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Quantitative computed tomography and aerosol morphometry in COPD and α_1-antitrypsin deficiency

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ABSTRACT: Relative area of emphysema below -910 Hounsfield units (RA-910) and 15th percentile density (PD15) are quantitative computed tomography (CT) parameters used in the diagnosis of emphysema. New concepts for noninvasive diagnosis of emphysema are aerosol-derived airway morphometry, which measures effective airspace dimensions (EAD) and aerosol bolus dispersion (ABD).

Quantitative CT, ABD and EAD were compared in 20 smokers with chronic obstructive pulmonary disease (COPD) and 22 patients with α_1-antitrypsin deficiency (AAD) with a similar degree of airway obstruction and reduced diffusion capacity.

In both groups, there was a significant correlation between RA-910 and PD15 and pulmonary function tests (PFTs). A significant correlation was also found between EAD, RA-910 and PD15 in the study population as a whole. Upon separation into two groups, the significance disappeared for the smokers with COPD and strengthened for those with AAD, where EAD correlated significantly with RA-910 and PD15. ABD was similar in the two groups and did not correlate with PFT and quantitative CT in either group.

In conclusion, based on quantitative computed tomography and aerosol-derived airway morphometry, emphysema was significantly more severe in patients with α_1-antitrypsin deficiency compared with patients with usual emphysema, despite similar measures of pulmonary function tests.

KEYWORDS: Aerosol science, airway obstruction, α_1-antitrypsin deficiency, emphysema, quantitative computed tomography

Pulmonary emphysema is defined in pathological terms [1], and lung biopsy is considered the gold standard to establish an accurate diagnosis. However, in clinical practice, lung biopsy is rarely used on this indication, because of the relatively high risk of the procedure and the availability of noninvasive methods of investigation that help to establish the diagnosis. A widely used method is the measurement of the forced expiratory volume in one second (FEV_1), which has the advantage of being inexpensive and easy to obtain; however, FEV_1 has low sensitivity [2, 3] and poor correlation to the degree of tissue destruction [4]. Accurate assessment of the severity of emphysema and identification of possible subtypes are pivotal in understanding the natural history of this complex disease. This will provide an opportunity to monitor the therapeutic effects of available and future remedies. In addition, a precise noninvasive diagnosis of emphysema at an early stage may further motivate patients to quit smoking; nevertheless, counselling to assist smoking cessation should be given, even in the absence of clinical, physiological and radiological features of emphysema.

Computed tomography (CT), and particularly high-resolution CT, reveals areas of low attenuation, which are the radiological equivalent of tissue loss seen in pathology specimens [5, 6]. CT is highly specific and sensitive in diagnosing emphysema [7], and *in vivo* studies have shown a correlation with pathology ranging 0.7–0.9 [7–9]. Due to their digital nature, CT images can be objectively evaluated by computer analysis to assess the presence and severity of emphysema. Commonly applied CT-derived measures of emphysema are the relative area of emphysema below -910 Hounsfield units (RA-910) [10] and the 15th percentile density (PD15) [11], which are derived from the histogram of pixel attenuation values obtained from image analysis.

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Other novel concepts suggested for noninvasive diagnosis of emphysema are aerosol-derived airway morphometry (ADAM), which measures effective peripheral airspace dimensions (EAD) [12], and aerosol bolus dispersion (ABD), which is a measure for convective gas mixing in the lungs [13]. Studies have shown that both parameters are significantly increased in patients with emphysema [14–16], reflecting enlargement of the distal airspaces and ventilation inhomogeneities. The purpose of this study was to compare quantitative CT, pulmonary function tests (PFTs), ABD and EAD in patients with chronic obstructive pulmonary disease (COPD), and assess the differences in these parameters between patients with usual COPD and patients with α_1-antitrypsin deficiency (AAD).

MATERIALS AND METHODS

Patients

This was a prospective study in which 43 patients (>50 yrs old) with COPD were initially included. One patient was subsequently excluded because CT showed multiple pulmonary metastases from a primary colon cancer. Of the remaining 42 patients, 20 patients (six males and 14 females) had usual COPD, and 22 (10 males and 12 females) had AAD of PI*ZZ phenotype verified by isoelectric focusing. COPD in both groups was defined as FEV1/forced vital capacity (FVC) <70% and FEV1 <80% predicted post-bronchodilator [17]. All patients with usual COPD were current smokers with a smoking history of >20 pack-yrs. No ex-smokers with usual COPD were included in the study. Two patients with AAD were life-long nonsmokers and 20 patients were ex-smokers for ⩾6 months before the study start. No active smokers with AAD were included. All 42 patients were free of any concomitant severe pulmonary or extrapulmonary disease. The study was approved by the Ethics Committee of the County of Copenhagen, Denmark, and all participants provided informed written consent. Patient characteristics are shown in table 1.

