Original Article

Quantification of Emphysema in Chronic Obstructive Pulmonary Disease by Volumetric Computed Tomography of Lung

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Abstract

Background and Objectives. Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease with small airway inflammation and emphysema. Emphysema is permanent enlargement of air spaces distal to terminal bronchioles accompanied by destruction of alveolar walls. These morphological changes can be studied on quantitative computed tomography (CT).

Methods. Thirty-four patients diagnosed to have COPD as per Global Initiative for Chronic Obstructive Lung Disease guidelines underwent chest CT using full inspiration with low dose radiation protocol. Pulmo-CT® software was used to analyse the scans. The primary aim was to quantify emphysema and emphysema clusters and secondary aim was to assess correlation between percentage emphysema and lung function.

Results. Their mean [standard deviation (SD)] age was 66.4 (7.0) years; 11 (32.4%) were current smokers (median pack years 45.5). Their mean (SD) forced expiratory volume in the first second (FEV_1%) was 55.6 (17.6), mean (SD) % emphysema was 26.8 (11.1), mean (SD) lung density was –848.35 (29.5) Hounsfield units (HU), median (interquartile range) %cluster class 4 emphysema was 22.4 (13.5–32.6). There was no significant difference in %low attenuation volume (%LAV) in current and ex-smokers (p=0.4); across various severity grades of COPD (p=0.15). Further, no significant correlation was observed between %emphysema and post-bronchodilator FEV_1%.

Conclusions. Volumetric CT can detect and quantify emphysema. Majority of emphysema clusters in COPD are ≥25mm. The %emphysema does not correlate to the severity of the disease. Quantitative CT is a good objective method to study emphysema and can be used to phenotype COPD radiologically. **[Indian J Chest Dis Allied Sci 2015;57:155-160]**

Key words: COPD, Volumetric CT, Low attenuation volume (LAV), Percentage emphysema and Hounsfield Units.

Introduction

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines chronic obstructive pulmonary disease (COPD) as a common preventable and treatable disease characterised by persistent airflow limitation that is usually progressive and associated with enhanced chronic inflammatory response in the airways and lung to noxious particles or gases.[1] Pathologically COPD involves small airways, lung parenchyma and pulmonary vasculature leading to small airway inflammation, emphysema and pulmonary hypertension. Emphysema is defined as permanent enlargement of air spaces distal to terminal bronchioles accompanied by destruction of alveolar walls. Emphysema can be centrilobular, panlobular, paraseptal and bullous. Histologically centrilobular emphysema is characterised by the loss of respiratory bronchioles while panlobular is uniform destruction of secondary pulmonary lobule. These pathological changes cannot be assessed by conventional chest radiographs but can be well studied on computed tomography (CT). Various CT techniques are available to quantify emphysema[2] and many studies have addressed the ability of CT to accurately quantify the extent and severity of emphysema.[3-5] Multi-detector row CT (MDCT) provides non-invasive methods to study the lung pathology. Apart from quantifying the overall lung destruction, CT helps in identifying the specific location in the lung where emphysema has occurred and also evaluate changes in small and large airways by measuring the airway wall thickness. Therefore, CT is able to precisely define the pathological process in COPD. We can now understand the natural history of COPD, quantify its extent, assess its progression, investigate structure-function relationship and also study the impact of therapeutic interventions based on radiological phenotypes.[6]

Hayhurst and colleagues[7] were first to quantify emphysema severity with CT and showed that Hounsfield units (HU) frequency distribution curves of patients with histologically proven emphysema differed significantly from patients without emphysema. In the 1980s and 1990s, the images were 10mm in thickness and these appeared blurry because of averaging of structures within the slice. With the

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advent of MDCT, we get thinner slices of entire chest within a single breath-hold of 5–15 seconds. These new CT scanners can visualise the airways, vessels and accurately measure lung density.

