA, Zanen J, de Maertelaer V, De Vuyst P, Dumortier P, Yernault JC. Macroscopic assessment of

pulmonary emphysema by image analysis. *J Clin Pathol* 1995; 48: 318–322.
25. Kalender WA, Fichte H, Bautz W, Skalej M. Semiautomatic evaluation procedures for quantitative CT of the lung. *J Comput Assist Tomogr* 1991; 15: 248–255.
26. Turner P, Whimster WF. Volume of emphysema. *Thorax* 1981; 36: 932–937.
27. Morgan MDL. Detection and quantification of pulmonary emphysema by computed tomography: a window of opportunity. *Thorax* 1992; 47: 1001–1004.
28. McLean A, Warren PM, Gillooly M, MacNee W, Lamb D. Microsopic and macroscopic measurements of emphysema: relation to carbon monoxide gas transfer. *Thorax* 1992; 47: 144–149.
29. Gould GA, Redpath AT, Ryan M, *et al*. Parenchymal emphysema measured by CT lung density correlates with lung function in patients with bullous disease. *Eur Respir J* 1993; 6: 698–704.
30. Rienmüller RK, Behr J, Kalender WA, *et al*. Standardized quantitative high resolution CT in lung diseases. *J Comput Assist Tomogr* 1991; 15: 742–749.
31. Hartley PG, Galvin JR, Hunninghake GW, *et al*. High-resolution CT-derived measures of lung density are valid indexes of interstitial lung disease. *J Appl Physiol* 1994; 76: 271–277.
32. Gillooly M, Lamb D. Airspace size in lungs of lifelong nonsmokers: effect of age and sex. *Thorax* 1993; 48: 39–43.
33. Moudgil H, Morrison D, Gillooly M, *et al*. Computerised tomographic (CT) lung density as a measure of distal airspace size: defining normality. *Am J Respir Crit Care Med* 1994; 149: A1021.
34. Kalender WA, Reinmüller R, Seissler W, Behr J, Welke M, Fichte H. Measurement of pulmonary parenchymal attenuation: use of spirometric gating with quantitative CT. *Radiology* 1990; 175: 265–268.
35. Lamers RJ, Thelissen GR, Kessels AG, Wouters EF, van Engelshoven, JM. Chronic obstructive pulmonary disease: evaluation with spirometrically controlled CT lung density. *Radiology* 1994; 193: 109–113.
36. Archer DC, Coblentz CL, deKemp RA, Nahmias C, Norman G. Automated *in vivo* quantification of emphysema. *Radiology* 1993; 188: 835–838.
37. Zerhouni EA, Boukadoum M, Siddiky MA, *et al*. A standard phantom for quantitative CT analysis of pulmonary nodules. *Radiology* 1983; 149: 767–773.
38. Murata K, Khan A, Rojas KA, Herman PG. Optimization of computed tomography technique to demonstrate the fine structure of the lung. *Invest Radiol* 1988; 23: 170–175.