Objective: Patients with lung emphysema show increased aerosol-derived dimensions of peripheral airspaces and increased aerosol bolus dispersion (AD). To apply these tests in epidemiologic studies, the objective of this pilot study was to investigate whether morphometric changes caused by lung fibrosis can be distinguished from those caused by emphysema.

Design: This study was designed as a cross-sectional study in which airspace dimensions and AD in patients with emphysema and in patients with fibrosis were compared. Forty patients participated in the study: 20 patients had high-resolution CT (HRCT)-proved lung emphysema and 20 patients had HRCT-proved lung fibrosis. All patients underwent conventional lung function tests, aerosol-derived airway morphometry (ADAM), and AD measurements.

Results: Patients with lung emphysema showed normal dimensions of small airways but enlarged airspace dimensions in the lung periphery. Patients with fibrosis showed in all lung depths increased airspace dimensions. AD was increased in patients with emphysema but was normal in patients with fibrosis.

Conclusions: These results show that when using ADAM and AD, morphometric changes caused by emphysema can be distinguished from those caused by fibrosis with high sensitivity and specificity.

Key words: convective gas mixing; lung emphysema; lung fibrosis; lung morphometry

Abbreviations: AD = aerosol bolus dispersion; ADAM = aerosol-derived airway morphometry; D_{200} = dispersion of boluses inhaled into 200 cm³ volumetric lung depth; D_{400} = dispersion of boluses inhaled into 400 cm³ volumetric lung depth; D_{600} = dispersion of boluses inhaled into 600 cm³ volumetric lung depth; D_{800} = dispersion of boluses inhaled into 800 cm³ volumetric lung depth; EAD_{4%} = EAD for a relative volumetric lung depth of 0.04; EAD_{10%} = EAD for a relative volumetric lung depth of 0.1; EAD_{20%} = EAD for a relative volumetric lung depth of 0.2; IPF = interstitial pulmonary fibrosis; ITGV = intrathoracic gas volume; MEF_{25} = maximal expiratory flow rates at 25% vital capacity; MEF_{50} = maximal expiratory flow rates at 50% vital capacity; PE = pulmonary emphysema; P_{ROC} = area under a receiver-operating characteristics curve; R = particle recovery; RV = residual volume; TLC = total lung capacity; TLCO = transfer factor for carbon monoxide; tp = breath-holding time; VC = vital capacity; Vp = volumetric lung depth; Vp,r = relative Vp; Vs = particle settling velocity

Lung emphysema and pulmonary fibrosis are both responsible for destructive changes in the architecture of the lung periphery. Emphysema is characterized by enlargement of distal airways and acini with destruction of alveolar walls. Pulmonary fibrosis is defined as an inflammatory process involving alveolar walls and adjacent airspaces leading to remodeling of the lung structure caused by interstitial and intra-alveolar deposition of connective tissue. Additionally, pulmonary fibrosis is associated with a distention of airspaces caused by scar contraction.

In patients with lung emphysema, peripheral airspace dimensions assessed by aerosol-derived airway morphometry (ADAM) have been shown to be increased. On the other hand, in these patients,
aerosol bolus dispersion (AD) indicates increased convective gas mixing within the lungs because of inhomogeneities in lung ventilation. However, it is unknown whether or not the morphometric changes present in patients with pulmonary fibrosis can be detected with ADAM and whether or not these changes are similar to those of patients with emphysema. In this case, the specificity of ADAM to detect emphysema in, for example, epidemiologic studies or in occupational medicine would be reduced. There is only limited information available about AD in patients with pulmonary fibrosis.

Therefore, in this pilot study, 20 subjects with pulmonary fibrosis and 20 subjects with emphysema underwent ADAM, AD, and conventional lung function tests. The data obtained from these patients were compared with data from healthy subjects previously published.