In 1988, the density mask was introduced and is based on a pre-defined voxel as a threshold to differentiate between areas of normal attenuation values and areas of low attenuation (LAA).[8] The density mask technique is defined as the percentage of LAA of total lung volume that contains voxels of lower attenuation value below –950HU. This type of densitometry analysis correlated with lung function.[9] The strongest pathologic correlation with emphysema at macroscopic[10] and microscopic[11] level has been observed at –950HU on 1mm non-contrast enhanced high resolution filtered images. Another method used is the 15th percentile cut-off in the attenuation distribution curve. It provides the HU under which 15% of voxels are distributed. However, densitometric analysis can not differentiate from centrilobular, panlobular, para-septal and bullous emphysema. This analysis is done by visual scoring (qualitative) but has inter-observer and intra-observer variability.[12]

It is difficult to detect earliest form of pulmonary emphysema on CT where size of lesion is less than 5mm on qualitative analysis.[13] It has also been observed that this method consistently under-estimates the extent of disease.[13] Intra- and inter-observer variations in visual assessment were significant, and hence, limited the reliability of this method. Therefore, research has been directed towards objective methods to quantify emphysema.

The primary aim of our study was to quantify total percentage of emphysema and emphysema clusters in COPD patients using inspiratory MDCT scans. The secondary aim was to assess the correlation between percentage emphysema and lung function.

Material and Methods

A sample size of 34 was calculated considering the standard deviation (SD) of 15.8 from a previous study[14] and assuming a desired total width of 95% confidence intervals as 11. In this observational descriptive study, we enrolled 34 tobacco smoke associated COPD patients reporting to out-patient clinic of a respiratory diseases hospital. After obtaining informed consent, patients aged 40 years or more were enrolled. Chronic obstructive pulmonary disease was diagnosed as per GOLD guidelines 2009[1] basing on post-bronchodilator ratio of forced expiratory volume in the first second (FEV_1) to forced vital capacity (FVC) less than 70% in stable clinical condition. We excluded patients with biomass smoke associated COPD, bronchial asthma, pulmonary tuberculosis, lung resection, bronchiectasis, diagnosis of silicosis, asbestosis or pulmonary fibrosis and patients who had experienced acute exacerbation of COPD four weeks prior to enrollment. This study was approved by the Institutional Ethics Committee. Spirometry was performed as per American Thoracic Society (ATS)/European Respiratory Society (ERS) 2005 guidelines[15] using Master Screen Diffusion spirometer (Jaeger, Germany). The parameters measured were FEV_1, FVC, FEV_1/FVC.

Computed tomography of the chest was performed using Siemens Somatom Definition AS (Siemens Healthcare, Germany), MDCT without intravascular contrast material. Automatic calibration and automated quality control tests were done daily and periodically as per built-in machine standards. A low dose radiation protocol was used (140 kVp and milliamperes (mAs) were set by Care dose 4D protocol). Care dose 4D offers a real-time anatomic exposure control, adjusting the dose according to patient's anatomy and position during the scan. The lung was scanned from apex to base in supine position. Inspiratory scans were acquired in a single breath-hold period and for this a trained technician coached the patient on correct inspiratory breath-hold technique. The images were then reconstructed using a kernel B40f and analysed using the Pulmo–CT® software. The trachea, main bronchi, mediastinal structures and soft tissue were selectively removed by the software. Lung density values were calculated by the density mask technique. Percentage of emphysema was defined as percentage of total voxels within the lung field below –950HU; also called %low attenuation volume (%LAV) less than –950HU. Clusters of emphysema were also analysed and defined as Class 1: if area of low attenuation below –950HU measuring $\geq$2mm to <8mm (blue); Class 2: $\geq$8mm to <15mm (green); Class 3; $\geq$15mm to <25mm (yellow); and Class 4: $\geq$25mm (red). The analysis was available in the form of histogram, tables and coloured images.

Statistical Analysis

Continuous variables were expressed as mean [standard deviation (SD)], median [inter-quartile range (IQR)]. Categorical variables were expressed as percentage. One-way analysis of variance (ANOVA) was used to compare percentage low attenuation volume and severity grades of COPD and Pearson's correlation to test relationship between %LAV and post-bronchodilator FEV_1 (%), and FEV_1/FVC (%). A p-value <0.05 was considered statistically significant.