Pulmonary function tests

Each patient underwent PFTs prior to ABD studies and CT of the lungs. PFTs were performed according to European Respiratory Society recommendations [18, 19]. Patients visited the respiratory laboratory in the morning (Dept of Respiratory Medicine, Gentofte University Hospital, Hellerup, Denmark). A pressure-compensated flow plethysmography (Vmax 229; SensorMedics, Bilthoven, The Netherlands) was applied. First, three maximal forced expirations were recorded, and patients who demonstrated baseline FEV1 values <80% predicted underwent a reversibility test 15 min after the inhalation of 1 mg of terbutaline. Reversibility ⩾15% and ⩾200 mL resulted in exclusion from the study. Patients with irreversible airflow obstruction then underwent measurement of static lung volumes (*i.e.* total lung capacity (TLC) and residual volume (RV)). Carbon monoxide transfer coefficient (K_{CO}) was measured by the single-breath technique; alveolar volume (V_A) was obtained by the dilution of methane during the single-breath manoeuvre. The carbon monoxide diffusion capacity ($D_{L,CO}$) was calculated as the product of K_{CO} and V_A. Predicted values for PFT parameters were calculated according

TABLE 1 Characteristics of patients, and results of pulmonary function, quantitative computed tomography, aerosol-derived airway morphometry and aerosol bolus dispersion (ABD) tests

	All patients	Usual COPD	AAD	p-value
Subjects n	42	20	22	
Males/females	16/26	6/14	10/12	
Age yrs	63±8	67±7	60±6	<0.001
Smoker/ex-smoker/nonsmoker	20/20/2	20/0/0	0/20/2	
Height cm	169±8	165±6	171±9	0.020
Weight kg	69±14	63±10	74±16	0.009
FEV1 % pred	48±13	51±13	45±13	NS
FVC % pred	87±15	86±14	87±15	NS
FEV1/FVC	46±11	48±10	43±13	NS
TLC % pred	116±13	109±11	122±12	<0.001
RV % pred	170±41	154±40	184±36	0.012
RV/TLC	0.55±0.07	0.56±0.07	0.54±0.07	NS
$D_{L,CO}$ % pred	49±17	52±13	47±19	NS
K_{CO} % pred	61±19	67±18	55±19	0.032
RA-910 HU	29.7±16.8	19.3±11.2	39.2±15.5	<0.001
PD15 g·L^{-1}	69.8±27.6	87.3±21.4	53.8±22.8	<0.001
EAD20 mm	0.80±0.38	0.64±0.31	0.95±0.38	0.017
ABD600 cm^3	620±142	602±153	634±135	NS

Data are presented as n and mean±SD, unless otherwise stated. COPD: chronic obstructive pulmonary disease; AAD: α_1-antitrypsin deficiency; FEV1: forced expiratory volume in one second; % pred: % predicted; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; $D_{L,CO}$: carbon monoxide diffusing capacity of the lung; K_{CO}: carbon monoxide transfer coefficient; RA-910: relative area of emphysema below -910 Hounsfield units (HU); PD15: 15th percentile density; EAD20: effective peripheral airspace dimensions for a relative volumetric lung depth of 20% of the intrathoracic lung volume at breath hold; ABD600: ABD for boluses inhaled into a volumetric lung depth of 600 cm^3; NS: nonsignificant.

to the reference values proposed by the European Community for Steel and Coal [18, 19]. Results are shown in table 1.

Computed tomography

CT scans were performed as low-dose multi-slice CT using the LightSpeed QX/i (GE Medical Systems, Milwaukee, WI, USA). Volume scans of the entire lung were acquired and no contrast medium was used. Image acquisition was performed with 5-mm collimation, rotation time 0.8 s, 30-mm table feed per rotation (pitch$_x$=1.5), corresponding to a total scan time of 10–12 s. The voltage across the X-ray tube was 140 kV and the tube current was 40 mA. The field of view was 40 cm and the matrix size was 512×512. Patients were scanned at suspended full inspiration in the supine position in a caudal–cranial direction (z-axis) to avoid breathing artefacts at the level of the diaphragm. Images were reconstructed using low spatial-resolution algorithm (soft).

