

# Computed tomography assessment of lung structure and function in pulmonary emphysema

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Computed tomography (CT) is an imaging method providing transverse anatomical images in which the value of each picture element (*i.e.* pixel) corresponds to the X-ray attenuation of a defined volume of tissue (*i.e.* voxel). The X-ray attenuation values for each set of projections (*i.e.* slice) are registered by the computer and organised in a matrix form. The number of calculated pixels determines the image matrix size, influences the image resolution, and should thus be as high as possible. In clinical practice, the matrix size is actually 512×512 pixels. The X-ray attenuation, also called tissue density, is numerically expressed in Hounsfield units (HU). The scale of attenuation values range from -1000 HU, corresponding to the attenuation value of air, to 3,000 HU, 0 HU corresponds to the attenuation value of water. The thousands of pixels included in one scan make CT the most precise morphological method able to assess *in vivo* the pulmonary structure [1].

In pulmonary emphysema, the major advantage of CT is that in addition to providing data concerning overall lung destruction, it also identifies the specific locations in the lung where the alveolar surface has been destroyed. The ability to estimate the extent and severity of pulmonary emphysema during life is important for several reasons. First, accurate detection of lung destruction when it appears and careful mapping of its progression are required to understand the natural history of emphysema. Secondly, the treatment of advanced disease by lung volume reduction surgery (LVRS) requires knowledge of the location of the lesions and objective methods of assessing the surgical results [2]. Thirdly, CT could be a sensitive way of quantitating the progression of emphysema as the determination of the efficacy of replacement therapy in patients with  $\alpha_1$ -antitrypsin deficiency [3]. Fourthly, studies suggesting that alveolar number and surface-to-volume ratio can be restored by other therapeutic measures in rats, with elastase-induced emphysema, implies the future need for measurements that can accurately assess the effectiveness of such therapeutic interventions [4, 5]. Fifthly, the detection of early emphysema may prevent the occurrence of obstructive ventilatory impairment by smoking cessation or medical intervention [6].

Numerous studies have addressed the capability of CT to accurately quantify the extent and severity of pulmonary emphysema [7, 8]. In order to verify if CT is adequately validated and to suggest possible directions for further studies, this chapter provides an overview of the previously published studies that were based on quite different methods. Indeed, studies have been based on subjective visual grading or on objective indexes derived from attenuation values, on two-dimensional or on three-dimensional approaches, and on scans obtained after deep inspiration or expiration.

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Since pulmonary emphysema is defined by pathological criteria as an abnormal permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of the alveolar walls, and without obvious fibrosis, new methods of diagnosis and quantification must be validated by comparisons with histopathology [9]. Morphologically, the presence and extent of emphysema can be determined by macroscopic or by microscopic assessment of a lung specimen. A brief review regarding the most widely used macroscopic and microscopic methods will be given first.

## **Histopathological quantification of pulmonary emphysema**

### ***Macroscopic methods***

Two main methods were traditionally used to macroscopically quantify the severity of emphysema: the point counting developed by DUNNILL [10] and the panel grading proposed by THURLBECK *et al.* [11]. Point counting calculates the proportion, expressed as a percentage, of a lung section occupied by emphysematous spaces by using a transparent plastic sheet with a grid drawn on it and placed over the lung section. The points of this grid lay 1 cm apart and are situated at the angles of equilateral triangles with 1 cm sides. The percentage of the lung involved by emphysema is given by the number of points superimposed on emphysematous spaces  $\times 100$  and divided by the number of points on the whole lung section. This method is truly quantitative and can be performed on several sections obtained throughout a lung specimen but it is tedious and time consuming. Panel grading method is based on the comparison of paper-mounted sagittal lung sections against a set of standards scoring emphysema from 0–100 at intervals of 5 or 10. Scores of  $\leq 25$  indicate mild emphysema; 25–50, moderate emphysema; and  $\geq 50$ , severe emphysema [11]. This method is quick, but not really quantitative and is a method of ranking emphysema according to several categories of severity. Moreover, this technique underestimates the extent of panlobular emphysema and does not permit combined grading of several sections from the same lung specimen, although it has been shown that an adequate assessment of emphysema cannot be made from a single lung slice [12].

In order to measure the extent of emphysema on numerous paper-mounted lung sections, the current authors developed a computer-assisted method following the principles of the point-counting method and calculating the relative area, expressed as percentage of lung macroscopically occupied by emphysema. This method has the advantage of being quick, precise, and highly reproducible and permits the combination of data from several slices obtained throughout a lung specimen [13].

