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Aerosol-derived Airway Morphometry (ADAM) in Patients with Lung Emphysema Diagnosed by Computed Tomography – Reproducibility, Diagnostic Information and Modelling

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Abstract
Gravitational deposition of monodisperse particles can be used to determine effective airway diameter (EAD). The aim of our study was to assess intraindividual variability of EAD in healthy subjects and patients with emphysema, to compare EAD in patients with different degree and type of emphysema, and to evaluate whether parametric or model analysis would improve the results. EAD was measured *vs* volumetric lung depth (LD) in 11 healthy subjects (FEV_1 107%pred) and 41 patients with emphysema (FEV_1 60%pred; 8/9/24 mild/moderate/severe, 18/7/16 centriacinar/panacinar/bullous according to HRCT). Repeated measurements in LDs of 6-30% showed coefficients of variation of 7.0-10.4% in healthy subjects and 8.3-11.9% in emphysema. Average EAD in 10-16% LD was increased in emphysema, in particular moderate and severe ($p<0.05$, each). The slope of EAD in 10-16% LD differed between healthy subjects and emphysema, especially bullous and centriacinar. Patients with severe emphysema also showed a different slope compared to mild emphysema and controls. The parameters of the power function used for data fitting also showed differences between controls and emphysema, as well as between centriacinar *vs* panacinar and bullous emphysema. In a three-compartment lung model only the diameter of the intermediate compartment was enlarged in emphysema. We conclude that in using aerosol-derived airway morphometry, reproducibility of repeated measurements is acceptable. Average values and slopes of the EAD curve, as well as a power function for data fitting, were sensitive in the detection of type and severity of emphysema. In contrast, application of a lung model did not improve the results.

Key words: Airway dimensions, lung model, parametric fitting, diagnostic power

Introduction

The technique of gravitational deposition of monodisperse particles has been introduced to estimate effective airspace dimensions within the lung [1] (for a review see [2]). Enlarged peripheral airspaces are found in diseases such as lung emphysema. While conventional chest radiography [3] and pulmonary function tests [4] are helpful in the diagnosis of fully developed emphysema, they are insufficient in the detection of early stages of diffuse lung emphysema. They also do not perform well in quantifying the extent of alterations in this disease. Thus alternative, preferentially non-invasive, methods that offer such information are of interest in lung emphysema.

As demonstrated by the study of papain-induced emphysema in animals [5], aerosol-derived airway morphometry (ADAM) is a sensitive tool in the detection of early stages of emphysema. The method is also capable of detecting and quantifying the enlargment of peripheral airspaces in patients with manifest emphysema [6-8]. In these studies airspace dimensions were expressed in terms of effective airspace diameter (EAD) as a function of absolute volumetric lung depth ranging from 200 to 800 mL.

Compared to the approach of taking absolute lung depth as a reference, variability is reduced when EAD is plotted against relative lung depth in terms of percent endinspiratory lung volume. The improvement is due to the elimination of the proximal shift of the aerosol [9]. For relative depths between 2 and 30 % of endinspiratory volume, reference values of airway dimensions are available that have been determined in 79 healthy subjects [10]. In assessing the clinical usefulness of the aerosol method, information on the intraindividual variability of EAD measurements in healthy subjects and patients with emphysema would be helpful. Such data are still lacking.

Available data indicate a high sensitivity and specificity of EAD values in recognising the presence or absence of emphysema in patients with bronchitis. Patients were categorized according to high-resolution computed tomography (HRCT) [11], which was either visually graded [12] or quantified by densitometry [13].

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Aerosol technique and HRCT seem to be complementary in their ability to detect different forms of emphysema [14]. Whereas CT is more sensitive with regard to localised lesions, aerosol morphometry is particularly suitable for revealing diffuse alterations. These analyses used peripheral EAD data. No attempt was made to take advantage of the characteristics of the EAD *vs* lung LD curve. Furthermore, the possibility to extrapolate LD into the lung periphery beyond 30 % of endinspiratory volume by using appropriate models was not explored. This raises the question whether analysis of EAD values by parametric functions or lung models that are capable of condensing information allows to further improve their diagnostic usefulness.

Based on these considerations, the aim of the present study was (1) to evaluate intraindividual variability of EAD in healthy subjects and patients with emphysema, (2) to determine EAD in patients with different degree and type of emphysema and to assess the diagnostic reliability of the method, (3) to evaluate whether a parametric analysis of the EAD data or the application of a lung model would improve the usefulness of the method. The present detailed and advanced analysis relies on basic data a summary of which has been included in a state-of-the-art article comparing the results of different investigators [15].

Materials and Methods

Patients

Fourty-one patients with lung emphysema (35m/6f; age: 36-82 y; Table 1) and 11 healthy nonsmokers (7m/4f; age, 22-47 y; Table 1) were enrolled into this study. Patients were either smokers or ex-smokers. The diagnosis of emphysema was based on clinical [16], as well as lung function [17] and radiological criteria [11, 18]. Nine patients had severe homozygotic a1-antitrypsin deficiency. In 4 patients with a history of tobacco smoking and symptoms of chronic bronchitis, the diagnosis of emphysema relied exclusively on high-resolution computed tomography (HRCT). Thirty-eight patients received long-term anti-obstructive and/or anti-inflammatory therapy. Acute reversibility of airway obstruction (ΔFEV_1>15 %) after inhalation of a β_2-adrenoceptor agonist was shown by 4 patients but none of them reported symptoms of asthma. Conventional CT was available in 8 out-patients with severe bullous emphysema; the remaining 33 patients with emphysema underwent a HRCT. According to CT results, patients were assigned to three subgroups of different severity and three subgroups of different type. The healthy subjects were free of cardiopulmonary disease and non-atopic. They also did not have had exposure against noxious agents. Lung function was always within the normal range [17|. HRCT was carried out in 7 of the healthy subjects. The study was approved by the local Ethics Committee and informed written consent was obtained from all participants.