CT images were analysed using Pulmo-CMS (MEDIS Medical Imaging Systems, Leiden, The Netherlands). The program automatically detects the lung contours in contiguous (or overlapping) images using a region-growing algorithm to separate lung tissue from the thoracic wall and mediastinum at a threshold of -380 HU. The lung contours are then checked in each slice to ensure the correctness of the procedure and to edit the contours, if necessary. Afterwards, a frequency distribution of the pixel attenuation values of the total lung is generated. From this histogram, the total lung volume, the volume of air, RA$_{-910}$ and PD$_{15}$ are extracted. RA$_{-910}$ (also called the emphysema index) relies on the ''density mask'' concept, first described by MULLER *et al.* [10], and is defined as the percentage of voxels with attenuation values below -910 HU. The density mask provides an overall percentage of lung involvement by emphysema. PD$_{15}$ is also extracted from the histogram of pixel attenuation values and is defined as the density value in HU at which 15% of the voxels have lower densities. By adding 1,000, the density values can be converted into g·L^{-1} units (*e.g.* PD$_{15}$ of -950 HU corresponds to 50 g·L^{-1}, *i.e.* 15% of the voxels have a density <50 g·L^{-1}).

Aerosol morphometry

Monodisperse aerosol particles uniformly settle in calm air with a constant velocity (v_s). The motion of these particles, suspended within intrapulmonary airways or airspaces during breath holding, leads to particle deposition on airway or airspace surfaces. The particle-loss rate is larger for particles suspended within small airspaces than for particles located within large airspaces. The decline in particle number with time can be used to evaluate peripheral airspace dimensions [12].

For this purpose, the lungs are filled by an inspiration of a monodisperse aerosol. The inspired aerosol volume can be considered as comprised of small volume elements, which penetrate longitudinally into different volumetric lung depths (V_P). During a breath-holding period (t), the particles settle onto airway surfaces. The reduction of the particle concentration in a defined volume element is measured in the expired air. The particle recovery (R) is defined as the ratio of particle concentration in an exhaled and inhaled volume element, and R decreases with increasing breath-holding time (t). For each lung depth, this relationship can be approximated by the exponential function:

$$R(V_p) = \exp(-1.27\, v_{st}/EAD) \quad (1)$$

EAD is calculated for each volumetric lung depth V_P by fitting an exponential function to the recovery values measured for each lung depth and the corresponding breath-holding times.

The evaluation of R(V_P) requires the measurement of the particle concentration in the volume element penetrating into lung depth V_P during inspiration and in the volume element exhaled after exhalation of the aerosol volume V_P. This is achieved by continuous monitoring of particle concentration with an on-line, open-flow system combining aerosol photometry and pneumotachography. In this study, EAD was calculated for a relative volumetric lung depth of 20% of the intrathoracic lung volume at breath hold (EAD$_{20}$).

Aerosol bolus dispersion

Gas transport in the lungs is due to diffusion and convection. Since monodisperse aerosol particles with diameters 0.5–1 mm behave like a ''nondiffusive gas'', they can be used as tracers for convective gas transport [13]. Therefore, a small volume (bolus) of the inspired air is labelled with these particles. During inspiration, particles are convectively transported into air volumes, which are initially particle free. Therefore, in the exhaled air, the aerosol particles are distributed over a larger air volume than in the inhaled air and the bolus is dispersed.

The width of an exhaled aerosol bolus inhaled into a certain volumetric lung depth V_P can be quantified by its volumetric half width (H$_{50}$), which is defined as the air volume in which the particle concentration exceeds half the maximum concentration. To account for the contribution of the width of the inhaled bolus (H$_{50,i}$) to the width of the exhaled bolus (H$_{50,e}$), a corrected half-width ABD is introduced, which is given by:

$$ABD = \sqrt{(H_{50,e})^2 - (H_{50,i})^2} \quad (2)$$

In this study, ABD was calculated for boluses inhaled into a volumetric lung depth of 600 cm^3 (ABD$_{600}$).

Particle generation and classification

Monodisperse di-2-ethylhexyl sebacate (DEHS) droplets were produced by heterogeneous nucleation of DEHS vapour on NaCl nuclei in nitrogen. The aerosol was then diluted with particle-free air to achieve a particle concentration of 2×10^4 cm^{-3}. The terminal settling velocity (v_s) of the droplets was measured in a convection-free sedimentation cell. Particle size throughout the study was ~0.9 μm.

Statistical analysis

Pearson's correlation was performed to evaluate the relationship between PFTs, CT parameters and aerosol parameters. The unpaired t-test was used to investigate the statistical significance of differences between groups. The requested level of significance was 0.05.