**Materials and Methods**

**Subjects**

Twenty patients with chronic interstitial pulmonary fibrosis (IPF; 13 men, 7 women) and 20 patients with pulmonary emphysema (PE; 13 men, 7 women) participated in the study (Table 1). Anamnestic data were evaluated by a questionnaire based on American Thoracic Society recommendations. The smoking habits of the patients were quantified by using the cumulative cigarette consumption expressed as pack-years.

The diagnosis of chronic IPF was based on clinical, histologic, and radiographic (CT of the chest) evidence. For all patients, the time between the onset of symptoms and participation in the study was >3 months. Pulmonary fibrosis was caused by idiopathic pulmonary fibrosis (n = 12), sarcoidosis stage III (n = 4), hypersensitivity pneumonitis (n = 2), systemic lupus erythematosus (n = 1), and progressive systemic sclerosis (n = 1). Honeycombing, defined as the presence of well-defined ringlets approximately 3 to 12 mm in diameter on thin-section high-resolution CT was present in five patients. Two patients were current smokers, 8 patients were former smokers, and 10 patients were nonsmokers.

The diagnosis of PE was based on the results of a CT of the chest. Except for three patients with known α1-antitrypsin deficiency, all patients had a long history of heavy cigarette consumption.

Informed written consent was obtained from each subject. The study protocol was approved by the Ethics Committee of the Medical School of the Ludwig-Maximilians-University, Munich, Germany.

**ADAM**

Monodisperse aerosol particles settle in calm air with a constant particle settling velocity (Vs). Within the lung, this gravitational motion leads to particle deposition onto airway and alveolar surfaces, and the particle concentration is reduced with increasing time. Particle loss rate is high if the particles are located in small airspaces and small if they settle in large airspaces. This decline in particle number concentration as a function of time can be used to calculate airspace dimensions.

To measure aerosol-derived airspace dimensions in human subjects, the lungs are filled with particles of a uniform number concentration by a tidal inspiration of a monodisperse aerosol. The inspired tidal volume can be considered to be composed of infinitesimally small volume elements that penetrate into different volumetric lung depths (Vps). During the breath-holding time (tp), the particles settle onto the airway and alveolar surfaces and the number concentration in each volume element decreases. This reduction of aerosol concentration in each volume element can be measured by assessing the particle recovery (R) as a function of tp. R is defined as the ratio of the particle number concentration in an exhaled volume element to the concentration in the inhaled aerosol.

$R = \exp (-1.27 \frac{V_{stp}}{EAD})$  

In the proximal lung, the effective airspace dimension (EAD) represents the diameter of conducting airways. In the peripheral lung, EAD is closely related to the mean linear intercept.

To compare EAD among subjects of different lung size, lung depth is not quantified simply by the volume Vp, which was used frequently in the past, but it is normalized to the relative Vp (Vp,r), where $Vp,r = Vp / Vl$ and Vl is the end-inspiratory lung volume at which breath holding is performed. By this normalization, differences in EAD caused by differences in total lung capacity (TLC) among subjects are reduced.

**AD**

Gas transport in the lungs is the result of diffusion and convection. Because monodisperse aerosol particles with diameters between 0.5 μm and 1 μm behave like a “nondiffusive gas,” they can be used as tracers for convective gas transport. Therefore, a small volume (bolus) of the inspired air is labeled with these particles. During respiration, particles are convectively transported into air volumes that are initially particle free. In the exhaled air, the aerosol particles are therefore distributed over a larger air volume than in the inhaled air; the bolus is dispersed.