Aerosol-derived Airway Morphometry (ADAM)

Measurements were performed using monodisperse (0.8-1.0 μm aerodynamic diameter) particles of di-2-ethylhexyl sebacate [9, 10] and prototype equipment developed by Pari GmbH, Starnberg, Germany. Because of the constant settling velocity the gravitational loss of particles during breathholding is greater the smaller the airways are. The average diameter thus derived in a fixed lung depth has been termed effective airway diameter EAD. Similarly, the relative loss increases with the time of breathholding. Based on this, it can be shown [1, 15] that the particle recovery from each lung depth, R(LD), is related to EAD at this lung depth,, settling velocity (v_s) and breathholding time (t_p) by $R(LD) = \exp(-1.27 \cdot v_s \cdot t_p / EAD(LD))$. By determining R(LD), EAD can be derived for each depth.

Inspiration was performed at a flow rate of 250 mL/s until 85 % of total lung capacity (TLC) was reached. Breathholding time ranged between 2 and 15 s. Expiration was again performed at 250 mL/s. Data were plotted as curves of EAD versus lung depth (LD) expressed as percent of endinspiratory lung volume at which breathholding was performed. During measurements, the settling velocity of the aerosol was determined every 30 min using a convection-free sedimentation channel, a laser light source, video camera, and particle tracking program.

In all healthy subjects (n = 11) and a subgroup of patients with emphysema (n = 10), EAD was deter-

Table 1. Characteristics of patients.

Group	n	Age y	Height cm	VC %pred	FEV_1 %pred	MEF_{50} %pred	ITGV %pred	RV %pred	TLCO %pred
Healthy	11	33 ± 8	175 ± 9	108 ± 9	107 ± 9	93 ± 21	124 ± 15	92 ± 20	119 ± 16
Emphysema all	41	55 ± 9	175 ± 9	93 ± 17	60 ± 26	29 ± 23	166 ± 42	173 ± 58	82 ± 24
Severity									
mild	8	61 ± 8	176 ± 8	100 ± 14	74 ± 18	54 ± 30	129 ± 13	128 ± 26	91 ± 14
moderate	9	52 ± 5	181 ± 10	102 ± 13	74 ± 18	38 ± 17	151 ± 30	151 ± 50	96 ± 17
severe	24	54 ± 10	176 ± 8	86 ± 17	47 ± 22	17 ± 13	184 ± 42	197 ± 57	73 ± 25
Type									
centriacinar	18	55 ± 9	175 ± 9	94 ± 15	67 ± 27	36 ± 28	148 ± 34	152 ± 47	84 ± 20
panacinar	7	49 ± 6	175 ± 9	89 ± 25	42 ± 26	13 ± 14	192 ± 50	203 ± 44	67 ± 22
bullous	16	53 ± 9	180 ± 7	92 ± 17	60 ± 24	28 ± 17	175 ± 40	185 ± 68	86 ± 28

Mean ± SD are given. For explanation of abbreviations see Methods

mined repeatedly (8-10fold) within one month to assess intraindividual variability. In these subjects, lung function was also assessed repeatedly (at least 5 measurements).

Computed Tomography (CT) of the Thorax

CT was carried out by a high resolution (HR) technique in 6 sections, whereby scans were obtained using 3 s scan time, 2 mm slice thickness, 70 mA tube current and 130 kV voltage (Siemens AG, Erlangen, Germany). Based on a published method [19], two radiologists independently evaluated patients by visual grading. In each slice the degree of destruction was expressed as the percentage of emphysematous structures. For final evaluation, mean percentages of destruction over the slices were taken. Patients were categorized into three subgroups of severity: mild (destruction <25 %), moderate (25-50 %), and severe (>50 %).

In addition, patients were categorized into subgroups of different type of emphysema according to morphological criteria. Centriacinar emphysema was defined via areas of low attenuation grouped near the centers of secondary pulmonary lobules without showing a wall, located mainly in the upper part of the lung. Panacinar emphysema was defined as uniform destruction of lobules, leading to widespread areas of low attenuation. Bullous destructions were defined as holes of greater than 1 cm diameter, without visible boundary. When more than one of these criteria applied, the patient was assigned to the predominant type.

Regarding the severity of emphysema, judgements by the two radiologists were coincident in 33 of 41 patients. In case of disagreement, the mean of their scores was used. Regarding the type of emphysema, there was coincidence in 38 patients. In the three cases of disagreement the radiologists were asked to agree upon a final category.

Lung Function Measurement

Lung function was measured within 3 h prior to aerosol morphometry. Inspiratory vital capacity (VC), forced exspiratory volume in 1 s (FEV_1), forced midexpiratory flow rate (MEF_{50}), as well as total lung capacity (TLC), intrathoracic gas volume (ITGV) and residual volume (RV) were determined in a body plethysmograph (Masterlab, Jaeger, Höchberg, Germany). Furthermore, the transfer factor for carbon monoxide (TLCO) was assessed by the single breath method (Masterlab, Jaeger, Höchberg, Germany).