### ***Microscopic methods***

Several methods have been designed to quantify emphysema microscopically. The mean linear intercept (Lm) is defined as the ratio of the length of a test line placed on a microscopic lung sample divided by the number of intercepts of this test line with alveolar walls [10]. The airspace wall per unit volume (AWUV) is a measurement expressing the alveolar surface area per unit of lung volume and is derived from Lm. As pointed out by THURLBECK and MÜLLER [8] neither the loss of alveolar surface nor Lm and AWUV are sensitive methods for recognising emphysema. Indeed, Lm is normal in 32% of emphysematous patients [14] and AWUV is abnormal only in 26% of surgically resected patients with severe macroscopic emphysema [14, 15]. More recently, the current authors used a computer-based method to measure the distance between alveolar walls in the

lung parenchyma [16, 17]. As summarised by MÜLLER and THURLBECK [18] this is a measurement of the average transection distance between walls of alveoli, alveolar ducts, and alveolar sacs considered together; it is not the average alveolar diameter and this term is less ambiguous than Lm.

The destructive index (DI), which is defined as a percentage of destroyed alveolar and alveolar-duct space, was introduced as objective criteria of alveolar wall destruction by SAETTA *et al.* [19]. DI has three components: breaks in alveolar walls (DIb), metaplasia of type II cells and some degree of fibrosis in alveolar wall (DIc), and the so-called classic emphysema (DIe). In the study by SAETTA *et al.*, DIb was increased in smokers in whom the size of the airspace was still normal and, therefore, this parameter could be an early indication of lung destruction. Nevertheless, an increased DIb could also be related to an increased number and size of fenestrae in the normal parenchyma, adjacent to emphysema, or to abnormal properties of elastic tissue in smokers without macroscopic emphysema [8]. BOREN [20] reported the presence of holes in alveolar walls of normal lung specimens and suggested that holes  $>20\ \mu\text{m}$  in diameter were abnormal. NAGAI *et al.* [21] measured the size of these holes and found that only 0.2% of normal subjects have fenestrae  $>20\ \mu\text{m}$  in diameter. Alveolar destruction could thus be defined as the presence of holes, also called fenestrae, larger than this diameter, probably the earliest pathological evidence of emphysema [22].

## Computed tomography quantification of pulmonary emphysema

### *Subjective computed tomography quantification*

Subjective CT quantification of emphysema is based on the visual assessment of areas of vascular disruption and decreased attenuation without clear margins, in comparison with contiguous normal parenchyma [23]. In 1986, BERGIN *et al.* [24] visually estimated the percentage area that demonstrated changes suggestive of emphysema on contiguous 10-mm thick CT sections on a study group of 32 patients. On the basis of significant correlations between CT visual scores and macroscopic emphysema graded with a picture-grading system adapted from THURLBECK *et al.* [11] on midsagittal sections, these authors concluded that CT is a useful adjunct in assessing the presence and extent of emphysema. In 1987, by comparing the CT scores of 1-mm thick high-resolution CT (HRCT) slices performed at five levels of 20 *post mortem* inflated lung specimens and the pathological scores obtained at the same anatomic levels, HRUBAN *et al.* [25] demonstrated that HRCT is able to distinguish emphysematous lungs from normal lungs even in the mildest degrees. Applying the same methods in a population of mild emphysematous patients, KUWANO *et al.* [26] obtained statistically significant correlations between the scores established on the HRCT slices and macroscopic grading as well as between the CT scores and the microscopic DI [26]. MILLER *et al.* [27] assessed the extent of emphysema by superimposing a grid with squares corresponding to  $1\ \text{cm}^2$  on CT images and determining the percentage of squares containing emphysema [27]. Comparing these results obtained on 10-mm and 1.5-mm thick CT sections to the grading panel of parasagittal standards established by THURLBECK *et al.* [11], they found CT insensitive in detecting the earliest lesions of emphysema [27].

In all these studies by BERGIN *et al.* [24], HRUBAN *et al.* [25] KUWANO *et al.* [26] and MILLER *et al.* [27] mental adjustments were required in order to apply the top-to-bottom grading panel to horizontal images. In addition, the grading system is not really quantitative but is a method of ranking emphysema according to categories of severity [11]. To overcome these limitations, the authors applied a quantitative computer-assisted

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method to horizontal paper-mounted lung sections producing results on a continuous scale [13]. All these pioneer studies have shown that the extent of emphysema visually scored on CT scans correlates significantly with the extent of emphysema scored on macroscopic lung sections obtained from resected specimens. Most of these studies concerned centrilobular emphysema and were not based on objective CT quantification applied to thin-section CT scans [28].

## Objective computed tomography quantification

### *Attenuation measurements*

In order to quantify objectively pulmonary emphysema, several lung attenuation parameters, based on the histogram analysis of the frequency distribution of the attenuation value of the lung, have been developed [29]. The most commonly used methods are based on the measurement of the mean lung attenuation, the areas of lung occupied by attenuation values lower than predetermined thresholds [16, 30–34], and a predetermined percentile of the lung attenuation distribution curve [3, 35].