Results

Their mean (SD) age was 66.4 (7.0); all were male tobacco smokers (Table 1). As per GOLD guidelines, five patients had mild COPD while 17 and 11 patients had moderately severe and severe COPD respectively; one patient had very severe COPD.

Tables 2 (A and B) shows the quantitative CT findings. The mean (SD) lung density was –848.35

Table 1. Patient characteristics (n=34)

Variable	Observations
Males [No. (%)]	34 (100)
Age (years) [mean (SD)]	66.4 (7.0)
Current smokers [No. (%)]	11 (32.4)
Ex-smokers [No. (%)]	23 (67.6)
Pack years [median (IQR)]	45.5 (28.7–70.2)
Post-bronchodilator FEV_1% [mean (SD)]	55.6 (17.6)
Post-bronchodilator FEV_1/FVC [mean (SD)]	50.6 (10.0)
Severity of COPD	**(No.)**
Mild	5
Moderate	17
Severe	11
Very severe	1

Definition of abbreviations: COPD=Chronic obstructive pulmonary disease; SD=Standard deviation; IQR=Inter-quartile range

(29.5) HU and the mean (SD) 25th percentile on the attenuation distribution curve was –956.2 (29.8) HU. Mean (SD) %emphysema was 26.8 (11.1). Emphysema was uniformly distributed in both the lungs (26.3%, 27.3% in right and left lung, respectively), of which Class 4 %emphysema was the most common cluster [median (IQR) 22.4 (13.5–32.6)]. There was no significant difference in the mean (SD) %LAV in current smokers [29.1(9.9)] and ex-smokers [25.7 (11.6)] (p=0.4).

Table 2A. Quantitative CT findings

Variable	Observations*
Mean lung density (HU)	–848.35 (29.5)
Right lung density (HU)	–846.6 (34.0)
Left lung density (HU)	–849.7 (27.3)
25th Percentile (HU)	–956.2 (29.8)
50th Percentile (HU)	–898.7 (26.3)
75th Percentile (HU)	–820.2 (41.7)
Total lung volume (mL)	4793.5 (1009.8)
Right lung volume (mL)	2546.3 (542.6)
Left lung volume (mL)	2247.2 (494.7)
%LAV	26.8 (11.1)
Right lung	26.3 (11.1)
Left lung	27.3 (11.5)

* All data are expressed as mean (standard deviation)

Definition of abbreviations: CT=Computed tomography; HU=Hounsfield units; %LAV=%Low attenuation volume

Table 2B. Cluster class volume

Clusters Class Volume (%)	Total Lung*	Right Lung*	Left Lung*
Class 1	1.0 (0.4–1.7)	0.7 (0.4–1.9)	0.7 (0.4–1.5)
Class 2	1.0 (0.4–1.8)	1.0 (0.4–1.8)	0.9 (0.4–1.7)
Class 3	0.31 (0.07–0.5)	0.3 (0.0–0.5)	0.3 (0.07–0.5)
Class 4	22.4 (13.5–32.6)	20 (12.2–33.0)	23.6 (14.1–33.9)

*Data are expressed as median (interquartile range)

There was also no significant difference between %LAV and severity grades of COPD (Table 3). When whole group was studied, there was no significant correlation between %emphysema and post-bronchodilator FEV_1% [correlation co-efficient (r)=0.05, p=0.75] and post-bronchodilator FEV_1/FVC (%) (r=–0.097, p=0.59).

Table 3. Severity of COPD and emphysema

Severity of COPD	No.	LAV%*	p-value
Mild	5	23.0 (12.1)	
Moderate	17	30.6 (10.7)	0.15
Severe	11	21.8 (10.0)	
Very Severe	1	34.5	

*All data are expressed as mean (standard deviation)

Definition of abbreviations: COPD=Chronic obstructive pulmonary disease; LAV=Low attenuation volume

We also observed that individuals with similar levels of physiologic impairment may have substantial, little or no emphysema (Figures 1 and 2). Both these patients had FEV_1 of 30%; but the %emphysema was 10.5% for the patient in figure 1 while it was 18.9% for the patient in figure 2. Further, patient in figure 2 had larger clusters of emphysema.

