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Regional lung response to bronchodilator reversibility testing determined by electrical impedance tomography in chronic obstructive pulmonary disease

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1Department of Anesthesiology and Intensive Care Medicine, University Medical Center Schleswig-Holstein, Campus Kiel, Kiel, Germany; 2Department of Biomedical Engineering, Furtwangen University, Villingen-Schwenningen, Germany; and 3Department of Pneumology, Medical Clinic, Research Center Borstel, Germany

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Vogt B, Zhao Z, Zabel P, Weiler N, Frerichs I. Regional lung response to bronchodilator reversibility testing determined by electrical impedance tomography in chronic obstructive pulmonary disease. Am J Physiol Lung Cell Mol Physiol 311: L8–L19, 2016. First published May 17, 2016; doi:10.1152/ajplung.00463.2015.—Patients with obstructive lung diseases commonly undergo bronchodilator reversibility testing during examination of their pulmonary function by spirometry. A positive response is defined by an increase in forced expiratory volume in 1 s (FEV1). FEV1 is a rather nonspecific criterion not allowing the regional effects of bronchodilator to be assessed. We employed the imaging technique of electrical impedance tomography (EIT) to visualize the spatial and temporal ventilation distribution in 35 patients with chronic obstructive pulmonary disease at baseline and 5, 10, and 20 min after bronchodilator inhalation. EIT scanning was performed during tidal breathing and forced full expiration maneuver in parallel with spirometry. Ventilation distribution was determined by EIT by calculating the image pixel values of FEV1, forced vital capacity (FVC), tidal volume, peak flow, and mean forced expiratory flow between 25 and 75% of FVC. The global inhomogeneity indexes of each measure and histograms of pixel FEV1/FVC values were then determined to assess the bronchodilator effect on spatial ventilation distribution. Temporal ventilation distribution was analyzed from pixel values of times needed to exhale 75 and 90% of pixel FVC. Based on spirometric FEV1, significant bronchodilator response was found in 17 patients. These patients exhibited higher postbronchodilator values of all regional EIT-derived lung function measures in contrast to nonresponders. Ventilation distribution was inhomogeneous in both groups. Significant improvements were noted for spatial distribution of pixel FEV1 and tidal volume and temporal distribution in responders. By providing regional data, EIT might increase the diagnostic and prognostic information derived from reversibility testing.

EIT; pulmonary function testing; COPD; spirometry; ventilation distribution

PULMONARY FUNCTION TESTING (PFT) by spirometry is a clinical routine method used in patients with lung diseases both for diagnostic and prognostic reasons to assess the natural disease history and the effect of treatment. In selected groups of patients with obstructive lung diseases, an inhalation of a short-acting bronchodilator is indicated to establish the reversibility of airway obstruction. In patients with chronic obstructive pulmonary disease (COPD), the comparison between PFT findings acquired before and after the bronchodilator inhalation allows the assessment of attainable lung function and the presence of airway hyperresponsiveness (32). Bronchodilator reversibility testing is primarily carried out for disease staging in these patients as recommended by the recently updated Global Strategy for the Diagnosis, Management and Prevention of COPD-2016 issued by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (http://goldcopd.org/).

In a clinical setting, the presence or absence of significant response to bronchodilator is typically established based on a single lung function measure derived from PFT by use of spirometry or whole body plethysmography. An increase in forced expiratory volume in 1 s (FEV1) determined from the forced full expiration maneuver is used as the most frequent criterion (6, 7). Relative increase in FEV1 by more than 12% compared with baseline accompanied by an absolute increase by more than 200 ml is considered an appropriate threshold value for classifying the test as significant according to the recommendations of the American Thoracic Society (ATS), the European Respiratory Society (ERS), and the GOLD Initiative (6, 33). Nonetheless, the suitability of this single criterion-based patient classification to predict the disease phenotype, progression, response to therapy, and outcome has been questioned in several studies (1, 6, 20, 45).

This may be related with the fact that FEV1 but also other conventional PFT measures only provide an average, global information on lung function without taking regional lung function heterogeneity into account. Imaging methods might offer an option how this regional information could be assessed. However, most of the existing radiological methods are not suitable for several reasons: Their use is associated with increased radiation load [chest radiography, computed tomography (CT), ventilation scintigraphy]. The examinations costs are rather high and patients can only be examined in specialized laboratories (CT, magnetic resonance imaging). Continuous examinations allowing the analysis of dynamic effects are not possible. Finally, mainly morphological but not functional information is obtained from radiological examinations.