HAYHURST *et al.* [36] in the first pathological CT comparative study using numbers for attenuations showed that the distribution curve of these densities was significantly shifted towards the lowest attenuation values in patients with emphysema compared with normal individuals. In a CT pathologically correlation study based on microscopic measurements, GOULD *et al.* [35] showed that the lowest fifth percentile of the histogram of attenuation values was significantly correlated with AWUV. The lowest fifth percentile depends on the extent of emphysema but is also influenced by the relative amount of higher attenuation values, corresponding to airway walls, blood vessels, and any infiltrate, which tends to displace the histogram to the right [37, 38]. Consequently, if emphysema is associated with other pulmonary disorders, the lowest fifth percentile should underestimate the extent of emphysema. To overcome this limitation, an absolute threshold should be used and the relative area of lung occupied by attenuation values lower than this threshold measured [28]. In 1988, MÜLLER *et al.* [32] used a CT commercially available programme called Density Mask® (General Electric Medical Systems, Milwaukee, WI, USA) that highlights pixels within a given attenuation range and automatically calculates the area of highlighted pixels. In this study, MÜLLER *et al.* [32] compared the relative area highlighted on a single 1-cm thick CT scan, after injection of contrast material, with the corresponding macroscopic section of the fixed-lung cut in the same plane as the CT scan and graded using a modification of the picture-grading system from THURLBECK *et al.* [11]. The highest correlation was observed with attenuation values lower than -910 HU, and as a consequence this threshold was recommended for the identification of emphysema. Nevertheless, significant correlations indicate that only CT and pathological scores are statistically linked, but do not imply that the percentage area obtained by CT quantifications are equal to the percentage area occupied by emphysema on the pathological specimen. In addition, the proposed threshold might be influenced by the injection of contrast material. Furthermore, the grading panel does not represent the extent of lung involved by emphysema and underestimates panlobular emphysema especially in initial stages.

In an attempt to determine the best attenuation threshold for the recognition of emphysema, the authors applied 1-mm thick CT sections, which is a programme that automatically recognises the lungs, traces the lung contours, determines histograms of attenuation values, and measures the lung area occupied by pixels included in the predetermined range of attenuation value [39]. On thin CT sections obtained from the lung apices to the bases with 1-cm intervals, the authors calculated the relative area of lung,

expressed in percentage, occupied by attenuation values lower than various thresholds ranging from -900– -970 HU. On a first study based on 63 patients with lung resection, the authors compared the CT data with the macroscopic extension of the emphysema measured, on horizontal paper mounted whole-lung sections [40], using the authors previously validated computer-assisted method [13]. It was shown that the only threshold for which there was no significant difference between the distribution of the CT measurements and the distribution of macroscopic measurements was -950 HU. Thresholds <-950 HU underestimated emphysema, and thresholds >-950 HU overestimated emphysema. The case-by-case comparisons between the relative area occupied by attenuation values <-950 HU (RA: relative area; RA<sub>950</sub>) and the relative area of lung macroscopically occupied by emphysema were not identical in every patient: the mean of the absolute values of the differences between the RA<sub>950</sub> and the relative area of lung macroscopically occupied by emphysema was 4.9% and ranged from 0.1–19.9%. These data suggested thus that the relative area of lung occupied by attenuation values <-950 HU calculated on thin-section CT scans obtained at full inspiration was a method allowing an objective quantification of macroscopic emphysema *in vivo* and with an acceptable error [33].

Since McLEAN *et al.* [41] recommended that pulmonary emphysema should be measured microscopically rather than macroscopically, comparisons between CT and morphometry should include microscopic measurements. Using AWUV as a microscopic measurement of the alveolar wall surface in 28 subjects referred for surgical resection of lung tumours, GOULD *et al.* [35] reported significant correlations between AWUV and the lowest fifth percentile of the frequency distribution curve of attenuation values ( $r=-0.77$ ,  $p<0.001$ ) calculated on 13-mm thick CT sections. In a more recent study based on 38 patients also referred for lung resection, the authors measured mean interwall distance (MIWD) and mean perimeter (MP) and compared the percentage surface area of lung occupied by attenuation values lower than thresholds ranging from -900– -970 HU to the microscopic indexes. The authors showed that the highest correlation was obtained with -950 HU ( $r=0.70$ ). Thus both, the macroscopic, as well as the microscopic study conducted by the current author group suggests that RA<sub>950</sub> is a valuable measurement of the extent of pulmonary emphysema [33].

In order to predict the lung surface-to-volume ratio from CT attenuation values, COXSON *et al.* [42] considered -910 HU as a threshold and compared CT measurements with histological estimates of surface area. The lung volume was calculated by summing the voxel dimensions in each slice, and the lung weight was estimated by multiplying the mean lung attenuation value with the lung volume. From these measurements, COXSON *et al.* [42] derived the regional lung inflation and expressed it as  $\text{mL}\cdot\text{g}^{-1}$ . A comparison of the amount of emphysema detected in the same lobe by both CT and point counting of the resected specimen showed that the volume fraction of lesions >5 mm in diameter measured by morphometry is similar to the fraction of lung inflated >10.2  $\text{mL}\cdot\text{g}^{-1}$ . It also showed that lesions <5 mm in diameter corresponded to the fraction of the lung inflated between 6.0 and 10.2  $\text{mL}\cdot\text{g}^{-1}$  and that regions inflated <6.0  $\text{mL}\cdot\text{g}^{-1}$  are morphologically normal. This method appeared more accurate than the surface area occupied by emphysema since these authors observed a reduced surface-to-volume ratio in mild emphysema whereas surface area and tissue weight were decreased only in severe disease.