Discussion

Quantitative CT is a good objective method to quantify the percentage of lung having emphysema. In healthy individuals, the normal mean lung density on inspiratory scan is between –700 HU to –900 HU with a mean of –800 HU. In our patients with COPD the mean lung density was –848.35 HU, suggesting that emphysema is not detected on assessing overall mean lung density. The mean 25th percentile of mean lung density (MLD) was –956.2 HU, which is in the definition of emphysema range, thereby suggesting that percentile value helps in detecting emphysema. First percentile value is optimal for correlation with histology.[4] However, because of concern regarding artifact from image noise and truncation artifact at first percentile level, most studies use the 15th percentile threshold.[16,17]

We found that emphysema was equally distributed in both the lungs with cluster Class 4 being the largest collection of emphysematous spaces in lung. The mean LAV% was 26.8%. The distribution of emphysema in healthy individuals ranged from 1.07%[14] using a Siemens scanner to 2.73% in healthy military divers and submariners using a Philips scanner.[18] It is important to remember that quantitative measures can differ according to the CT scanner used, and hence, scanning parameters must be ascertained before comparing the results.[19] Even when repeating scans in longitudinal studies, it is recommended to keep the same scanning protocol.[20]

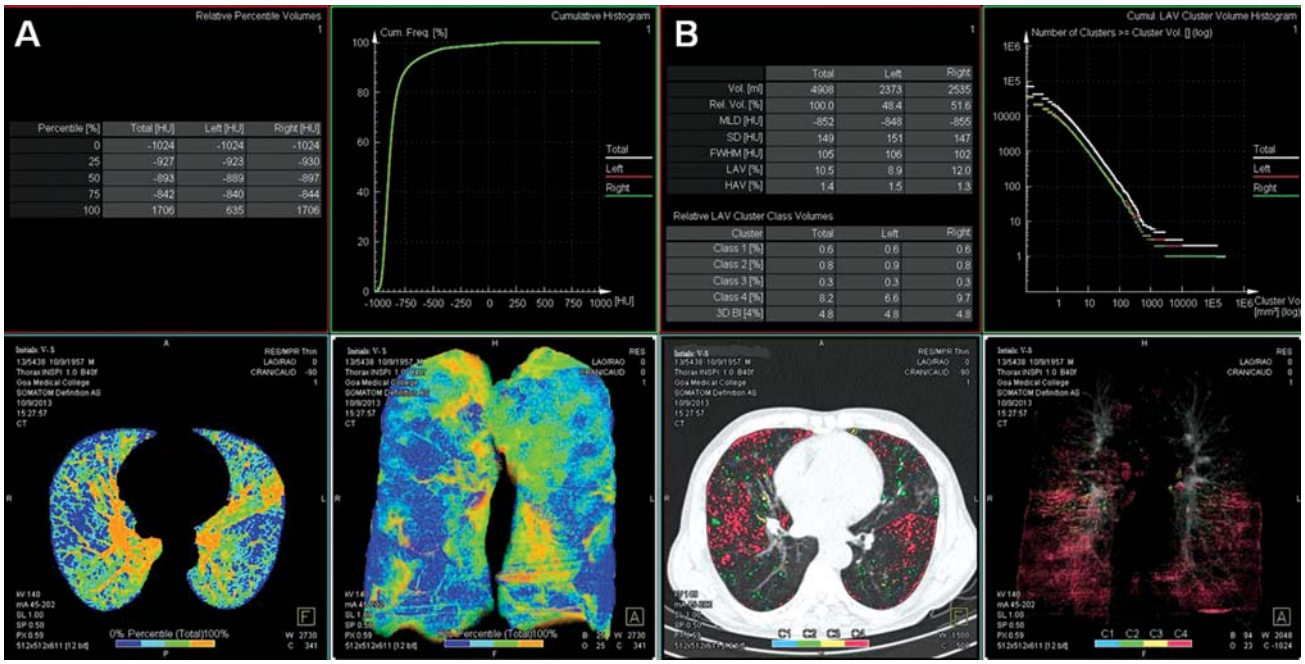

Figure 1. Distribution of relative percentile volumes: (A) in an ex-smoker (44 pack years) with severe COPD (post-bronchodilator FEV_1 30%). Quantitative data displaying average HU values by percentile. As shown in left upper panel, average density is calculated for the lowest 25th percentile expressed in HU. For this patient, the values were –923 HU for left lung and –930 HU for right lung. Distribution of relative low attenuation volume cluster class, and (B) of the same patient. All low density foci fall in class 4 category, with right lung more extensively involved. Graphical representation of these data is shown in upper panel, right.