A possible alternative diagnostic and monitoring imaging method to assess regional lung function and determine regional bronchodilator responsiveness might be electrical impedance tomography (EIT). EIT measures electrical bioimpedance of...
body tissues, and its use has no known risks (4, 5, 26, 34). EIT is radiation free and fully noninvasive. Thanks to its small size and easy transportability EIT can be used anywhere. Continuous examinations are possible. The ability of EIT to reliably measure regional lung air volume changes has been validated by use of different reference techniques in multiple studies (9, 14, 22, 39, 48). Because of very high scan rates of modern EIT devices, chest EIT can trace rapid changes of electrical properties of pulmonary tissue, even during high airflow rates (35).

The number of publications on EIT lung imaging is continuously increasing (10). Most of the studies were conducted with the aim of promoting the use of EIT in intensive care medicine, mainly for monitoring of mechanically ventilated critically ill patients. In these patients, EIT might enable rapid personalized adjustment of ventilator settings and optimize ventilator therapy. There exist only a few studies showing the potential of EIT for examination and monitoring of regional lung function in other patient groups (11, 50, 52, 54). No time or therapy-dependent changes in regional lung function were assessed by EIT in these studies and often only a very small number of subjects was studied.

Therefore, the aim of our study was to examine a relatively large group of patients with COPD by EIT during conventional PFT using spirometry before and repeated after the bronchodilator inhalation. We wanted to determine the regional post-bronchodilator response in terms of spatial and temporal heterogeneity of multiple EIT-derived regional lung function measures compared with baseline conditions.

MATERIALS AND METHODS

We studied 35 patients [22 men and 13 women, 70 ± 10 yr (mean age ± SD), 76 ± 18 kg body wt, 171 ± 9 cm height] with an established diagnosis of COPD in an inpatient pulmonary department. The study was approved by the institutional ethics committee, and written, informed consent was obtained from all study participants. The patients were admitted to the hospital for optimization of their therapy and they were examined during the routine PFT with bronchodilator reversibility testing on the second day of their stay in the hospital. Dyspnea, cough, and expectoration were the major causes of hospital admission. All but one patient were current or former smokers. Seven patients were classified as moderate (GOLD 2), 10 as severe (GOLD 3), and 18 as very severe COPD (GOLD 4). None of the patients was treatment naïve. All patients received a combination therapy of two or more drugs. The medication comprised long-acting β-agonists (32 patients), short-acting β-agonists on demand (17 patients), anticholinergics (30 patients), inhaled corticosteroids (29 patients), systemic corticosteroids (21 patients), and theophylline (1 patient). The whole body plethysmography records revealed that hyperinflation was diagnosed in 34 of 35 patients. Of these patients only 8 had a mild and all other patients a moderate or severe hyperinflation. Emphysema was documented in 28 of 29 patient records where the results of previous radiological (chest radiography or computed tomography) examinations were included. Large bullae were not documented.

All patients were examined on four separate occasions: During baseline conditions 5 min before the inhalation of a short-acting β2-agonist salbutamol and 5, 10, and 20 min after inhalation. The bronchodilator was administered in two doses of 100 μg of salbutamol each via a spacer according to the standard procedure used in the pulmonary function laboratory where the study took place. EIT examinations (Goe-MF II, CareFusion, Höchberg, Germany) were carried out in parallel with conventional spirometry (Jaeger pneumotachograph, CareFusion, Höchberg, Germany). All patients were examined in a seated position during tidal breathing and subsequent forced full expiration maneuver. The patients were classified as having reversible airway obstruction when postbronchodilator FEV1 increased by more than 12% and 200 ml.

EIT images were acquired at the maximum available scan rate of up to 44 images/s by using an array of 16 self-adhesive electrodes (Blue Sensor L-00-S, Ambu, Ballerup, Denmark). The placement of the electrodes took ~10 min. The EIT data acquisitions lasted ~90 s, resulting in data sets of up to 4,000 single EIT images. These images had the resolution of 32 × 32 image pixels. In each image pixel, the normalized impedance (Z) differences between the instantaneous and reference pixel Z were plotted. The reference Z in each pixel was calculated as the average Z during the tidal breathing phase preceding the ventilation maneuver. In EIT taxonomy, these values are often called “relative impedance changes” (rel. ΔZ) and we use this term throughout the text.