Analysis of the EAD versus LD Curve

Average EAD and EAD slope

To compare EAD values between patients and healthy subjects, average values of EAD between 10 and 16 % LD ($EAD_{10\text{-}16}$) as well as the linear slope of the EAD *vs* LD curve between 10 and 16 % of LD ($EAD_{10\text{-}16}$ slope) were computed [15]. In healthy subjects, EAD data could be evaluated between 2 and 30 % LD. In contrast, some patients with emphysema delivered only data between 2 and 16 % LD, owing to their severe lung hyperinflation. As a result, in all subjects EAD data ranging between at least 2 and 16 % LD were available.

Fitting of EAD curves

To describe the shape of the EAD curve, different types of parametric functions were fitted to the data. For the description presented here we selected the function that yielded the best fit. This was a three-parameter power function of the form: $EAD(LD) = EAD_{peri} + EAD_{diff} \cdot LD^{ELD}$. An example is given in Fig. 1. In this function, EAD_{peri} describes the part of EAD which is related to lung periphery and reached for large values of LD. Parameters EAD_{diff} and ELD together describe the slope of the EAD curve at low lung depths. EAD_{diff} represents the amplitude of the change from central to peripheral airways; thus the sum of EAD_{peri} and EAD_{diff} gives central airways EAD. Theoretically this sum represents the value extrapolated backwards to volume zero. It might therefore assume large values, as the power function is obviously inadequate in describing the uppermost airways. The exponent ELD describes the relative steepness of the transition from zero to large LD. It should be noted that the value of ELD was negative, as airway diameters decrease with lung depth; the more negative the value, the steeper the fall of EAD towards lung periphery. The power function has a natural interpretation when one assumes that average airway diameters change from airway generation to generation by a constant factor and that volumetric lung depth is linearly related to consecutive airway generations.

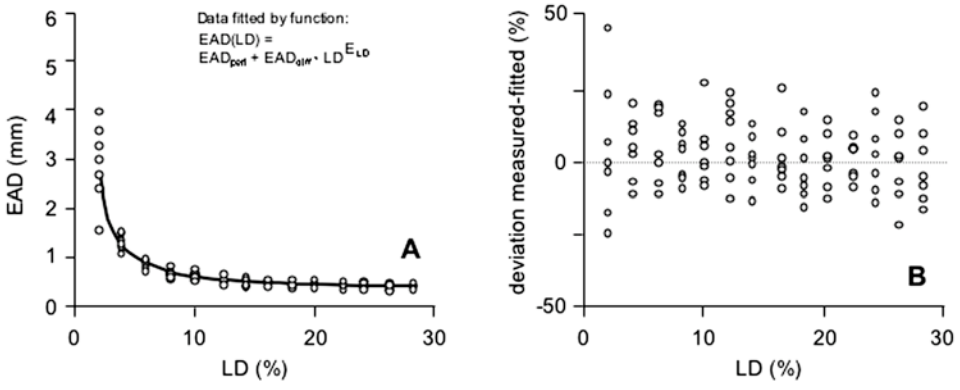

Fig. 1. Representative example of the data observed in 7 repeated measurements of effective airway diameter EAD versus lung depth LD in one individual as well as of the fit by the power function used for phenomenological description (panel A). Panel B describes the difference between measured data and fitted curve at each lung depth in percent relative to the value of the curve.

The three parameters EAD_{peri}, EAD_{diff} and E_{LD} were estimated by fitting the function to the data of each individual subject having repeated measurements, using a standard quasi-Newton iteration procedure and the least-squares criterion. As the least-squares procedure is a special case of the maximum likelihood method, minimum estimates of the asymptotic standard errors of the parameters could be derived from the matrix of second derivatives.

Analysis by a three-compartment lung model

To extrapolate EAD into greater lung depths than those directly measurable, we applied a three-compartment lung model [20]. The analysis was performed only in the 11 healthy subjects and 19 patients with emphysema (8 centriacinar, 5 panacinar, 6 bullous) who had repeated measurements, because the complex fitting procedure seemed meaningful only if the ratio between the number of data points and the number of parameters was acceptable. The model comprised a central, an intermediate and a peripheral compartment, of volumes V_1, V_2 and V_3, and of airway diameters D_1, D_2 and D_3, respectively (Fig. 2). The volume distribution of the inspiratory airflow was assumed to be broadened with increasing lung depth according to a Gaussian function whose width was proportional to volumetric lung depth. The model was fitted to the basic data describing the exhaled aerosol concentration as a function of expired volume and breathholding time. The fit was achieved by a specially designed iteration procedure in which mean square deviations between model and data were computed. To reduce the number of parameters, D_1 was assumed *a priori* as either 2 or 10 mm. The parameter estimates thus obtained were compared with each other to check whether the value of D_1 was critical. The sum of V_1, V_2 and V_3 was set equal to individual total lung capacity (TLC) [20]. Thus, the number of independent parameters was further reduced by one. Accordingly, quadratic deviations were computed on a four-dimensional grid for V_1, V_2, D_2, and D_3. The grid was repeatedly refined until those values were found which yielded the smallest sum of squares.

Statistical Evaluation

Mean values and standard deviations (SD) or standard errors (SEM) were computed for all variables. Groups were compared by the t-test. We did not introduce corrections for multiplicity of tests in this exploratory study. Correlation was quantified by linear correlation coefficients. The relative importance of different variables regarding the separation between groups was assessed by linear discriminant analysis; the analysis was used only for this purpose and not for prediction, as the sample size was not sufficient to establish an independent test group. The level of significance was assumed at $p<0.05$.