### Table 1—Anthropometric and Lung Function Data of Study Population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fibrosis</th>
<th>Emphysema</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>20</td>
<td>20</td>
<td>NS</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>13,7</td>
<td>13,7</td>
<td>NS</td>
</tr>
<tr>
<td>Age, yr</td>
<td>60 ± 11</td>
<td>62 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.68 ± 0.1</td>
<td>1.68 ± 0.08</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>77 ± 15</td>
<td>65 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>PY</td>
<td>27 ± 22</td>
<td>53 ± 35</td>
<td>0.03</td>
</tr>
<tr>
<td>VC, % predicted</td>
<td>65 ± 18</td>
<td>85 ± 25</td>
<td>0.01</td>
</tr>
<tr>
<td>TLC, % predicted</td>
<td>63 ± 15</td>
<td>120 ± 21</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ITGV, % predicted</td>
<td>69 ± 18</td>
<td>173 ± 44</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV, % predicted</td>
<td>64 ± 27</td>
<td>180 ± 68</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PEF, % predicted</td>
<td>96 ± 38</td>
<td>54 ± 29</td>
<td>0.0006</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>69 ± 22</td>
<td>46 ± 24</td>
<td>0.001</td>
</tr>
<tr>
<td>MEF25%, % predicted</td>
<td>58 ± 32</td>
<td>20 ± 18</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MEF50%, % predicted</td>
<td>72 ± 33</td>
<td>17 ± 17</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MEF75%, % predicted</td>
<td>90 ± 40</td>
<td>22 ± 22</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>rtot, kPa/L</td>
<td>0.42 ± 0.30</td>
<td>0.56 ± 0.30</td>
<td>NS</td>
</tr>
<tr>
<td>TLCO, % predicted</td>
<td>76 ± 61</td>
<td>76 ± 24</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Values are given as mean ± SD unless otherwise indicated. NS = not significant; PY = pack-years; PEF = peak expiratory flow; MEF25% = maximal expiratory flow rates at 75% VC; M = male; F = female; rtot = total airway resistance.
The width of an exhaled aerosol bolus inhaled into a certain Vp can be quantified by its volumetric half-width, $H_{50}$, which is defined as the air volume in which the particle number concentration exceeds half the maximal concentration. To account for the contribution of the width of the inhaled bolus, $H_{50,i}$, to the width of the exhaled one, $H_{50,e}$, a corrected half-width dispersion $D$ is introduced, which is given by

$$D = \sqrt{H_{50,e}^2 - H_{50,i}^2}$$  \hspace{1cm} (2)

**Instrumental Set-up and Inhalation Protocol**

ADAM and AD measurements are performed by using a probe (Respiratory Aerosol Probe; Fari, Starnberg, Germany). This computer-controlled device combines laser aerosol photometry with pneumotachography to measure the relative number concentration of stirred monodisperse aerosol particles as a function of the inspired air volume. Aerosol application is provided by a system of pneumatic valves, which allows the inhalation channel to be switched between particle-free air and an aerosol supply. All ADAM and AD measurements were performed at a constant airflow of 250 cm$^3$/s, and they were controlled by the subject using a visual flow signal.

The breathing maneuver for the determination of EAD started with an exhalation of one half the expiratory reserve volume followed by an inhalation of test aerosol up to 85% of TLC. After a predetermined t$p$, the subject exhaled until residual volume (RV) was reached. The breathing maneuver was repeated for tps of 2, 4, 6, 8, and 10 s duration. In this study, EAD was calculated for $V_{p,r}$ $= 0.04$ (EAD$_{4%}$), 0.1 (EAD$_{10%}$), and 0.2 (EAD$_{20%}$).

The breathing maneuver for the measurement of AD started from functional residual capacity, and the subjects inhaled particle-free air until the lung volume reached 85% TLC. During inspiration, an aerosol bolus with 25 cm$^3$ width was introduced into various Vps. The subjects then immediately exhaled until the entire aerosol bolus was recovered from the lungs or RV was reached. In this study, the dispersion of inhaled boluses was measured for the following Vps: $V_{p,r}$ reached. In this study, the dispersion of inhaled boluses was recovered from the lungs or RV was $V_{p,r}$ ($RV$) was reached. The breathing maneuver was repeated for tps with an exhalation of one half the expiratory reserve volume using a visual flow signal.