### ***Comparison between objective and subjective computed tomography quantification***

An advantage of computer-assisted quantification is the reproducibility of the technique across readers of varying expertise and experience, and across institutions, allowing more accurate comparison of results among different centers [43]. Conversely, the advantages of a subjective scoring system are the ease of its application and the not

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necessitating expense of dedicated softwares. In a series of 62 patients who underwent thin section CT prior to surgical lung resection, BANKIER *et al.* [44] compared subjective visual grading of pulmonary emphysema with macroscopic morphometry and objective CT quantification. Three readers of varying degrees of expertise subjectively graded emphysema in two reading sessions. All three readers systematically overestimated emphysema and the inter-observer agreement with weighted kappa's (interobserver agreement) ranged from 0.431–0.589. Independent of the level of expertise of the individual reader, the correlation between subjective scores and macroscopic results was weaker than the correlation between objective CT quantification and macroscopic morphological measurements. This study suggests that subjective visual grading should be supplemented with more reliable objective methods whenever a precise and reader-independent quantification of emphysema is required.

### ***Tissue characterisation***

Quantifications of pulmonary emphysema by computer-assisted methods are based on mathematical approaches, named metrics that may be used to describe the heterogeneity of the spatial distribution of the attenuation values within the reconstructed image [1]. These metrics include very simple parameters, such as the mean lung density to areas of low attenuation based on single or a range of densities [1]. Textural analyses are more complex metrics. In order to differentiate normal from emphysematous lungs and normal from emphysematous regions within one lung, UPPALURI *et al.* [45] developed an adaptive multiple features method (AMFM) based on textural analysis. With an electron-beam CT scanner, the group acquired two-dimensional slices of the whole lung with 3 mm collimation at maximal inspiration. Adjacent pixels with small differences of gray level were merged and first-order, as well as second-order, statistical measurements were separately computed for each slice. First-order measurements included: mean, variance, skewness of the attenuation distribution curve. Second-order measurements included: co-occurrence entropy, contrast, angular second moment, *etc.* The authors observed that second-order statistics and fractal dimension were sensitive to the gray level and spatial relationships between pixels in a region. These parameters can thus be used for tissue characterisation. The authors compared AMFM, mean-lung density, and the lowest fifth percentile of the distribution histogram of attenuation values to discriminate normal from emphysematous lungs. The accuracy of AMFM, mean-lung density, and the lowest fifth percentile was 100, 95 and 97%, respectively. However, there was no correlation between these three parameters and pulmonary function tests (PFTs). These authors explained this lack of correlation by there being too few a number of slices per subject and by the absence of patients with mild and moderate emphysema included in their study [1, 45].

In an attempt to detect early emphysema, MISHIMA *et al.* [30] quantified the size distribution of low attenuation area (*i.e.* <-960 HU) clusters on 2-mm thick HRCT slices obtained at full inspiration in healthy subjects (n=30) and chronic obstructive lung disease (COPD) patients (n=73). All normal subjects had low attenuation areas <30% of the total lung area and varied from 2.6–67.6% in COPD patients. The authors observed that the cumulative size distribution of the low attenuation area clusters followed a power-law distribution characterised by an exponent D. Although the COPD group of patients with low attenuation area <30% of the total lung area and the normal subjects had similar low attenuation areas, the corresponding D values were significantly smaller in the COPD patients. On the basis of an elastic-spring network model, the authors attributed this smaller value to the coalescence of smaller low attenuation area clusters into larger low attenuation area clusters in COPD patients. There was no correlation

between the value of D and PFTs except carbon dioxide diffusing capacity of the lung ( $DL_{CO}$ ). Assuming that the exponent D is related to the fractal dimension of the alveolar surface ( $df$ ), a measure of terminal airspace geometry complexity, a smaller D in a two-dimensional CT image is the consequence of larger low attenuation area clusters and represents the reduced  $df$  in COPD patients. These authors concluded that 30% could be the critical value of low attenuation area to discriminate normal and mild from severe COPD patients but that low attenuation area is not sufficiently accurate to distinguish early emphysematous patients from normal subjects. The value of D could be a sensitive parameter in order to detect terminal airspace enlargement that occurs in early emphysema.

More recently, on the basis of automated technique, CHABAT *et al.* [46] attempted to discriminate centrilobular emphysema, panlobular emphysema, constrictive obliterative bronchiolitis, and normal lung tissue. Local texture information was extracted from four regions of interest on thin-section CT scans obtained in 33 subjects and represented by first- and second-order measurements. Texture feature segmentation was applied after training and testing steps, based on the visual classification of these four patterns. Although possible coexistence of both types of pulmonary emphysema in the same individual, the proposed technique discriminated patterns of obstructive lung disease with a sensitivity ranging from 55–89%, a specificity from 88–92%, and a positive predictive value from 71–77%.