Definition of abbreviations: **COPD=Chronic obstructive pulmonary disease; FEV_1=Forced expiratory volume in the first second; HU=Hounsfield units**

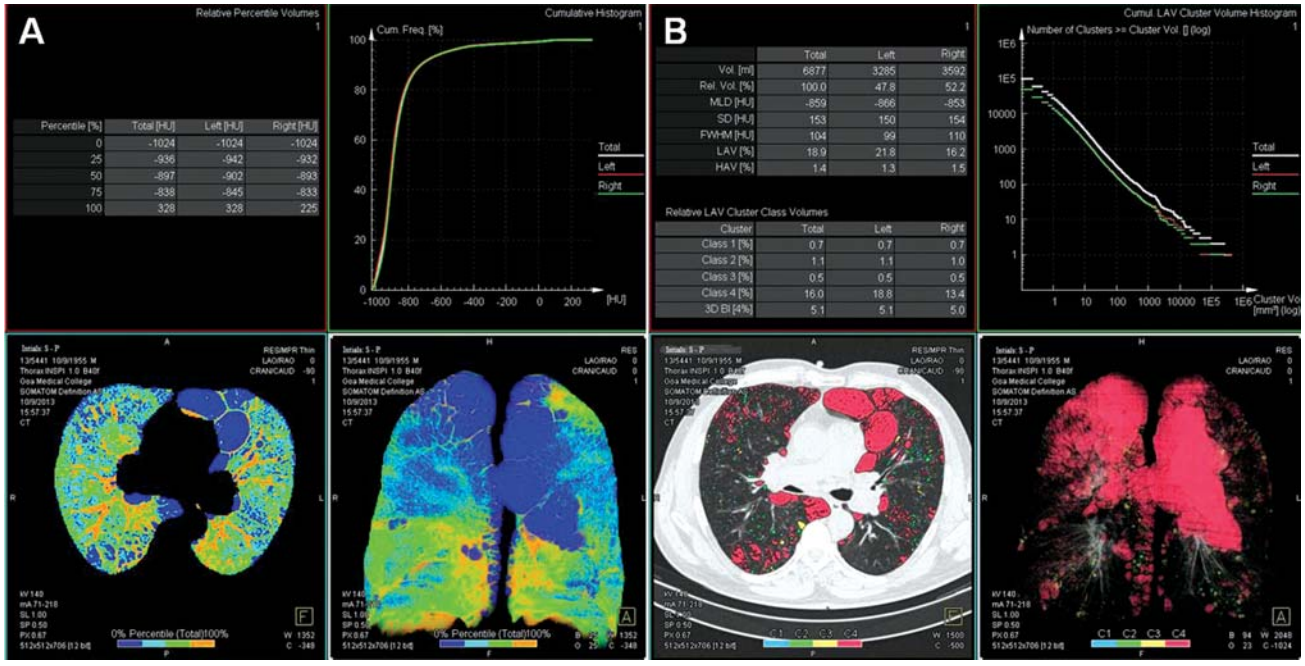

Figure 2. Distribution of relative percentile volumes; (A) in a current smoker (48 pack years) with severe COPD (post-bronchodilator FEV_1 30%). Quantitative data displaying average HU values by percentile. As shown in left upper panel, average density is calculated for the lowest 25th percentile expressed in HU. For this patient, the values were –942 HU for left lung and –932 HU for right lung. Distribution of relative low attenuation volume cluster class (B) of the same patient. All low density foci fall in class 4 category, with left lung more extensively involved. Graphical representation of these data is shown in upper panel, right.