RESULTS

Patient characteristics, pulmonary function tests and quantitative computed tomography

The mean age of the patients was 63 yrs (range 51–78 yrs). Patients with AAD were generally younger than patients with

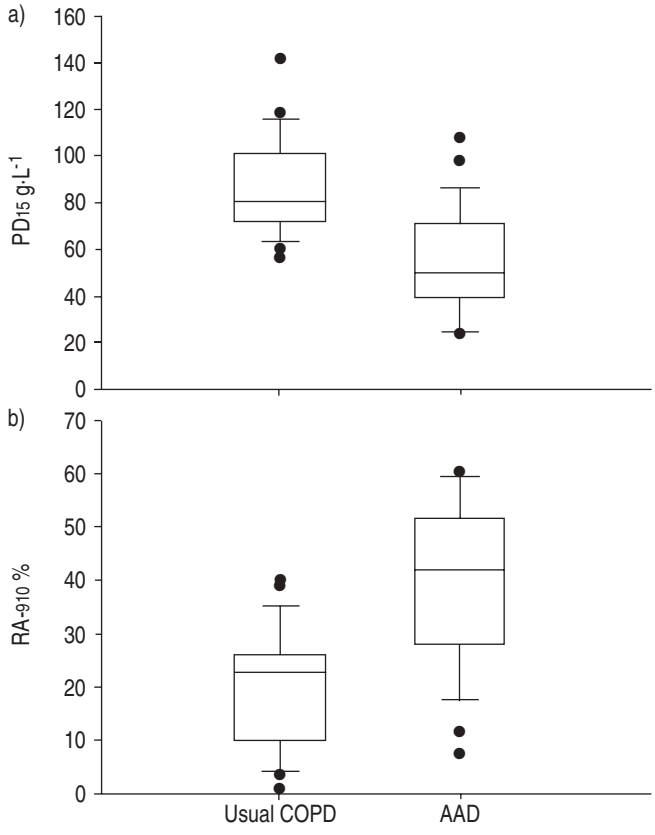

FIGURE 1. Box-plots of the 15th percentile density (PD_{15}) and relative area below -910 HU (RA_{-910}) in patients with α_1-antitrypsin deficiency (AAD) and patients with usual chronic obstructive pulmonary disease (COPD). The horizontal line represents the median. ●: outliers, *i.e.* observations below the 10th percentile and above the 90th percentile.

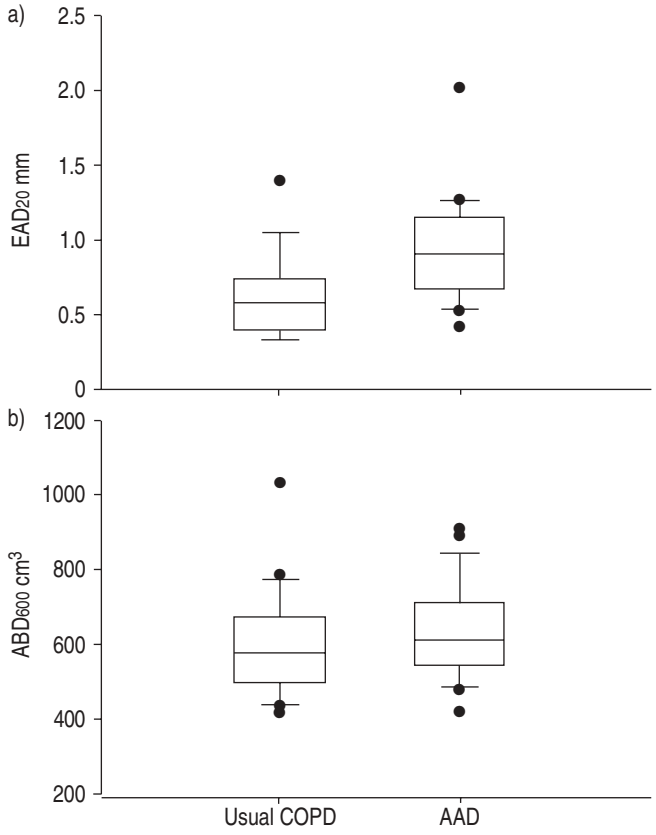

FIGURE 2. Box-plots of the effective airway diameter for a relative volumetric lung depth of 20% of the intrathoracic lung volume at breath hold (EAD_{20}) and aerosol bolus dispersion for boluses inhaled into a volumetric lung depth of 600 cm^3 (ABD_{600}) in patients with α_1-antitrypsin deficiency (AAD) and patients with usual chronic obstructive pulmonary disease (COPD). The horizontal line represents the median. ●: outliers, *i.e.* observations below the 10th percentile and above the 90th percentile.

usual COPD. Patient characteristics are shown in table 1. The degree of airway obstruction (FEV_1) and reduction in $D_{L,CO}$ in the two groups was similar, whether expressed in absolute values or % pred, calculated according to European equations [18, 19]. TLC and RV were significantly larger in patients with AAD, both in absolute and % pred values. In addition, lung density, as measured by either PD_{15} or RA_{-910}, was significantly different between the two groups (table 1; fig. 1).