Results

Intraindividual Variability

EAD values in healthy subjects were completely within the normal range [10], and outside this range in all subgroups of emphysema in lung depths >10 % (Fig. 3A). When the comparison between types of emphysema was restricted to severe emphysema in order to reduce the bias from different degrees of severity, there was still a clear-cut separation between the types of emphysema (see Fig. 3B). In the healthy subjects as well as the patients with emphysema coefficients of variation in 2 and 4 % lung depth, i.e. large airways, were always greater than in lung depths of 6 to 30 % including peripheral airways (Table 2).

For comparison intraindividual coefficients of variation of lung function were computed. Mean (±SD) values were 2.4 ± 2.0 % for VC, 3.2 ± 2.9 % for FEV_1, 4.4 ± 1.5 % for ITGV, and 6.9 ± 4.0 % for MEF_{50} in healthy subjects. Corresponding values in emphysema were 5.5 ± 3.0 % for VC, 10.5 ± 8.0 % for FEV_1, 4.9 ± 3.6 % for ITGV, and 14.4 ± 11.0 % for MEF_{50}.

Average EAD

$EAD_{10\text{-}16}$ was increased ($p<0.01$) in emphysema compared to healthy subjects (Table 3). It was also increased in the subgroups with moderate ($p<0.05$) and severe ($p<0.001$) emphysema. Furthermore, $EAD_{10\text{-}16}$ was larger ($p<0.01$, each) in severe compared to mild or moderate emphysema, whereby the latter two groups were not significantly different.

The distribution of $EAD_{10\text{-}16}$ showed little overlap between patients with emphysema and healthy subjects (Fig. 4A). In depths of 20-30 %, average EAD

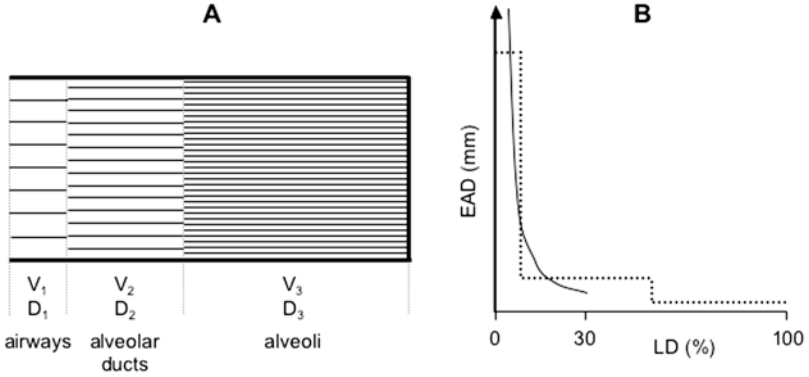

Fig. 2. Components of the lung model used for extrapolation into greater lung depths (panel A). The model comprised three sequential compartments of volumes V_1, V_2 and V_3 which summed up to individual total lung capacity (TLC). The compartments were assumed to be composed of parallel tubes of the respective diameters D_1, D_2 and D_3. Panel B illustrates how the continuous EAD *vs* LD curve was approximated by the discontinuous curve defined by the three volumes and diameters. The panel also demonstrates the extrapolation towards the lung periphery which was the rationale for the model approach.

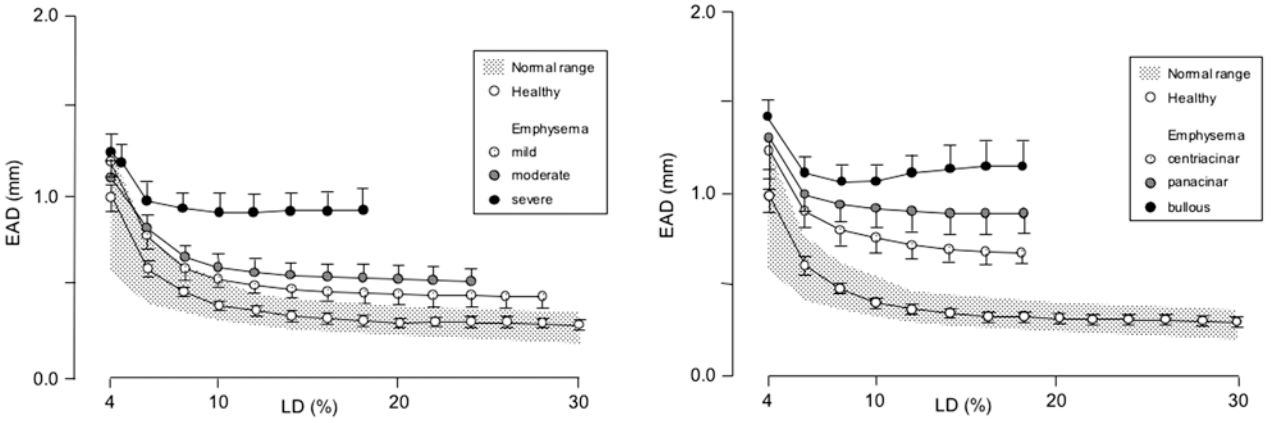

Fig. 3. Mean ± SEM values of EAD *vs* LD curves in the different groups of patients. The shaded area indicates the normal range as published previously [10]. The fact that curves covered different ranges towards the lung periphery was due to the fact that some patients could not be evaluated at greater lung depths because of severe hyperinflation. Panel A presents the data for all subjects, whereby patients with emphysema had been categorized according to severity, and panel B for the patients with severe emphysema only, whereby patients had been categorized according to the predominant type of emphysema.