## Factors influencing computed tomography densitometry

### *Age*

Morphometrical data from THURLBECK [47] and from GILLOOLY and LAMB [48] showed a significant correlation between airspace size and age. The increase of airspace size associated with advanced age could thus influence the CT density parameters and should be taken into account for longitudinal studies. In order to investigate the possible influence of age on density measurements, the current authors measured the RA950 in 42 healthy subjects who ranged in age from 23–71 yrs and the authors found a weak, but significant, correlation between age and the RA950 ( $r=0.328$ ;  $p=0.034$ ) [49]. These results are in accordance with those from SOEIJIMA *et al.* [50] who investigated 36 symptom-free nonsmoking subjects with normal lung function during a 5-yr follow-up period and showed that the percentage of RA960 increased with age, at least in the middle and lower lung zones.

### *Computed tomography parameters*

Since CT scanning parameters could influence the attenuation values and their distribution curve, MISHIMA *et al.* [51] compared the low attenuation area ( $<960$  HU) obtained with various numbers of slices ranging from 3–10, various slice thicknesses from 2–5 mm, and various electric tube currents ranging from 50–250 mA (milliampere). On the basis of image quality, exposure dose, and correlations with lung function tests, they suggested that three 2-mm thick CT sections, acquired with 200 mA tube current were the most appropriate parameters to assess pulmonary emphysema. Nevertheless, attention should be paid to radiation doses and quantification obtained by using low-dose CT should be investigated.

### *Number of computed tomography sections*

Pulmonary emphysema is heterogeneously distributed throughout the lung, from studies based on point counting, it is known that an adequate assessment cannot be

obtained from one lung slice alone [12], but radiation exposure is likely to favour sampling techniques rather than entire 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, but no CT study has defined the minimum number of scans necessary to provide accurate results. In the current authors' study, based on comparisons between HRCT and macroscopy, attempted to define a maximum interval distance between HRCT scans providing valid results. The RA950 was recalculated by successively considering one scan of two, one scan from three, one scan from four *etc.* and compared these results with the results obtained with 1-cm intervals. The individual variability of the RA950 was very heterogeneous from patient-to-patient and no bend in the relationship linking the coefficient of variation of RA950 and the interval distance was found. Consequently, no particular interval distance could be proposed as an optimal standard [33]. More recently, MISHIMA *et al.* [51] attempted to define the influence of the slice number on RA960 in 30 patients with COPD. These authors calculated correlation coefficients between RA960 respectively measured on five, three, and two CT sections and RA960 measured on 10 CT sections. The corresponding coefficients were 0.976, 0.953, and 0.908, indicating highly significant correlations. The authors concluded that three slices were sufficient to obtain the overall extent of emphysema but they did not report either the severity of the disease, in terms of functional deficit or the heterogeneity of its spatial distribution within the lungs.

### ***Spiral computed tomography***

Spiral CT scanning has the major advantage that the entire thorax is imaged during one single breathhold. This method involves simultaneous transport of the patient at a constant speed through the CT gantry while data are continuously acquired over multiple gantry rotations [52]. From spiral CT data, three-dimensional reconstructions, lung volume measurements, and quantification of lung disorders can be obtained. By using dedicated softwares that are currently available on almost all modern scanners, KAUCZOR *et al.* [53] compared lung volumes measured by spiral CT with those measured by plethysmography. They observed significant correlations between both measurements and an underestimation of total lung capacity (TLC) by 12%, measured by spiral CT, probably due to the supine posture of the subject in the CT scanner compared with the seated posture in the plethysmograph. Spiral CT data could be of great interest in the quantification of heterogeneously distributed lung disorders such as pulmonary emphysema, but no study has validated spiral CT parameters as compared to histopathology. Dedicated programmes reconstructing a three-dimensional model of the lungs, calculating their volume and providing the frequency-distribution curve of attenuation values within this lung volume can be applied on spiral CT data. Such a programme has been used by PARK *et al.* [54] who compared the percentage volume of the lung occupied by attenuation values lower than three thresholds (-900, -910, and -950 HU) with the percentage area of the lung occupied by attenuation values lower than these thresholds. They observed highly significant correlations ( $r \sim 0.98$ ) between lung attenuation measurements obtained with the three-dimensional model and those from two-dimensional images.

### ***Lung volume and size***

The possible role of CT scans obtained after deep expiration in the assessment of emphysema was first suggested by KNUDSON *et al.* [55] because correlations between CT measurements and lung-function tests were stronger in expiration than in inspiration. In

64 patients with airflow obstruction for most of them, these authors obtained 8-mm thick CT slices at two levels in upper-lung zones at full inspiration and full expiration and measured the percentage area of lung occupied by attenuation values  $<900$  HU. This percentage area was compared with various PFTs such as static lung compliance,  $DL_{CO}$ , and forced expiratory flow in one second ( $FEV_1$ ). The highest correlations between CT with physiological variables consistent with emphysema were observed with CT measurements obtained at full expiration.