The pixel waveforms of rel. ΔZ were further processed to generate regional counterparts of conventional pulmonary function measures obtained by spirometry. These EIT-derived measures represented regional exhaled volumes, expiratory flow rates, and expiration times. In detail, this analysis was performed as follows: The maximum value of rel. ΔZ at total lung capacity at the time point directly preceding the forced full expiration and the minimum value at residual lung volume by the end of full expiration were identified in each image pixel. The individual differences between these two values equaled pixel forced vital capacities (FVC). The differences between the maximum pixel rel. ΔZ values and the values reached after 1 s of forced expiration corresponded to pixel FEV1. The maximum rates of pixel rel. ΔZ change represented the pixel peak expiratory flows (PEF) and the average rates between 25 and 75% of pixel FVC equaled mean forced expiratory flows (PEF25–75). In the next step, pixel tidal volumes (VT) were calculated as average tidal variations of rel. ΔZ during the tidal breathing period preceding the maneuver. Pixel values of FEV1, FVC, PEF, PEF25–75, FEV1/FVC, and VT were used to characterize the spatial distribution of ventilation by calculating the global inhomogeneity (GI) indexes as described in (53). The GI index is the sum of the absolute differences between the median and the individual pixel values normalized to the sum of all pixel values. Finally, histograms of pixel FEV1/FVC were generated.

To assess the temporal distribution of ventilation an analysis of regional expiration times during the forced full expiration maneuver was carried out. The procedure was described in detail in (50). From each pixel waveform of rel. ΔZ, the time needed to exhale 75% (τ75) and 90% of pixel FVC (τ90) was calculated. To visualize the frequency distribution of these two measures, histograms of pixel τ75 and τ90 were plotted. The center expiration times were then calculated from each histogram.

The described EIT data analysis was carried out at baseline and the subsequent three postbronchodilator examination time points.

Statistical analysis was performed with GraphPad Prism 5.01 (GraphPad Software, San Diego, CA). Data are presented as mean values ± SD, unless otherwise indicated. Repeated-measures ANOVA with Bonferroni multiple-comparison test was used to examine the effects of the bronchodilator inhalation on the EIT-derived regional volumes, air flow rates, and expiration times as well as on the conventional global spirometric values. Unpaired t-test was used to assess the differences between patients with reversible and irreversible airway obstruction. The data were analyzed in the groups of patients with and without bronchodilator responsiveness, respectively, as well as in the whole study group. P values <0.05 were considered to be significant.

RESULTS

Based on conventional spirometric PFT, 17 patients (age 72 ± 8 yr, body weight 77 ± 19 kg, body height 171 ± 9 cm) were classified as having a significant response to the bronchodilator. Eighteen patients (68 ± 10 yr, 76 ± 17 kg, 171 ± 8 yr, body weight 77 ± 19 kg, body height 171 ± 9 cm) were classified as having a significant response to the bronchodilator.
10 cm) were classified as having an absent bronchodilator response. There were no statistical differences between these two groups regarding age, body weight, and height. The distribution of COPD severity was similar between the groups: 4 patients were classified as GOLD 2, 4 as GOLD 3, and 9 as GOLD 4 in the group with a positive response to the bronchodilator. In the group with an absent response, the corresponding numbers were 3, 6, and 9.

The spirometric findings are summarized in Tables 1 and 2. The values are reported as Z-scores according to the ATS/ERS recommendations (36, 43). (Z-scores show by how many standard deviations the individual patient’s measurement differs from the predicted value.) Global spirometric FEV1, FVC, and FEF25–75 increased significantly in patients with a significant postbronchodilator response; FEV1/FVC was not affected. All determined spirometric PFT measures remained unaffected in the other group.

Regional exhaled volumes (Fig. 1, A and B) and expiratory flows (Fig. 1, C and D) determined by EIT in the studied chest section during the forced full expiration were significantly affected by the bronchodilator inhalation in patients with a positive spirometric response to bronchodilator. The highest values were found after 20 min; however, significant postbronchodilator effects were partially noted even at earlier time points. For instance, a significant rise in FVC was identified already after 5 min. The corresponding values did not change in the other patient group at any examination time point (Fig. 2). In the pooled analysis, the EIT-derived FEV1 and FVC were impacted by the bronchodilator (P = 0.064 and P = 0.041, respectively) with significant increases noted only at 20 min after the administration. The expiratory flow rates were not affected.