Results of aerosol morphometry

Measurement of EAD at a relative lung depth (V_{pr}) of 20% was feasible in 16 patients with AAD and 15 patients with usual COPD. EAD_{20}, which indicates the presence of emphysema, was significantly higher in patients with AAD (mean±SD 0.95±0.38 mm) than patients with usual COPD (0.64±0.31 mm; p=0.017; fig. 2). In addition, EAD_{20} in both groups was significantly higher than values reported in healthy individuals (0.34±0.05 mm; p<0.001) [12].

Measurement of ABD_{600} was obtained from all patients with AAD and 17 patients with usual COPD. ABD_{600} was elevated in all patients with AAD (634±135 cm^3) and all patients with usual COPD (602±153 cm^3). In both groups, ABD_{600} was significantly higher than previously reported normal values in healthy individuals (346±53 cm^3; p<0.001) [13]. However, there was no statistically significant difference in ABD_{600} between the two patient groups (p=0.49; table 1; fig. 2).

Correlation between pulmonary function tests and computed tomography parameters

When the whole group was considered, there was highly significant correlation between PD_{15} and RA_{-910} on one side and measures of airway obstruction, hyperinflation and the diffusion capacity on the other. When each group was analysed separately, the same significant correlation was found, except for the correlation between RA_{-910} and $D_{L,CO}$ % pred in patients with usual COPD, which did not reach statistical significance (r=-0.44; p=0.05). Correlation coefficients are shown in table 2.

Correlation between pulmonary function test and aerosol morphometry

Results of the correlation analysis between EAD_{20} and ABD_{600} and PFTs in both groups are shown in table 2. In brief, EAD_{20} showed significant negative correlation with the diffusion capacity, both in patients with AAD and usual COPD. In both groups, no correlation was found between EAD_{20} and

TABLE 2 Correlation between pulmonary function test (PFT), computed tomography parameters and aerosol parameters for the whole patient group and for each subgroup

PFT	All patients				Usual COPD				AAD			
	PD_{15}	RA_{-910}	EAD_{20}	ABD_{600}	PD_{15}	RA_{-910}	EAD_{20}	ABD_{600}	PD_{15}	RA_{-910}	EAD_{20}	ABD_{600}
FEV_1	0.62**	-0.62**	-0.42*	-0.13	0.67**	-0.64**	-0.49	0.09	0.61**	-0.65**	-0.28	-0.29
FEV_1/FVC	0.61**	-0.62**	-0.40*	-0.17	0.81**	-0.75**	-0.46	-0.04	0.51*	-0.57**	-0.33	-0.23
TLC %	-0.71**	0.76**	0.33	0.11	-0.61**	0.68**	-0.13	-0.10	-0.55**	0.66**	0.27	0.20
RV %	-0.67**	0.73**	0.30	0.20	-0.56**	0.64**	-0.02	0.00	-0.64**	0.72**	0.16	0.33
$D_{L,CO}$	0.62**	-0.62**	-0.69**	-0.06	0.54*	-0.44	-0.61*	-0.17	0.78**	-0.77**	-0.76**	0.03
K_{CO}	0.66**	-0.65**	-0.74**	-0.05	0.49*	-0.40	-0.45	-0.15	0.71**	-0.72**	-0.83**	0.10

COPD: chronic obstructive pulmonary disease; AAD: α_1-antitrypsin deficiency; PD_{15}: 15th percentile density; RA_{-910}: relative area below -910 Hounsfield units; EAD_{20}: effective airway diameter for a relative volumetric lung depth of 20% of the intrathoracic lung volume at breath hold; ABD_{600}: aerosol bolus dispersion for boluses inhaled into a volumetric lung depth of 600 cm^3; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; $D_{L,CO}$: carbon monoxide diffusing capacity of the lung; K_{CO}: carbon monoxide transfer coefficient. *: $p<0.05$; **: $p<0.01$.

measures of airway obstruction and hyperinflation; however, EAD_{20} correlated significantly with FEV_1 and FEV_1/FVC, when all patients were considered. ABD_{600} in both groups did not correlate with any measurement of PFT.

Correlation between computed tomography parameters and aerosol morphometry

When all 42 patients were considered, a significant correlation was found between EAD_{20} and PD_{15} ($r=-0.67$; $p<0.001$) and RA_{-910} ($r=0.64$; $p<0.001$). Upon dividing the study population into two groups, the significance disappeared for the patients with usual COPD, and strengthened for the patients with AAD, where EAD_{20} showed a significant negative correlation with PD_{15} ($r=-0.80$; $p<0.001$) and a significant positive correlation with RA_{-910} ($r=0.71$; $p=0.002$). ABD_{600} was similar in both groups, and showed no significant correlation with PD_{15}, RA_{-910} or EAD_{20} in either group. Results of the correlation analysis are shown in table 3.