Table 2. Intraindividual coefficient of variation of repeated EAD measurements.

Lung depth (LD)§	Coefficient of variation (%) Healthy (n = 10)	Emphysema (n = 10)	
2	26.5 ± 10.7	38.4 ± 19.4	
4	13.1 ± 4.5	14.9 ± 6.3	
6	8.7 ± 4.5	8.3 ± 3.7	
8	7.6 ± 1.7	8.8 ± 4.5	
10	7.3 ± 2.0	8.6 ± 5.3	
12	7.1 ± 2.1	9.8 ± 3.4	
14	7.0 ± 2.5	9.4 ± 2.9	
16	7.5 ± 2.2	10.7 ± 6.6	
18	7.4 ± 2.4	11.0 ± 6.9	
20	8.0 ± 2.7	9.0 ± 3.2	(n=7)*
22	8.1 ± 2.9	9.6 ± 2.2	(n=6)*
24	8.7 ± 3.0	9.5 ± 2.4	(n=6)*
26	9.0 ± 3.5	10.1 ± 4.5	(n=6)*
28	9.5 ± 3.5	11.9 ± 7.2	(n=5)*
30	10.4 ± 3.9	9.1 ± 3.9	(n=4)*

Mean±SD are given. *The determination of EAD in greater lung depths was impossible in some patients because of severe hyperinflation. §expressed as percent of endinspiratory lung volume

(EAD_{20-30}) completely separated emphysema from healthy subjects, without overlap (Fig. 4B).

Slope of EAD

Mean slope of EAD between 10 and 16 % LD differed ($p<0.05$) between healthy subjects and patients with emphysema (Table 3). In bullous emphysema the slope was different from that of healthy subjects ($p<0.01$) and centriacinar emphysema ($p<0.05$), while in centriacinar emphysema and healthy subjects slopes were similar and showed a negative sign (Fig. 5). In the subgroup with panacinar emphysema the mean slope was nearly zero between 10 and 16 % LD. Furthermore, the subgroup with severe emphysema showed a larger slope than mild emphysema ($p<0.05$) and healthy subjects ($p<0.01$), as well as a positive sign of slope. There were either positive or negative correlations between average EAD and EAD slope (Fig. 6). Patients with centriacinar or bullous emphysema exhibited a large variation in EAD slope, whereas those with panacinar emphysema showed more homogeneous values, mostly near zero, except for one patient. When the analysis was confined to severe emphysema, a similar relationship between EAD slope and type of emphysema was observed as in the whole group of

Table 3. Average EAD values (EAD_{10-16}) between 10 and 16 % of volumetric lung depth (LD) and corresponding slopes.

Group	n	EAD_{10-16} (mm)	EAD_{10-16} slope (mm per %LD)
Healthy	11	0.380 ± 0.046	-0.0136 ± 0.0042
Emphysema all	41	0.776 ± 0.280 ***	0.0039 ± 0.0141 *
Severity			
mild	8	0.497 ± 0.043	-0.0148 ± 0.0065
moderate	9	0.576 ± 0.104 *	-0.0068 ± 0.0086
severe	24	0.900 ± 0.292 ***,§,#	0.0009 ± 0.0155 **,$
Type			
centriacinar	18	0.651 ± 0.186 **	-0.0137 ± 0.0069
panacinar	7	0.964 ± 0.239 ***	-0.0031 ± 0.0067
bullous	16	0.769 ± 0.361 ***	0.0069 ± 0.0148 **,&

Mean±SD are given. *p<0.05, **p<0.01, ***p<0.001 *vs* healthy subjects; $ p<0.05, § p<0.001 *vs* mild emphysema; # p<0.01 *vs* moderate emphysema; & p<0.05 *vs* centriacinar emphysema

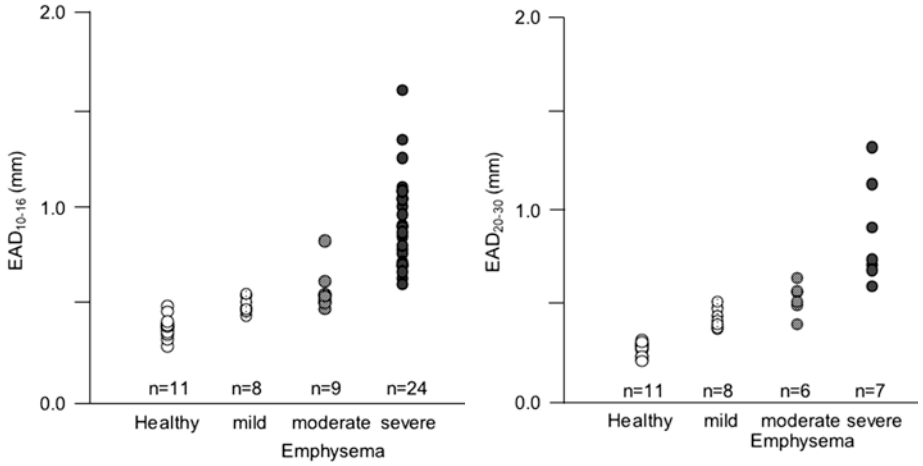

Fig. 4. Average EAD between 10 and 16 % of lung depth (panel A) in healthy subjects and patients with emphysema of different severity. Panel B shows analogous data for lung depths between 20 and 30 %. The reduction in sample size compared to panel A was due to severe hyperinflation in some patients which prevented measurements at these depths.