In order to investigate the possible role of quantitative CT during expiration, the current authors measured relative areas of lung occupied by attenuation values lower than various thresholds ranging from  $-800$ – $-970$  HU, at full inspiration and full expiration, in 89 patients who underwent surgical resection. Two different thresholds were found and respectively validated by comparisons with macroscopy ( $-910$  HU) and microscopy ( $-820$  HU), which were quite different than the threshold found valid for CT scans obtained at full inspiration ( $-950$  HU) [16, 33]. In addition, multiple regression analysis showed that CT measurements obtained at full expiration did not yield any additional significant information when compared with those obtained at full inspiration in order to predict the anatomic extent of emphysema. In a study based on visual scoring, NISHIMURA *et al.* [56] showed that expiratory CT underestimates the degree of emphysema as compared with inspiratory CT scans. To summarise, expiratory CT is not as adequate as inspiratory CT for measuring the extent of pulmonary emphysema. This conclusion suggests that possible errors, secondary to variations of lung volume at which the CT scans are obtained, could be avoided by using spirometrical triggering [51–53, 57].

In the current authors study on expiratory CT, correlations between PFTs and objective CT data, respectively obtained in deep expiration and in deep inspiration, were also examined [17]. A higher correlation between PFTs reflecting the airflow obstruction and the CT data obtained in expiration than in inspiration was observed, but correlations were similar between diffusing capacity and both inspiratory and expiratory data. It was concluded that expiratory CT reflects more on the expiratory airflow limitation and the subsequent air trapping than the reduction of the alveolar wall surface. These findings were confirmed by EDA *et al.* [58] and by LAMERS *et al.* [57] who also found higher correlations between PFTs reflecting the airflow obstruction and CT data obtained in expiration than in inspiration, whereas the correlations between diffusing capacity and CT data were similar [57, 58].

Independently to the lung volume at which the CT scan is obtained, the lung size could influence CT parameters. Morphometrical studies showed contradictory results, suggesting that either the number of alveoli in the human lung was [59–61] or was not [62] positively correlated with body length. In the cross-sectional study in 42 healthy subjects, a significant correlation between TLC and the mean lung attenuation (MLA) was found ( $r=-0.419$ ;  $p=0.006$ ) as well as between TLC and the  $RA_{950}$  ( $r=0.386$ ;  $p=0.012$ ) [49]. The larger the TLC in absolute value, the lower the MLA and the higher the  $RA_{950}$ . These results suggest that the relative amount of lung tissue per unit of volume is lower in larger lungs than in smaller lungs. Accordingly, because the structure of the alveolar wall is unrelated to the lung size, the dimensions of the airspaces should be greater in larger lungs than in smaller lungs.

## **Comparison between computed tomography quantification and pulmonary function tests**

Although PFTs may be short and long-term reproducible tests, they represent global measurements of lung function of more than ten million airways that contribute

unequally to airflow [63]. They are of limited value in the measurement of the obstruction of airways, particularly small airways that are predominantly affected in emphysema [63] and autopsy studies have shown that up to one-third of the lung can be destroyed by emphysema before respiratory function becomes impaired [45]. The insensitivity of PFTs to diagnose mild emphysema was confirmed by SANDERS *et al.* [64] who found that emphysematous features of emphysema were visually detected on CT scans in 69% of smokers with normal  $DL_{CO}$  with or without associated obstructive deficit. In this study, CT showed evidence of emphysema in 96% of patients selected on the basis of functional criteria of emphysema as suggested by the American Thoracic Society (ATS) such as decreased  $DL_{CO}$  (<80% predicted value) plus evidence of obstructive lung disease (decreased  $FEV_1$  <80% and/or increased residual volume:  $RV$  >120% predicted values). These authors concluded that CT may be more sensitive than PFTs in detecting mild emphysema.