DISCUSSION

Expiratory airflow limitation is the hallmark physiological change of COPD. However, the pathological changes of the disease precede airflow limitation by a number of years, and measures of airflow limitation correlate relatively poorly with the severity of emphysema and are insensitive in mild emphysema [4]. Studies have shown that mild-to-moderate emphysema can be present without reduction in FEV_1 [2, 3, 20]. Conversely, diffusion capacity has better correlation to the pathological extent of emphysema [4], but the method has relatively large variability and is unspecific for emphysema. GURNEY [21] put forward that measures of PFT give a global indication of lung function missing information about the morphological subtype, anatomical distribution and severity of tissue involvement. This is clearly supported by the current study, which shows that two distinct subgroups of patients with different degrees of emphysema may have similar FEV_1 and $D_{L,CO}$.

The severity of emphysema was assessed noninvasively by two completely different approaches: a radiological approach using quantitative CT, and a physiological approach using aerosol probing to measure the diameter of the distal airspaces. CT is more sensitive than PFT in the diagnosis of pulmonary emphysema, and investigators have suggested quantitative CT to assess the severity of emphysema [10, 22, 23]. Both visual [6, 24] and computer assessment [8, 10, 22, 25] of CT in emphysema have shown a good correlation with the pathological extent of emphysema, thus reflecting the characteristic feature of the disease, namely permanent airspace enlargement without obvious fibrosis [1]. The same aspect of the disease is studied by ADAM, which measures airspace dimensions. For

TABLE 3 Correlation between computed tomography parameters and aerosol parameters for the whole patient group and for each subgroup

	All patients[#]		Usual COPD[¶]		AAD[+]	
	PD_{15}	RA_{-910}	PD_{15}	RA_{-910}	PD_{15}	RA_{-910}
EAD_{20}	-0.67**	0.64**	-0.22	0.15	-0.80**	0.71**
ABD_{600}	-0.18	0.17	0.00	-0.06	-0.26	0.24

COPD: chronic obstructive pulmonary disease; AAD: α_1-antitrypsin deficiency; PD_{15}: 15th percentile density; RA_{-910}: relative area below -910 Hounsfield units; EAD_{20}: effective airway diameter for a relative volumetric lung depth of 20% of the intrathoracic lung volume at breath hold; ABD_{600}: aerosol bolus dispersion for boluses inhaled into a volumetric lung depth of 600 cm^3. [#]: n=42; [¶]: n=20; [+]: n=22. **: $p<0.01$.

the distal airspaces, EAD can be considered to be equivalent to the mean linear intercept [26].

The most common morphological subtype of emphysema is centrilobular emphysema (CLE), which is strongly associated with smoking. The morphological subtype associated with AAD is panlobular emphysema (PLE), characterised by uniform destruction of the pulmonary lobules with lower lobe predominance. In the current study, CT lung density using both RA-910 and PD15 revealed twice as much extensive emphysema in patients with AAD than smokers with CLE, despite the two groups being clinically matched and having the same degree of airflow limitation and reduction in diffusion capacity. The correlation between CT parameters and PFT parameters shows that CT performs equally well for parameters of airway obstruction (FEV_1 and FEV_1/FVC), hyperinflation (TLC and RV) and alveolar surface area ($D_{L,CO}$) for the whole population, for patients with AAD and usual COPD. Regarding alveolar surface area, CT performance is better for AAD than for usual COPD; this is a clear reflection of the more extensive alveolar destruction associated with PLE in AAD.

The marked difference in quantitative CT between the two groups cannot simply be explained by the difference in hyperinflation. GEVENOIS *et al*. [27] studied the effect of acute and chronic hyperinflation on CT lung density in a group of asthmatics. They found that CT lung density, using CT mean lung density (MLD) and relative area below -950 HU (RA-950), did not change significantly after bronchial challenge inducing air trapping in a group of mild asthmatics. Furthermore, lung density in a second group of patients with chronic asthma and hyperinflation was not different from the control group, despite a significant difference in RV and TLC [27].

EAD was obtained at a V_{pr} of 20% of the intrathoracic gas volume at breath hold, because this lung depth certainly represents peripheral lung regions [16]. A total of 15 patients with usual COPD (75%) and 16 with AAD (73%) were able to respire the air volume necessary for obtaining EAD_{20}. The fact that the measurement was inconclusive in one-quarter of the study population is a clear limitation of the technique and the current study. EAD_{20} of all patients was greater than in normal individuals; nevertheless, the higher values in patients with AAD confirm the CT finding that distal airspaces in those patients are larger, again reflecting more severe lung destruction than in usual COPD. However, the potential of CT to separate the two subgroups seems to be much bigger than for EAD (figs 1 and 2).