Table 4. Estimates of the parameters used for fitting EAD *vs* LD curves.

Group	n	EAD_{peri} (mm)	EAD_{diff} (mm)	E_{LD}
Healthy	11	0.29 ± 0.03	14.4 ± 12.1	- 2.00 ± 0.32
Emphysema				
centriacinar	8	0.46 ± 0.14 ***	8.1 ± 4.8	- 1.74 ± 0.27
panacinar	5	1.01 ± 0.29 ***,§	32.6 ± 25.4 #	- 3.88 ± 1.00 ***,§
bullous	6	0.95 ± 0.41 ***,$	48.1 ± 40.5 *,#	- 3.81 ± 1.47 **,$

The function used was $EAD(LD) = EAD_{peri} + EAD_{diff} * LD^{ELD}$. Parameter estimates were computed only for patients having repeated measurements. Mean ± SD values are given. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ *vs* healthy subjects; # $p<0.05$, $ $p<0.01$, § $p<0.001$ *vs* centriacinar emphysema

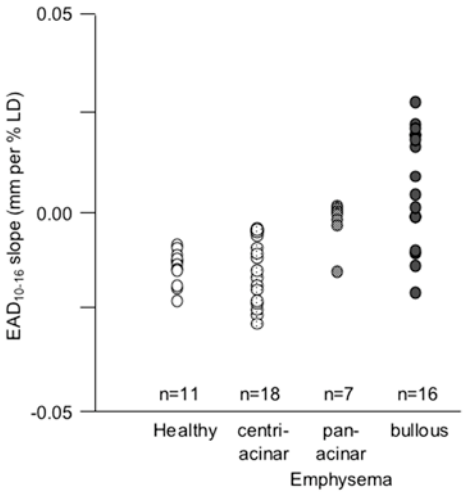

Fig. 5. Slope of EAD between 10 and 16 % of lung depth in healthy subjects and patients with emphysema of different type, whereby all patients with emphysema had been included.

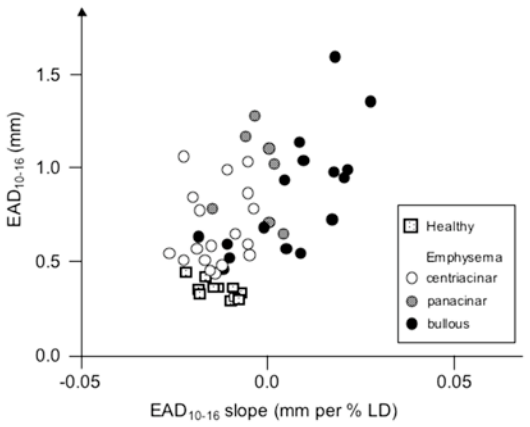

Fig. 6. Relationship between average EAD and slope of EAD between 10 and 16 % of lung depth in healthy subjects and patients with emphysema of different type. Aall patients with emphysema have been included. Though there was a positive correlation between both indices when taken overall, the relationship was different in different subgroups, being positive in bullous emphysema and inverse in healthy subjects.

patients with emphysema (see Fig. 3B).

Analysis of the EAD Curve by a Power Function

These analyses were performed only in patients having repeated measurements. Correlation coefficients describing the quality of fitting were always greater than 0.97. As the primary aim of this approach was to recognise the type of emphysema, statistical comparisons were performed only regarding the type. EAD_{peri} was significant lower in the healthy subjects compared to centriacinar, panacinar and bullous emphysema ($p<0.001$, each, Table 4). Furthermore, EAD_{peri} of panacinar ($p<0.001$) and bullous emphysema ($p<0.01$) was greater than that of centriacinar emphysema. In the these two subgroups, also EAD_{diff} was greater than in centriacinar emphysema ($p<0.05$, each), and in bul-

Table 5. Estimates of volumes V_1, V_2 and V_3, and of diameters D_2 and D_3 of the three-compartment lung model, whereby diameters of 2 mm and 10 mm have been assumed for the central compartment D_1.

Group	n	V_1 (% TLC)	V_2 (% TLC)	V_3 (% TLC)	D_2 (mm)	D_3 (mm)
D_1 assumed as 2 mm						
Healthy	7	14.20 ± 1.62	39.70 ± 0.97	46.11 ± 1.64	0.83 ± 0.43	0.062 ± 0.026
Emphysema all	17	14.56 ± 2.15	40.03 ± 0.83	45.41 ± 2.78	1.30 ± 0.48*	0.053 ± 0.048
Type						
centriacinar	8	14.95 ± 0.70	39.85 ± 0.65	45.21 ± 1.28	1.03 ± 0.40	0.041 ± 0.020
panacinar	5	14.45 ± 2.42	40.24 ± 0.69	45.31 ± 2.84	1.60 ± 0.32	0.090 ± 0.078
bullous	4	13.92 ± 3.85	40.14 ± 1.36	45.94 ± 5.11	1.47 ± 0.57	0.031 ± 0.018
D_1 assumed as 10 mm						
Healthy	7	14.04 ± 1.84	40.37 ± 0.57	45.58 ± 2.19	0.70 ± 0.34	0.060 ± 0.027
Emphysema all	17	14.17 ± 3.66	40.26 ± 0.74	45.57 ± 3.76	1.14 ± 0.47*	0.053 ± 0.043
Type						
centriacinar	8	14.96 ± 0.76	40.07 ± 0.92	44.97 ± 1.50	0.85 ± 0.31	0.041 ± 0.019
panacinar	5	14.55 ± 2.45	40.19 ± 0.39	45.26 ± 2.66	1.35 ± 0.43	0.086 ± 0.067
bullous	4	12.11 ± 7.38	40.73 ± 0.60	47.17 ± 7.50	1.48 ± 0.49	0.036 ± 0.012