The spatial heterogeneities of pixel FVC, PEF, and FEF25–75 quantified by the GI indexes were not affected by the bronchodilator inhalation either in the group with a significant (Fig. 3) or absent spirometric response to reversibility testing (Fig. 4). Only the GI of FEV1 fell slightly in the former group 10 min after the bronchodilator inhalation (Fig. 3A). No postbronchodilator changes in the GI of FEV1 were found in nonresponders (Fig. 4A). The pooled analysis revealed a significant effect of the bronchodilator only on the GI of FEV1 (P = 0.021) with lower values at all postbronchodilator time points.

Histograms of pixel FEV1/FVC ratios revealed the high heterogeneity of their distribution in both patient groups at baseline (Fig. 5, A and E). The histograms exhibited slight changes in the distribution of pixel FEV1/FVC with a tendency toward less broad distribution in both groups after the bronchodilator (Fig. 5, B–D and F–H); the center values were not affected. The changes in the GI indexes of pixel FEV1/FVC remained insignificant in both groups (Fig. 6, C and D); in the pooled data, a small effect was noted (P = 0.036). The average regional FEV1/FVC determined by EIT in the examined chest section increased to some extent 20 min after the bronchodilator administration in responders (Fig. 6A).

The analysis of EIT data registered during the tidal breathing period revealed an increase in regional Vt (Fig. 7A) and reduced inhomogeneity of its spatial distribution (Fig. 7C) in the group with a significant spirometric response to the bronchodilator inhalation. No such effects were identified in the other group. On contrary, a trend toward more heterogeneous tidal ventilation distribution was found (P = 0.078) (Fig. 7D). A trend to higher regional postbronchodilator Vt was found in the pooled data (P = 0.069).

Histograms of t75 (Fig. 8, A and E) and t90 (Fig. 9, A and E) showed the high temporal heterogeneity of ventilation in both groups of patients during baseline. In patients with an absent spirometric bronchodilator response, the postbronchodilator histograms remained very similar and comparable with the prebronchodilator ones for both t75 and t90 (Figs. 8, 9, F–H). In patients with a significant response, clear shifts of the t75 and t90 values to the left, i.e., to shorter expiration times, were found during all three postbronchodilator phases. The effects were most pronounced during the earliest phase after 5 min (Figs. 8B and 9B). These changes are also evidenced by the diagrams in Fig. 10, showing the significantly reduced t75 and t90 expiration times in all patients in the responder (Fig. 10, A and C) but not in the nonresponder group (Fig. 10, B and D). The effect of the bronchodilator on both expiration times was discernible in the pooled data with P values of 0.001 each, with significantly shorter t75 and t90 at 5 and 10 min after the administration.

**DISCUSSION**

The results of our study show that EIT can determine the spatial and temporal heterogeneity of ventilation in patients with COPD. Regional effects of a short-acting bronchodilator were identified by using a set of different EIT lung function measures obtained during the forced full expiration maneuver. These measures characterized regional exhaled volumes, expiratory flow rates, and expiration times at different time intervals after the bronchodilator inhalation. An intriguing finding

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**Table 1. Spirometry results in patients with a positive response to the bronchodilator reversibility test**

<table>
<thead>
<tr>
<th>Time</th>
<th>FEV1 (Z score)</th>
<th>FVC (Z score)</th>
<th>FEV1/FVC (Z score)</th>
<th>FEF25–75 (Z score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-5’</td>
<td>-3.17 ± 0.72*</td>
<td>-2.23 ± 1.14*</td>
<td>-2.77 ± 0.92</td>
<td>-2.54 ± 0.56*</td>
</tr>
<tr>
<td>+5’</td>
<td>-3.14 ± 0.72*</td>
<td>-2.22 ± 1.14*</td>
<td>-2.77 ± 0.92</td>
<td>-2.54 ± 0.56*</td>
</tr>
<tr>
<td>+10’</td>
<td>-3.14 ± 0.72*</td>
<td>-2.22 ± 1.14*</td>
<td>-2.77 ± 0.92</td>
<td>-2.54 ± 0.56*</td>
</tr>
<tr>
<td>+20’</td>
<td>-3.14 ± 0.72*</td>
<td>-2.22 ± 1.14*</td>
<td>-2.77 ± 0.92</td>
<td>-2.54 ± 0.56*</td>
</tr>
</tbody>
</table>

Values are means ± SD. FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; FEF25–75, mean forced expiratory flow between 25% and 75% of FVC; −5’, 5 min before; +5’, 5 min after; +10’, 10 min after; +20’, 20 min after the bronchodilator inhalation; *significantly different from control (P < 0.001).