BEINERT *et al*. [14] reported EAD in 25 patients with COPD, 14 with usual COPD and nine with AAD admitted for *i.v.* substitution therapy. The mean EAD in usual COPD was 0.64 ± 0.15 mm, which is similar to the results in the current study. In addition, they noticed that patients with AAD had the largest EAD values (1.14 ± 0.31 mm). Their figures are significantly higher than those reported in the current study ($p<0.05$), probably as a result of more severe illness. BEINERT *et al*. [14] measured MLD in 10 patients, five with AAD, and found the closest relationship to EAD ($r=-0.82$; $p<0.05$). However, MLD is more influenced by the partial volume effects and pixels with higher CT density than the parameters used in the current study (PD15 and RA-910).

EAD_{20} in patients with usual COPD was significantly higher than in healthy individuals, which suggests the presence of a certain degree of emphysema in most patients with COPD. This is also confirmed by the high RA-910 and low PD15. Pathological studies have shown a high incidence of CLE and paraseptal emphysema in heavy smokers with or without airway obstruction [28]. *Post mortem* studies have shown that emphysema is common in autopsies, and mild degrees of emphysema have been reported in 50–70% of cases [29].

There is an important difference between the two study groups; all patients with usual COPD were current smokers, whereas 20 patients with AAD were ex-smokers and two were life-long nonsmokers. This factor may contribute to the significant difference in airspace size assessed by EAD and lung density assessed by quantitative CT. Some of the difference might be due to the ongoing inflammation and excessive mucus secretion in smokers with usual COPD [30]; however, the inflammatory changes only partially subside after smoking cessation [31]. This is evident in patients with AAD, where progressive airway obstruction and tissue destruction take place, despite smoking cessation. The probable contribution of small airway disease to the difference between the two groups is difficult to assess in the current design. To the current authors' knowledge, there are no comparative or longitudinal studies of the influence of smoking cessation on distal airspace size or lung density changes. These are undoubtedly interesting areas for future research.

The current authors are not aware of any previous study of ABD_{600} in patients with AAD. ABD_{600} was similarly increased in the two patient groups, reflecting similar degrees of disturbances in lung ventilation. It has been shown previously that ABD is increased in patients with emphysema [15, 32]. ABD is also slightly increased in smokers without airway obstruction [32], in children with mild asthma [33], and in patients with cystic fibrosis [34]. Those and other studies have shown that ABD assesses different aspects of the pulmonary physiology than PFT. This is also clear from the current results, which show no significant correlation between ABD and any measure of PFT. However, one study in patients with emphysema has shown some correlation between ABD_{600} and FEV_1 ($r=-0.37$; $p<0.05$), but no correlation to static lung volumes and diffusion capacity [35]. ABD_{600} seems to be sensitive to the early changes in lung physiology that lead to ventilation inhomogeneity; however, the method is unspecific for emphysema and is incapable of assessing the severity of emphysema and differentiating between subtypes of emphysema. This is also obvious from the correlation analysis with CT lung density, which did not reveal any significant correlation, even in patients with AAD with more severe emphysema. In contrast to the current findings, KOHLHAUFL *et al*. [16] reported a significant correlation between ABD_{600} and relative area below -900 HU, relative area below -925 HU, RA-950, MLD and visual scoring of emphysema. The explanation for this discrepancy is not clear.

In conclusion, the current study shows remarkable differences in quantitative computed tomography parameters and effective peripheral airspace dimension between smokers with usual chronic obstructive pulmonary disease and patients with

α_1-antitrypsin deficiency. These differences seem to be closely related to the pathological changes that are characteristic of the subtype of emphysema, and can only partly be explained by differences in pulmonary function tests.