Definition of abbreviations: **COPD=Chronic obstructive pulmonary disease; FEV_1=Forced expiratory volume in the first second; HU=Hounsfield units**

We also assessed the relationship between lung function and emphysema and did not find a significant correlation between lung function [post-bronchodilator FEV_1 (%)] and %emphysema. The %emphysema in mild COPD was similar to patient with moderate and severe COPD. Therefore FEV_1 alone does not explain the amount of emphysema in lung. As reported earlier,[21] we had observed that individuals with similar level of physiologic impairment may have substantial, little or no emphysema (Figures 1 and 2). In one study,[22] no correlation was observed between emphysema and FEV_1 in smokers without COPD and COPD stage 1 (r=–0.008, p=0.94). In another study,[23] also no correlation was noted between FEV_1 and %emphysema but mean airway luminal area and wall percentage showed significant correlation. However, a negative correlation between %emphysema and FEV_1% ranging from –0.67 to –0.09 was reported.[24,25] Our observations could have possibly been influenced by a small sample size.

Quantitative CT is used to assess outcome in therapeutic trial of COPD. In a recent study,[26] it was observed that airway wall thickening as assessed by CT was significantly reduced with combined bronchodilator therapy in COPD patients. Phenotyping the lung radiologically can identify emphysema predominant COPD, and hence, management can be personalised to treat the radiological phenotypes. Also as early emphysema does not manifest with clinical symptoms of COPD, it is advisable to get quantitative CT done in smokers. The CT findings may help in encouraging the patient to stop smoking as emphysema is also known to increase the risk of lung cancer in such patients.[27] Patients with COPD may also be followed up longitudinally with quantitative CT to assess the rate of progression of emphysema or response to therapeutic interventions.

There are some limitations to this study. The sample size was small and we could not study correlation between lung function to %emphysema. We also did not analyse airway wall thickening and air trapping which would complete the radiological phenotyping of COPD. Quantitative CT appears to be a useful tool to detect, quantify and phenotypically classify emphysema in tobacco smoke associated COPD.

Conclusions

Quantitative computed tomography is a good objective tool to detect and quantify emphysema in tobacco smoke associated COPD. %emphysema does not correlate to severity of COPD, hence, QCT can be use to phenotype COPD radiologically.