**Table 2. Spirometry results in patients with an absent response to the bronchodilator reversibility test**

<table>
<thead>
<tr>
<th>Time</th>
<th>FEV1 (Z score)</th>
<th>FVC (Z score)</th>
<th>FEV1/FVC (Z score)</th>
<th>FEF25–75 (Z score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-5’</td>
<td>-3.62 ± 0.90</td>
<td>-3.61 ± 0.95</td>
<td>-3.58 ± 0.97</td>
<td>-3.60 ± 0.94</td>
</tr>
<tr>
<td>+5’</td>
<td>-3.61 ± 0.95</td>
<td>-3.58 ± 0.97</td>
<td>-3.60 ± 0.94</td>
<td>-3.60 ± 0.94</td>
</tr>
<tr>
<td>+10’</td>
<td>-3.58 ± 0.97</td>
<td>-3.60 ± 0.94</td>
<td>-3.60 ± 0.94</td>
<td>-3.60 ± 0.94</td>
</tr>
<tr>
<td>+20’</td>
<td>-3.58 ± 0.97</td>
<td>-3.60 ± 0.94</td>
<td>-3.60 ± 0.94</td>
<td>-3.60 ± 0.94</td>
</tr>
</tbody>
</table>

Values are means ± SD. FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; FEF25–75, mean forced expiratory flow between 25% and 75% of FVC; −5’, 5 min before; +5’, 5 min after; +10’, 10 min after; +20’, 20 min after the bronchodilator inhalation.
was that a significant postbronchodilator response was identified during quiet tidal breathing as well.

Conventional PFT by spirometry is the gold standard diagnostic and monitoring tool in COPD (31–33, 37). Spirometry is a widespread and easy method for global lung function examination. The classical lung function measures, like the exhaled volumes and flow rates, are well established. However, their limitation is that they are derived from measurements carried out at the mouth and that they are effort dependent. Thus they only characterize the global, average function of the lungs and they may be falsely low when spirometry is performed in a nonstandard way or in noncooperating subjects.

Lung function is inherently inhomogeneous due to anatomical reasons, gravity, or posture. It is further impacted by age, smoking, and lung disease. In COPD, especially in the advanced disease stages, the pathological changes induced by chronic inflammation in the central and peripheral airways, lung parenchyma, and vasculature lead to multiple deleterious effects, like increased airway obstruction and parenchymal destruction that are not homogeneously distributed throughout the lungs.

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**Fig. 1.** Electrical impedance tomography (EIT)-derived regional exhaled volumes (A and B) and flow rates (C and D) in the examined chest cross section in patients with a significant spirometric response to the bronchodilator reversibility test during forced full expiration. The values were determined 5 min before and 5, 10, and 20 min after the bronchodilator inhalation. FEV₁, forced expired volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; FEF_{25–75}, mean forced expiratory flow between 25 and 75% of FVC; rel. ΔZ, relative impedance change. *P < 0.05; **P < 0.01; ***P < 0.001. Individual (open symbols, dotted lines) and mean values (solid symbols, solid lines) are shown, and P values are indicated.

**Fig. 2.** Electrical impedance tomography (EIT)-derived regional exhaled volumes (A and B) and flow rates (C and D) in the examined chest cross section in patients with an absent spirometric response to the bronchodilator reversibility test during forced full expiration. The values were determined 5 min before and 5, 10, and 20 min after the bronchodilator inhalation. FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; FEF_{25–75}, mean forced expiratory flow between 25 and 75% of FVC; rel. ΔZ, relative impedance change. Individual (open symbols, dotted lines) and mean values (solid symbols, solid lines) are shown, and P values are indicated.
the lungs. The resulting pathophysiological consequences, like airflow limitation and pulmonary hyperinflation, are therefore likewise inhomogeneous.