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REFERENCES

1 Snider GL, Kleinerman JL, Thurlbeck WM. 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.
2 Gurney JW, Jones KK, Robbins RA, *et al.* Regional distribution of emphysema: correlation of high-resolution CT with pulmonary function tests in unselected smokers. *Radiology* 1992; 183: 457–463.
3 Klein JS, Gamsu G, Webb WR, Golden JA, Muller NL. High-resolution CT diagnosis of emphysema in symptomatic patients with normal chest radiographs and isolated low diffusing capacity. *Radiology* 1992; 182: 817–821.
4 MacNee W, Gould G, Lamb D. Quantifying emphysema by CT scanning. Clinicopathologic correlates. *Ann N Y Acad Sci* 1991; 624: 179–194.
5 Foster WL Jr, Pratt PC, Roggli VL, Godwin JD, Halvorsen RA Jr, Putman CE. Centrilobular emphysema: CT-pathologic correlation. *Radiology* 1986; 159: 27–32.
6 Hruban RH, Meziane MA, Zerhouni EA, *et al.* High resolution computed tomography of inflation-fixed lungs. Pathologic-radiologic correlation of centrilobular emphysema. *Am Rev Respir Dis* 1987; 136: 935–940.
7 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.
8 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: 653–657.
9 Miller RR, Muller NL, Vedal S, Morrison NJ, Staples CA. Limitations of computed tomography in the assessment of emphysema. *Am Rev Respir Dis* 1989; 139: 980–983.
10 Muller NL, Staples CA, Miller RR, Abboud RT. ''Density mask''. An objective method to quantitate emphysema using computed tomography. *Chest* 1988; 94: 782–787.
11 Dirksen A, Friis M, Olesen KP, Skovgaard LT, Sorensen K. Progress of emphysema in severe alpha 1-antitrypsin deficiency as assessed by annual CT. *Acta Radiol* 1997; 38: 826–832.
12 Brand P, Rieger C, Beinert T, Heyder J. Aerosol derived airway morphometry in healthy subjects. *Eur Respir J* 1995; 8: 1639–1646.
13 Brand P, Rieger C, Schulz H, Beinert T, Heyder J. Aerosol bolus dispersion in healthy subjects. *Eur Respir J* 1997; 10: 460–467.
14 Beinert T, Brand P, Behr J, Vogelmeier C, Heyder J. Peripheral airspace dimensions in patients with COPD. *Chest* 1995; 108: 998–1003.
15 Kohlhaufl M, Brand P, Selzer T, *et al.* Diagnosis of emphysema in patients with chronic bronchitis: a new approach. *Eur Respir J* 1998; 12: 793–798.
16 Kohlhaufl M, Brand P, Rock C, *et al.* Noninvasive diagnosis of emphysema. Aerosol morphometry and aerosol bolus dispersion in comparison to HRCT. *Am J Respir Crit Care Med* 1999; 160: 913–918.
17 Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med* 2001; 163: 1256–1276.
18 Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993; 16: 5–40.
19 Cotes JE, Chinn DJ, Quanjer PH, Roca J, Yernault JC. Standardization of the measurement of transfer factor (diffusing capacity). Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993; 16: 41–52.
20 Sashidhar K, Gulati M, Gupta D, Monga S, Suri S. Emphysema in heavy smokers with normal chest radiography. Detection and quantification by HCRT. *Acta Radiol* 2002; 43: 60–65.
21 Gurney JW. Pathophysiology of obstructive airways disease. *Radiol Clin North Am* 1998; 36: 15–27.
22 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.
23 Flenley DC. Diagnosis and follow-up of emphysema. *Eur Respir J Suppl* 1990; 9: 5s–8s.
24 Bergin C, Muller N, Nichols DM, *et al.* The diagnosis of emphysema. A computed tomographic-pathologic correlation. *Am Rev Respir Dis* 1986; 133: 541–546.
25 Gevenois PA, De Vuyst P, De Maertelaer V, *et al.* Comparison of computed density and microscopic morphometry in pulmonary emphysema. *Am J Respir Crit Care Med* 1996; 154: 187–192.
26 Rosenthal FS. Aerosol recovery following breathholding derived from the distribution of chord length in pulmonary tissue. *J Aerosol Sci* 1989; 20: 267–277.
27 Gevenois PA, Scillia P, De Maertelaer V, Michils A, De Vuyst P, Yernault JC. The effects of age, sex, lung size, and hyperinflation on CT lung densitometry. *Am J Roentgenol* 1996; 167: 1169–1173.
28 Remy-Jardin M, Remy J, Gosselin B, Becette V, Edme JL. Lung parenchymal changes secondary to cigarette smoking: pathologic-CT correlations. *Radiology* 1993; 186: 643–651.
29 Newell JD Jr. CT of emphysema. *Radiol Clin North Am* 2002; 40: 31–42.
30 Hogg JC, Chu F, Utokaparch S, *et al.* The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 2004; 350: 2645–2653.
31 Willemse BW, Postma DS, Timens W, ten Hacken NH. The impact of smoking cessation on respiratory symptoms,

lung function, airway hyperresponsiveness and inflammation. *Eur Respir J* 2004; 23: 464–476.

32 Brand P, Tuch T, Manuwald O, *et al.* Detection of early lung impairment with aerosol bolus dispersion. *Eur Respir J* 1994; 7: 1830–1838.

33 Schulz H, Schulz A, Brand P, *et al.* Aerosol bolus dispersion and effective airway diameters in mildly asthmatic children. *Eur Respir J* 1995; 8: 566–573.

34 Anderson PJ, Blanchard JD, Brain JD, Feldman HA, McNamara JJ, Heyder J. Effect of cystic fibrosis on inhaled aerosol boluses. *Am Rev Respir Dis* 1989; 140: 1317–1324.

35 Kohlhaufl M, Brand P, Meyer T, *et al.* Detection of impaired intrapulmonary convective mixing by aerosol bolus dispersion in patients with emphysema. *Eur J Med Res* 1997; 2: 121–128.