The lack of sensitivity of PFTs to detect pulmonary emphysema can be explained by two reasons related to pulmonary zones in which ventilatory disorders are not assessed by conventional PFTs. First, the total airflow resistance of all respiratory bronchioles contributes little to the total airflow resistance of the lung [63]. Despite the high airflow resistance through one single respiratory bronchiole, the parallel connection of a high number of bronchioles leads to a wide total cross-sectional area and a drastically reduced airflow resistance [37]. Secondly, the upper-lung zone has a relatively high ventilation/perfusion ratio ( $V/Q$ ) compared with the lower-lung zone. Thus, in the relatively underventilated upper-lung zone, emphysema produces smaller measurable pulmonary dysfunction than in the lower zone. Consistently, GURNEY *et al.* [65] and HARAGUSHI *et al.* [66] showed that the extent of emphysema had higher correlations with  $DL_{CO}$  in the lower-lung zone than in the upper-lung zone, even though the upper-lung zone was more severely affected by emphysema. On the basis of the lobar distribution of emphysema as determined by CT, SAITOH *et al.* [67] reported, that the airflow limitation, the  $RV$  and the  $TLC$  were higher in the predominantly lower-lobe emphysematous group than in the predominantly upper-lobe emphysematous group. However, NAKANO *et al.* [34] reported that the correlations between the  $RA_{960}$ , and  $FEV_1$  or  $RV/TLC$  were higher in the lower lobes but the correlation between  $RA_{960}$ , and  $DL_{CO}$  was higher in the upper lobes. The authors attributed this discrepancy between their results and the other studies to the high incidence of severe emphysema in the upper lobe, which affects the  $DL_{CO}$  [34]. The central *versus* peripheral predominant location of emphysematous area determines also the importance of functional impairment. HARAGUSHI *et al.* [66] found higher correlations between PFTs, including  $FEV_1$  and  $DL_{CO}$ , and attenuation values of the central region than the peripheral region of lungs. This is in agreement with NAKANO *et al.* [34] who reported a higher incidence of emphysema in central region compared with the peripheral region. These authors explained the results by the move of particles deposition from outer-to-inner lung, by a greater stratified distribution of pulmonary blood perfusion in the outer rather than in the inner lung, and by the lymphatic drainage of particles from outer-to-inner lung, which is favoured by the ventilatory movements [34].

The correlation between CT indexes and  $DL_{CO}$  or  $DL_{CO}/$ alveolar volume ( $VA$ ) were extensively documented in numerous studies and ranged from -0.5– -0.75 [35, 68–71]. In the a study by GEVENOIS *et al.* [16], which compared CT with microscopic morphometry, a correlation coefficients was obtained between  $RA_{950}$  and microscopic indexes of the same degree of magnitude as between  $FEV_1/vital\ capacity\ (VC)$  or  $DL_{CO}/VA$  and these microscopic indexes ( $r \sim 0.70$ ). Considering the microscopic measurements of the method of reference, the  $RA_{950}$  and independent PFTs were entered using stepwise procedures. The relationships obtained revealed that  $DL_{CO}$  and the  $RA_{950}$  were sufficient to predict microscopical measurements.

More recently, using the three-dimensional model described above, PARK *et al.* [54] investigated the relationships between PFTs and percentage of lung volume occupied by attenuation values lower than three thresholds (-900, -910, -950 HU) and found moderate-to-high correlations between these percentage volumes and TLC ( $r=0.62-0.71$ ), FEV<sub>1</sub> ( $r=-0.57-0.60$ ), FEV<sub>1</sub>/forced vital capacity (FVC) ( $r=-0.75-0.82$ ), and DL<sub>CO</sub> ( $r=-0.57-0.64$ ). The percentage volume <-950 HU correlated more closely with DL<sub>CO</sub> and FEV<sub>1</sub> than did either the volumes <-910 and -900 HU. The authors concluded that lung densitometry derived from three-dimensional-lung models is an available alternative method compared with two-dimensional models for quantifying emphysema.

## Surgical treatment of emphysema

LVRS is a therapeutic option for severe debilitating emphysema, consisting of bilateral wedge resection of emphysematous lung by means of sternotomy, bilateral thoracotomy, or video-assisted thoracoscopic surgery [43]. This technique induces a one-time benefit improvement, peaking at 3–6 months after surgery, in terms of lung function, exercise tolerance, and quality of life [72–75]. The retrospective nature of patient selection and the inability to accurately quantify the amount of resected emphysematous lung tissue are two major obstacles that define criteria for a candidate's selection for LVRS [73]. Patients are usually selected on the basis of clinical, physiological and radio-anatomical assessments. Intolerable dyspnoea and exercise intolerance not palliated by medical therapy, and severe airflow obstruction, are the main clinical criteria. Conversely, anatomical features, consisting of lobar severity of emphysema, with a heterogeneous distribution of emphysema, are important for a better clinical outcome. Upper lobe predominance, greater amount of regional heterogeneity, and a larger percentage of normal- or mildly-emphysematous lung, showed the highest association with improvement of the quality of life and exercise tolerance [43].

In a study based on visual CT analysis of emphysema, WEDER *et al.* [76] showed that the mean increase in FEV<sub>1</sub> after LVRS was ~80, 40, and 35%, for heterogeneous, intermediately heterogeneous and homogeneous emphysema, respectively. However, this study revealed that preoperative characteristics of pulmonary function or chest CT morphology could not explain the post-operative improvement in term of FEV<sub>1</sub>.