References

1. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014. *Available from URL:* http://www.goldcopd.org. Accessed on August 21, 2015.
2. Nakano Y, Muro S, Sakai H, Hirai T, Chin K, Tsukino M, *et al.* Computed tomographic measurements of airway dimensions and emphysema in smokers: correlation with lung function. *Am J Respir Crit Care* 2000;162:1102–8.
3. Coxson HO, Rogers RM. Quantitative computed tomography of chronic obstructive pulmonary diseases. *Acad Radiol* 2005;12:1457–63.
4. Madani A, Zanen J, de Maertelaer V, Gevenois PA. Pulmonary emphysema: objective quantification at multi-detector row CT—Comparison with macroscopic and microscopic morphometry. *Radiology* 2006;238:1036–43.
5. Matsuoka S, Kurihara Y, Yagihasi K, Nakajima Y. Quantitative thin-section CT analysis of the enlargement and coalescence of low-attenuation clusters in patients with emphysema. *Respiration* 2007;74:136–41.
6. Coxson HO. Quantitative chest tomography in COPD research: chairman's summary. *Proc Am Thorac Soc* 2008;5:874–7.
7. Hayhurst MD, MacNee W, Flenley DC, Wright D, McLean A, Lamb D, *et al*. Diagnosis of pulmonary emphysema by computerised tomography. *Lancet* 1984;2:320–2.
8. Muller NL, Staples CA, Miller RR, Abboud RT. "Density Mask". An objective method to quantitate emphysema using computed tomography. *Chest* 1988;94:782–7.
9. Kinsella M, Muller NL, Abboud RT, Morrison NJ, DyBuncio A. Quantification of emphysema by computed tomography using a "density mask" program and correlation with pulmonary function tests. *Chest* 1990;97:315–21.
10. Gevenois PA, de Maertelaer V, De Vuyst P, Zanen J, Yernault JC. Comparison of computed density and macroscopic morphometry in pulmonary emphysema. *Am J Respir Crit Care Med* 1995;152:653–7.
11. Gevenois PA, De Vuyst P, de Maertelaer V, Zanen J, Jacobovitz D, Cosio MG, *et al*. Comparison of computed desity and microscopic morphometry in pulmonary emphysema. *Am J Respir Crit Care Med* 1996;154:187–92.
12. Hersh CP, Washko GR, Jacobson FL, Gill R, Estepar RS, Reilly JJ, *et al.* Interobserver variability in the determination of upper lobe predominant emphysema. *Chest* 2007;131:424–31.
13. Miller RR, Muller NL, Veda S, Morrison NJ, Staples CA. Limitation of computed tomography in the assessment of emphysema. *Am Rev Respir Dis* 1989;139:980–3.
14. Temizoz O, Etlik O, Sakarya ME, Uzun K, Arslan H, Harman M, *et al*. Detection and quantification of the parenchymal abnormalities in emphysema using pulmo-CT. *Comput Med Imaging Graph* 2007;31:542–8.
15. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R and Coates A; ATS/ERS Task Force. Standardisation of spirometry. *Eur Respir J* 2005;26:319–38.
16. Stolk J, Dirksen A, van der Lugt AA, Hutsebaut J, Mathieu J, de Ree J, *et al*. Repeatability of lung density measurements with low-dose computed tomography in subjects with alpha-1-antitrypsin deficiency-associated emphysema. *Invest Radiol* 2001;36:648–51.
17. Heussel CP, Herth FJ, Kappes J, Hantusch R, Hartlieb S, Weinheimer O, *et al.* Fully automatic quantitative assessment of emphysema in computed tomography: comparison with pulmonary function testing and normal values. *Eur Radiol* 2009;19:2391–402.
18. Mets OM, van Hulst RA, Jacobs C, van Ginneken B, de Jong PA. Normal range of emphysema and air trapping on CT in young men. *AJR Am J Roentgenol* 2012;199:336–40.
19. Stoel BC, Bakker ME, Stolk J, Dirksen A, Stockley RA, Pittulainen E, *et al*. Comparison of the sensitivities of 5 different computed tomography scanners for the

assessment of the progression of pulmonary emphysema: a phantom study. *Invest Radiol* 2004;39:1–7.
20. Coxson HO. Computed tomography and monitoring of emphysema. *Eur Respir J* 2007;29:1075–7.
21. Lynch DA, Al-Qaisi MA. Quantitative computed tomography in chronic obstructive pulmonary disease. *J Thorac Imaging* 2013;28:284–90.
22. Yasunaga K, Chérot-Kornobis N, Edmé JL, Sobaszek A, Boulenguez C, Duhamel A, *et al*. Emphysema in asymptomatic smokers: quantitative CT evaluation in correlation with pulmonary function tests. *Diagn Interv Imaging* 2013;94:609–17.
23. Yahaba M, Kawata N, Iesato K, Matsuura Y, Sugiura T, Kasai H, *et al*. The effects of emphysema on airway disease: correlations between multi-detector CT and pulmonary function tests in smokers. *Eur J Radiol* 2014;83:1022–8.
24. Akira M, Toyokawa K, Inoue Y, Arai T. Quantitative CT in chronic obstructive pulmonary disease: inspiratory and expiratory assessment. *AJR Am J Roentgenol* 2009;192:267–72.
25. Washko GR, Criner GJ, Mohsenifar Z, Sciurba FC, Sharafkhaneh A, Make BJ, *et al*. Computed tomographic-based quantification of emphysema and correlation to pulmonary function and mechanics. *COPD* 2008;5:177–86.
26. Hoshino M, Ohtawa J. Computed tomography assessment of airway dimensions with combined tiotropium and indacaterol therapy in COPD patients. *Respirology* 2014;19:403–10.
27. de Torres JP, Bastarrika G, Wisnivesky JP, Alcaide AB, Campo A, Seijo LM, *et al*. Assessing the relationship between lung cancer and emphysema detected on low-dose CT of the chest. *Chest* 2007;132:1932–8.