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Particle Production and Classification

Monodisperse di-2-ethylhexylsebacate droplets suspended in nitrogen were produced by heterogeneous nucleation of di-2-ethylhexylsebacate vapor on NaCl nuclei. The aerosol was then diluted with particle-free air to obtain a particle number concentration of about 2 x 10$^5$/cm$^3$. The size of the particles was classified by measuring the terminal Vs in a convection-free sedimentation cell. The average Vs (mean ± SD) throughout the study was 26 ± 3 μm/s, representing a mean geometric particle diameter of 0.9 μm.

Pulmonary Function Testing

Conventional pulmonary function tests were performed by using commercial devices. Body plethysmography and spirometry were performed using a Jäger-Masterlab (Erich Jaeger GmbH; Würzburg, Germany). The following parameters were measured: (1) lung volumes: TLC, vital capacity (VC), intrathoracic gas volume (ITGV), RV, and airway resistance; (2) spirometric and flow-volume parameters: peak expiratory flow, FEV$_1$, maximal expiratory rates at 25% VC (MEF$_{25}$), 50% VC (MEF$_{50}$), and 75% VC. Gas exchange was characterized by measurement of the transfer factor for carbon monoxide (Tlco). The single-breath method was used according to the guidelines of the European Respiratory Society. Carbon monoxide was measured as a function of the respired volume by a fast respiratory mass spectrometer (DLT 1100R, improved to fit scientific standard; Wagner; Worpswede, Germany). Measured lung function parameters were normalized to the reference values proposed by the European Community for Coal and Steel.$^{21}$

**Data Evaluation**

All statistical calculations were performed using an appropriate software package (SAS version 5, SAS Institute Inc; Cary, NC) on a personal computer. Differences between group averages were tested for significance using the $t$ test for independent samples. The requested level for significance was $p$ = 0.05. Correlation analysis was performed by using Pearson product-moment correlation analysis. The receiver-operating characteristics curve was used to evaluate the sensitivity and specificity of the aerosol parameters to distinguish patients with PE from patients with IPF. For each diagnostic parameter, the receiver-operating characteristics curve was calculated, showing the sensitivity of the parameter as a function of its specificity. To compare different receiver-operating characteristics curves, the area under each receiver-operating characteristics curve (PROC) was calculated. This area quantifies the probability that a randomly selected pair of patients with either PE or IPF is correctly ranked.$^{22}$ PROC is a measure of sensitivity and specificity of a diagnostic parameter. A PROC value of 1.0 represents maximal sensitivity and specificity.

The results are shown as box and whisker plots. The box indicates the 25 to 75% percentile range of the data, and the horizontal line within the box indicates the 50% percentile. The error bars above and below the box indicate the 10 to 90% percentile range, and the dots indicate the 5 to 95% percentile.

**Results**

Patients with IPF and PE showed no differences in anthropometric data (age, weight, height; Table 1).

In patients with IPF, lung volumes VC and TLC were mild to moderately reduced. RV was relatively well preserved. Because 50% of the patients were current or former smokers, a moderate airflow obstruction with decreased FEV$_1$, MEF$_{25}$, and MEF$_{50}$ was observed. The Tlco was reduced.

Patients with PE showed chronic irreversible hyperinflation inferred from elevated levels of TLC and ITGV, clear signs of chronic expiratory airflow limitation assessed by parameters of the flow-volume curve, and slightly reduced Tlco.

In comparison with the data from 79 healthy subjects published previously,$^{11}$ ADs for all Vps were significantly increased in patients with PE in contrast to patients with IPF (Fig 1; Table 2). Differences in ADAM were dependent on Vp (Fig 2; Table 2): compared with healthy subjects, EADs measured in $V_{p,r}$ were highest in patients with PE. In this lung depth, patients with PE showed normal values. In deeper lung depths, EAD was highest in patients with PE, but was also significantly increased in patients with IPF.
The sensitivity and specificity (Table 2) for the distinction of patients with PE were highest for the aerosol bolus parameters ($\text{PrOC}$, $>$ 0.9). For EAD, $\text{PrOC}$ was highest in the most proximal (EAD$_{4\%}$, 0.77) or in the deepest lung depth (EAD$_{20\%}$, 0.75), and it was lowest in between (EAD$_{10\%}$, 0.57).