Mean ± SD values are given. TLC: total lung capacity. * $p<0.05$ compared to healthy subjects

lous emphysema greater than in healthy subjects ($p<0.05$). Furthermore, the magnitude of the exponent ELD describing the relative steepness of the fall of EAD towards lung periphery was greater in panacinar and bullous emphysema compared to both centriacinar emphysema and healthy subjects ($p<0.01$, each).

Categorization of Emphysema via Average EAD and Power Function Parameters

Using the average $EAD_{10\text{-}16}$, 27/41 patients were correctly assigned as emphysema by discriminant analysis. The 11 healthy subjects were all classified as healthy. Using parameter EAD_{peri} of the fitting function, 31/41 patients were assigned correctly. When using EAD_{peri} and ELD, correct classification of emphysema was achieved in 35/41 patients. The two subtypes of bullous/panacinar emphysema on one hand *vs* centriacinar emphysema on the other were correctly separated by this combination in 17/23 patients.

Three-compartment Lung Model

Analysis by the model was not possible in 4 of the 11 healthy subjects and in 2 patients with bullous emphysema, owing to non-convergence of the algorithm. Table 5 shows the estimated parameters V_1, V_2, V_3, D_2 and D_3 in 7 healthy subjects and 19 patients. In both groups, values did not significantly change when the assumed diameter (D_1) of the central compartment (V_1) was raised from 2 to 10 mm. The diameter of the intermediate compartment (D_2) was found to be larger ($p<0.05$) in emphysema compared to healthy subjects; there were no statistically significant differences regarding the other parameters.

Discussion

The results of our study suggest that ADAM is a sensitive diagnostic method for detecting increased airspace dimensions in patients with lung emphysema of different severity and type. Intraindividual variability was acceptable and in most cases of the order of 10 %. Furthermore, EAD obtained in the healthy subjects was fully within the range reported previously [10], supporting the validity of our measurements.

The sensitivity of ADAM in detecting emphysematous alterations was higher in greater lung depths). Using EAD in depths between 20 and 30 % of endinspiratory lung volume, all patients recognised as having emphysema by CT could be separated from healthy nonsmokers and their values were outside the normal range [10] (Fig. 3A, 4B). This separation was not achievable by single lung function variables (Table 1), in accordance with previous findings [12-14]. Regarding EAD averaged over depths from 10 to 16 %, patients with emphysema also showed larger values than healthy subjects (Fig. 3A, 4A). However, there was some overlap and separation was not possible in each individual case. A relative lung depth of 10 to 16 % is comparable to an absolute depth of 800 ml as used in the first studies which already demonstrated that emphysema could be recognised by ADAM [6, 7]. However, data of individual subjects were not reported in these studies and CT classification was performed only in a subgroup of patients. Subsequent studies using visual or quantitative HRCT analysis have provided detailed information on the sensitivity and specificity of ADAM in the diagnosis of lung emphysema and indicated the clinical potential of the method [12-14, 21]. Our EAD data are fully in line with these findings.

We additionally analyzed whether the curve of EAD as a function of LD carried additional information. There was a remarkable difference in the shape of this curve between the types of emphysema (Fig. 3B, Table 3). Patients with centriacinar emphysema showed a similar shape of the EAD curve as healthy nonsmokers, whereas in panacinar or bullous emphysema the slope became more positive. This may have been partially an effect of the increasing severity of emphysema, as the latter patients showed more severe

disease. A plot of average EAD *vs* EAD slope (Fig. 6) indeed demonstrated a relationship between both variables. In healthy subjects there was a negative correlation between average EAD and EAD slope but in emphysema a positive one. The factor causing the negative relationship in healthy subjects is not clear, whereas the correlation in emphysema was mainly due to patients with bullous emphysema. No obvious correlation was present in centriacinar or panacinar emphysema.

The analysis of EAD slope in severe emphysema showed different slopes in different subtypes (Fig. 5), suggesting a potential diagnostic relevance, although there was a large overlap between subgroups. This may have been partially due to difficulties in categorizing subtypes by HRCT. It is known that many patients show mixed type disease, mostly a combination of centriacinar and bullous alterations. Therefore the decision for a single type was difficult in some cases. Setting up a group with signs of mixed emphysema did not help, as this was true for most cases. Another possible explanation for the great variability of EAD slope in bullous emphysema may be the fact that not all bullous structures were ventilated. Despite these difficulties, the differences in EAD slope between the types of emphysema can be interpreted as indicating that, on average, the classification via CT was adequate. This is underlined by the small intra-observer difference in categorizing emphysema type, as the radiologists agreed in 94 % of patients.

A possible explanation for the observation that in bullous and panacinar emphysema the EAD *vs* LD curve was nearly horizontal or even rising in peripheral lung depths, is the assumption of different ventilatory time constants in normal airways and bullous or panacinar structures. The aerosol coming from slow spaces would then dominate the endexspiratory part of the EAD curve, with the consequence of a larger EAD at a given volumetric depth.