In order to determine if quantitative CT provides relevant information for guiding patient selection, GIERADA *et al.* [2] compared CT quantification of pulmonary emphysema with FEV<sub>1</sub>, arterial oxygen tension ( $P_{a,O_2}$ ), and 6-min walk distance before and after LVRS. They showed that the values of quantitative CT indexes of global and regional emphysema severity were related to outcome measures after LVRS. Indexes of global emphysema severity include the mean lung attenuation, the percentage of whole lung with attenuation <-900 HU (emphysema index) and the percentage of whole lung with attenuation <-960 HU (severe emphysema index). Indexes of regional emphysema severity include emphysema indexes in the upper and lower halves of the lungs and the ratio of the emphysema index of the upper lung to that of lower lung. Post-operative improvement were better with a mean lung attenuation >-900 HU, an emphysema index of  $\geq 75\%$ , a severe emphysema index  $>25\%$ , a ratio of upper- and lower-lung emphysema indexes  $\geq 1.5$  and an upper-lung emphysema index  $>75\%$ . Considering other simple characteristics of the attenuation distribution curve, such as the standard deviation and the full width at half maximum, the authors did not identify the CT index for emphysema heterogeneity predictive of patient outcome.

As recently reviewed by KAZEROONI [43], a high upper-and lower-lung emphysema ratio has been the best predictor of improvement in term of FEV<sub>1</sub> and 6-min walk

distance until 2 yrs after bilateral apical LVRS. This ratio demonstrated a higher correlation with outcome than the percentage of emphysema of the whole lung and than the functional parameters reflecting hyperinflation such as RV, TLC, RV/TLC ratio and FEV<sub>1</sub>, or DL<sub>CO</sub> [43]. So, quantitative CT could play an important role in identifying potentially suitable candidates and standardising the pre-operative imaging evaluation of these candidates.

## New perspectives in pharmacotherapy

For many years it was hypothesised that in patients with  $\alpha_1$ -antitrypsin deficiency ( $\alpha_1$ -ATD), replacement therapy could prevent the progression of pulmonary emphysema. In a double-blind controlled study performed over a 3-yr period and involving 56 patients with  $\alpha_1$ -ATD deficiency of PI\*ZZ phenotype and moderate-to-severe emphysema, DIRKSEN *et al.* [3] estimated the loss of lung tissue by calculating the 15th lowest percentile of the attenuation distribution curve. DIRKSEN *et al.* [3] found that this loss tended to be higher in the group of untreated patients as compared with the group of patients treated by  $\alpha_1$ -AT infusion (p=0.07). In addition, power analysis showed that this protective effect would reach statistical significance in a similar trial with 130 patients in contrast to calculations based on annual decline of FEV<sub>1</sub> showing that 550 patients would need to show a 50% reduction in the annual decline. These authors concluded that lung density measurements could be more sensitive than PFTs for detecting the progression of emphysema and that CT may facilitate future randomised clinical trials.

## Conclusion

CT scanning is of particular interest for the *in vivo* diagnosis and quantification of pulmonary emphysema because this imaging technique offers measurements of both morphological and functional information with the possibility to interrelate structure and function. The presence and extent of pulmonary emphysema can be roughly estimated by visual assessment of CT sections but objective quantification is more accurate and more reproducible. This review showed the possible important role of CT in the diagnosis and quantification of pulmonary emphysema. Nevertheless, this technique is not yet standardised and important questions are still unsolved. Further studies are needed for the following purposes: 1) To establish normal values of reference. 2) To investigate the reproducibility of CT measurements. 3) To investigate the influence of image acquisition parameters on the CT measurements. 4) To compare the accuracy of various CT indexes based on a percentile of the frequency distribution curve such as the fifth or the 15th lowest one, on absolute thresholding such as RA950 or RA910, on regional lung inflation, or on a fractal dimension. 5) To evaluate the accuracy of CT to quantify as well as to diagnose pulmonary emphysema and to recognise subtypes of emphysema. 6) To validate new CT techniques such as multidetector systems. 7) To investigate the ability of CT to discriminate emphysema from other COPDs.

## Summary

Accurate diagnosis and quantification of pulmonary emphysema during life is important to understand the natural history of the disease, to assess the extent of the

disease, and to evaluate and follow-up therapeutic interventions. Since pulmonary emphysema is defined on pathological criteria, new methods of diagnosis and quantification should be validated by comparisons against histological references. Recent studies have addressed the capability of computed tomography (CT) to accurately quantify pulmonary emphysema. These studies, overviewed in this article, have been based on CT scans obtained after deep inspiration or expiration, on subjective visual grading and on objective measurements of attenuation values by using dedicated softwares providing numerical data, on two-dimensional and on three-dimensional approaches, and compared CT data with pulmonary function tests. More recently, textural analyses were applied on CT scans to assess the presence, the extent, and the types of emphysema.

Quantitative CT has already been used in patient selection for surgical treatment of pulmonary emphysema and in pharmaco-therapeutical trials. However, despite numerous and extensive studies already available, this technique has not yet been standardised and important questions about how to best use the CT for the quantification of pulmonary emphysema are still unsolved.

**Keywords:** Computed tomography, emphysema, diagnosis-emphysema.

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