AD and EAD data showed the following correlations with conventional lung function parameters. In subjects with emphysema, EAD$_{4\%}$ correlated positively with MEF$_{25}$ ($r$ = 0.6; $p$ = 0.01), and D$_{400}$ correlated positively with TLC (% predicted; $r$ = 0.51; $p$ = 0.02). In patients with IPF, EAD$_{10\%}$ correlated negatively with ITGV (% predicted; $r$ = −0.54; $p$ = 0.02), TLC (% predicted; $r$ = −0.55; $p$ = 0.01), and Tlco (% predicted; $r$ = −0.70; $p$ = 0.004). Additionally, D$_{200}$ correlated positively with peak expiratory flow (% predicted; $r$ = 0.47; $p$ = 0.04).

**DISCUSSION**

AD is increased in patients with PE, but is normal in patients with IPF. In both patient groups, ADAM showed increased airspace dimensions compared with the control group. However, the pattern of increased airspace dimensions was different between the two patient groups. Patients with PE showed normal EAD values in proximal lung depth. Inasmuch as this lung depth ($Vp,r$ = 0.04) is, for the patients with PE, on average about 200 to 250 cm$^3$, this likely represents the most peripheral parts of the conducting airways. With further increasing lung depth, ie, with penetration into the respiratory zone of the lung, patients with PE showed larger airspace dimensions than did healthy subjects. Patients with IPF, on the other hand, showed enlarged airways for both proximal lung depths and in the lung periphery.

There is some evidence that the changed EAD values in patients with PE indeed reflect alterations in

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**Table 2—Significance Levels of Differences Between the Study Groups for Various Parameters and PrOC for the Distinction Between Patients With IPF and PE**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>H vs PE</th>
<th>H vs IPF</th>
<th>PE vs IPF</th>
<th>PrOC PE vs IPF</th>
</tr>
</thead>
<tbody>
<tr>
<td>EAD$_{4%}$</td>
<td>NS</td>
<td>$&lt;0.0001$</td>
<td>0.02</td>
<td>0.77</td>
</tr>
<tr>
<td>EAD$_{10%}$</td>
<td>$&lt;0.0001$</td>
<td>$&lt;0.0001$</td>
<td>NS</td>
<td>0.57</td>
</tr>
<tr>
<td>EAD$_{20%}$</td>
<td>$&lt;0.0001$</td>
<td>$&lt;0.0001$</td>
<td>0.09</td>
<td>0.75</td>
</tr>
<tr>
<td>D$_{200}$</td>
<td>$&lt;0.0001$</td>
<td>NS</td>
<td>$&lt;0.0001$</td>
<td>0.83</td>
</tr>
<tr>
<td>D$_{400}$</td>
<td>$&lt;0.0001$</td>
<td>NS</td>
<td>$&lt;0.0001$</td>
<td>0.93</td>
</tr>
<tr>
<td>D$_{600}$</td>
<td>$&lt;0.0001$</td>
<td>NS</td>
<td>$&lt;0.0001$</td>
<td>0.92</td>
</tr>
<tr>
<td>D$_{800}$</td>
<td>$&lt;0.0001$</td>
<td>NS</td>
<td>$&lt;0.0001$</td>
<td>0.91</td>
</tr>
</tbody>
</table>

*H = healthy subjects.*
peripheral lung structure. Apart from a number of studies demonstrating the observed increase of EAD in patients or animal models with PE,\textsuperscript{3–6} it has been shown that peripheral EAD increases slightly with increasing age of the subject in a pattern similar to that observed by Brand et al.,\textsuperscript{10} Thurlbeck,\textsuperscript{23} and Zeman et al.\textsuperscript{24}