In the interpretation of our findings we have to rely on the methodological validity of the method. Accuracy and resolving power have previously been proven by an experimental lung model [22]. Furthermore, peripheral airway diameter (LD 20-30 %), including the zone of alveolar ducts and acini, as determined by ADAM showed good agreement with histologically assessed diameters of the acinus [23]. There was also agreement between post mortem data of the Mean Linear Intercept (Lm) which was found to be 0.38 mm on average, and the results of ADAM, yielding a mean EAD of 0.42 mm [24].

Interestingly, the known increase of Lm with increasing age [19] appears to be reflected in the EAD of healthy subjects, as there was a significant correlation between peripheral EAD and age [10]. The effect, however, was small and seems negligible in clinical applications. Interestingly, the healthy subjects studied by us also showed a trend towards a relationship between age and EAD ($r = 0.45$), though due to the small number of subjects ($n = 11$) the correlation was not statistically significant. In our study age was different between healthy subjects and patients with emphysema, but the effect of the difference in age on average EAD could be estimated from published data [10, 25] to be no more 0.03 mm.

Another methodical issue is the use of computed tomography for the diagnosis of emphysema and classification of severity and subtype. We used CT as it is the only known method directly demonstrating anatomical correlates of emphysema. ADAM also provides information on lung structure but only indirectly [24]. Conventional lung function indicates the presence of emphysema via functional effects and is not particularly specific compared to CT [4, 26, 27], with correlation coefficients of about 0.5. There are, however, also studies reporting stronger correlations between CT classification of emphysema and lung function [28]. Obviously, the strength of correlation depends on the proportion of patients with severe disease, since early stages of emphysema are difficult to detect even by CT and not revealed by lung function measurements [26, 27]. The relative insensitivity of lung function compared to aerosol morphometry has also been indicated by a recent study in patients with a1-antitrypsin deficiency [28]. Regarding visual CT scores and pathologic scores, correlations coefficients of 0.59 to 0.90 have been found in centriacinar emphysema [26], while the assessment of severity in panacinar emphysema is more difficult [25].

Computed density has been claimed to be a more objective measure than subjective scores in the diagnosis of emphysema [29-31], despite the difficulties in the presence of hyperinflation, a case in which qualitative visual grading may be more sensitive than density evaluation [11]. We used the method of visual grading since some CT scans were provided by outpatients and a retrospective analysis by computation of density was not possible.

Only three categories of severity were used instead of a quasi-continuous score as previously used to compare CT findings with pathology scores [19]. The aim of our study was not the quantification of the degree of emphysema *per se* but the assessment of groups of different severity for the purpose of comparison. In doing so inter-observer variability of the radiologists was 80.5 % and within the range of 80 to 90 % reported previously [11, 26, 31]. We therefore do not think that improper analysis of CT scans has handicapped our study.

For evaluating EAD we used the average EAD between 10 and 16 % LD, a lung depth that was achievable in all patients including those with severe hyperinflation. At the same time this range was considered still peripheral enough to be informative in the diagnosis of emphysema. Obviously, however, the sensitivity of separating healthy subjects from patients with emphysema was reduced by the limited range of averaging (Fig. 4A,B).

We tried to condense the information contained in the curve by analyzing its form by a power function. All three parameters carried relevant information on the type of emphysema, though the power of the analysis was limited by the fact that only the subgroup of patients having repeated measurements was analyzed. Though the results might not seem different from those obtained for average EAD and EAD slope, the condensation of information by the fitting procedure was remarkable and led to marked differ-

ences between the subgroups (Table 4). In particular the intercept EAD_{peri} and the exponent ELD were informative. Compared to that, the parameter EAD_{diff} seemed to be stronger affected by the variability at low relative lung depths which led to large estimated diameters towards volume zero, where the model obviously became inadequate. The same was true for greater lung depths when the curved bent upwards in bullous emphysema (Fig. 3B). Irrespective of this, fitting of EAD *vs* LD curves by the power function might be helpful in order to obtain typical parameters.

To derive information on EAD in lung depths greater than those directly measurable would be particularly helpful in patients with hyperinflation. A lung model might allow this sort of extrapolation, and we therefore adopted the three-compartment model proposed by Rosenthal that had been fitted to data obtained by the bolus technique [20]. Our results demonstrate that the model is also applicable with the single breath technique. However, the model did not improve the diagnostic power of the aerosol morphometry. In particular, the estimated airway diameter of the third compartment, representing alveolar ducts and alveoli, did not provide relevant information. This is probably explained by the fact that this diameter was totally based on extrapolation; even part of the second compartment was subject to extrapolation. This far-reaching extrapolation seems to be too unreliable when having no direct information on the lung periphery. On the other hand, with regard to central airways, the results were not critically dependent on the airway diameter of the first compartment. The fact that long-range extrapolation relies on complete adequacy of the model used, was also demonstrated by the fact that the values extrapolated by the power function towards the mouth (EADdiff) often took extreme values that were unrealistic even at volume zero.

From the data presented here we conclude that aerosol-derived airway morphometry (ADAM) is sensitive in the detection of enlarged airspace dimensions in emphysema, even in patients without significant impairment in lung function. In addition to average EAD, the slope of the EAD curve appears to confer information about the type of emphysema. A similar result was obtained when using a power function to condense the information into three parameters. A more refined three-compartment lung model, however, was not capable of improving the result compared to the more phenomenological analyses.

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