In contrast to patients with PE, in whom airspace enlargement is caused by permanent enlargement of distal airways and acini with destruction of alveolar walls, patients with IPF have scar contraction, which increases the traction on airway walls, resulting in the distention of small bronchi.\textsuperscript{1,2} This fact may explain our result that patients with IPF show the highest increase of EAD in the most central Vp measured in this study, and the differences diminish for increasing lung depth. In patients with IPF, changes in EAD are more likely caused by abnormalities of small bronchi rather than those of the acinar region. Patients with PE, on the other hand, have normal EAD values in proximal lung depths, but EAD is increased in the lung periphery. Lung destruction in these patients is confined predominantly to the acinus.

It has been shown previously that AD is increased in patients with PE.\textsuperscript{8,9} Although AD slightly increases with increasing TLC,\textsuperscript{10} the difference in dispersion between patients with PE and healthy subjects is too large to be explained by differences in TLC between both groups. The increased dispersion in patients with PE was interpreted as a functional consequence of lung destruction that increases expiratory airway closure, collateral ventilation, inhomogeneities of time constants, and pendelluft. Patients with IPF, on the other hand, showed normal AD. Considering the differences in pathophysiologic conditions between PE and IPF, the result of this study can be interpreted in the following way:

1. Lung destruction in patients with PE decreases airway elasticity, resulting in airway collapse during exhalation. In patients with IPF, stiffening of lung tissue prevents small airways from collapsing\textsuperscript{1,2} during exhalation, thereby preventing a delayed recovery of inhaled aerosols from diseased lung regions, which may increase AD.

2. Because lung destruction is much less pronounced in patients with IPF compared with patients with PE, collateral ventilation is likely to be less important. Therefore, particle redistribution through collateral channels, which also may increase AD, is probably much less in the IPF patients.

3. During slow breathing, as performed during the AD measurements, regional lung ventilation is pre-

\textbf{Figure 2.} Box plot of EAD\textsubscript{4%}, EAD\textsubscript{10%}, and EAD\textsubscript{20%} for patients with IPF or PE and for healthy subjects (H).
dominantly determined by lung compliance. Because inhomogeneities in compliance may be considered to be much less in patients with IPF than it is in patients with PE, ventilatory inhomogeneities caused by differences in local time constants are also less, and thus bolus dispersion in these patients is more normal.

This study corroborates the hypothesis that AD measurements, especially in combination with ADAM, may be a powerful tool for detecting the presence of PE in patients with COPD. Patients with PE have enhanced AD and enlarged peripheral EAD values. Even considering AD alone, patients with PE can be separated from patients with chronic obstructive bronchitis with high sensitivity and specificity, because it has been shown that concomitant bronchitis does not affect either AD or ADAM. Furthermore, in this study, it has been shown that, using AD and ADAM in combination, patients with IPF can be clearly separated from patients with PE. Although some patients with IPF show enlarged peripheral airspace dimensions, this enlargement is more pronounced in shallow Vps and can therefore be easily distinguished from peripheral airspace enlargement in patients with PE. Additionally, patients with IPF have normal AD, which is not the case in patients with PE. If patients show increased airspace dimensions, the sensitivity and specificity (PROC) of AD to distinguish between patients with IPF and patients with PE is > 0.9.

Because both techniques are noninvasive, they may be especially suitable for applications in epidemiology and occupational medicine. If in such studies, for example, COPD risk groups are screened for PE, it is of particular importance that changes in lung morphology caused by reasons other than PE can be clearly distinguished from those caused by PE.

Conclusions

The presence of PE can be detected with ADAM and AD. IPF can be distinguished from PE by differences in AD and a different pattern of changes in ADAM. Therefore, in epidemiologic studies and in occupational medicine, both techniques seem to be useful for the detection of PE in humans. The specificity of the aerosol tests is not impaired by subjects with changes in lung morphology caused by fibrosis. The practical value of these results should be confirmed by further prospective studies.

References

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