EIT has been shown capable of detecting the spatial heterogeneity of lung ventilation induced by the mentioned effects of gravity (12), posture (12, 21, 28, 41), aging (11, 50), smoke (40), mode of ventilation (spontaneous vs. artificial) (13, 17, 24, 25, 29), or lung disease (2, 3, 19, 27, 30). The most frequent lung diseases monitored by EIT in a clinical setting were the adult and infant respiratory distress syndromes.

Spontaneously breathing patients with chronic obstructive lung diseases as in our study have only seldom been studied so far (16, 42, 50, 52, 54). In an earlier study from our group, we confirmed the higher degree of ventilation heterogeneity in COPD patients compared with healthy young and elderly adult subjects (50). Patients with a chronic history of asthma exam-
ined by EIT exhibited significantly more heterogeneous ventilation distribution than age-matched healthy controls (16). Zhao et al. (52, 54) found the heterogeneously deteriorated lung function using EIT in adult patients with cystic fibrosis. Compared with healthy volunteers, patients with cystic fibrosis had significantly higher baseline ventilation inhomogeneity that changed in the course of deep lung inflation (52). The latter findings were based on the same GI index used to characterize the regional distribution of various EIT measures derived from the forced full expiration maneuver and tidal breathing in the present study.

Our study participants mostly suffered from advanced COPD with severely and very severely compromised lung function resulting from pronounced structural changes with

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\text{FEV}_{1\text{EIT}}/\text{FVC}_{\text{EIT}}
\]

Fig. 5. Histograms of pixel ratios of forced expiratory volume in 1 s (FEV\textsubscript{1}) and forced vital capacity (FVC) (mean values ± SE) obtained from chest EIT imaging in patients with a positive (A–D) and an absent spirometric response to reversibility testing (E–H). Black dotted lines show the mean center FEV\textsubscript{1}/FVC values. The values were determined 5 min before (A and E) and 5 (B and F), 10 (C and G), and 20 min (D and H) after the bronchodilator inhalation.
Fig. 6. EIT-derived regional ratios of forced expiratory volume in 1 s and forced vital capacity (A and B) and the heterogeneity of their distribution (C and D) in the examined chest cross section in patients with a significant (A and C) and an absent spirometric response to reversibility testing (B and D). The values were determined 5 min before and 5, 10, and 20 min after the bronchodilator inhalation. FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; rel. ΔZ, relative impedance change; GI, global inhomogeneity index; **P < 0.01. Individual (open symbols, dotted lines) and mean values (solid symbols, solid lines) are shown, and P values are indicated.

Fig. 7. EIT-derived regional tidal volumes (A and B) and the heterogeneity of their distribution (C and D) in the examined chest cross section in patients with a significant (A and C) and an absent spirometric response to reversibility testing (B and D). The values were determined 5 min before and 5, 10, and 20 min after the bronchodilator inhalation. VT, tidal volume; rel. ΔZ, relative impedance change; GI, global inhomogeneity index; **P < 0.01. Individual (open symbols, dotted lines) and mean values (solid symbols, solid lines) are shown, and P values are indicated.
very small or absent in our study. The GI index is a robust parameter compressing the information on the degree of ventilation heterogeneity into one number. The GI indexes of all volumes and flows derived by EIT from the forced full expiration maneuver, except for the small improvement of FEV\(_1\) distribution in spirometric responders, did not change. Because of this finding and the significant increases in regional FEV\(_1\), FVC, PEF, and FEF\(_{25-75}\) determined by EIT along with an absent improvement of regional FEV\(_1\)/FVC in patients with a significant spirometric response to the bronchodilator inhalation, we presume that the major effect of the bronchodilator was the reduction in lung hyperinflation. This is a plausible finding because the reduced hyperinflation is not necessarily associated with reduced ventilation heterogeneity in COPD.

Fig. 8. Histograms of pixel times required to exhale 75% (\(t_{75}\)) of pixel forced vital capacity (mean values ± SE) in patients with a significant (A–D) and an absent spirometric response to reversibility testing (E–H). The values were determined 5 min before (A and E) and 5 (B and F), 10 (C and G), and 20 min (D and H) after the bronchodilator inhalation. Black dotted lines show the mean center expiration times. *\(P < 0.05\); **\(P < 0.01\).
patients. It confirms the results of a study in which improved 
FEV₁ and inspiratory capacity were found after the admin-
istration of an anticholinergic agent but the grossly abnor-
mal ventilation heterogeneity showed no significant im-
provements (47).

In conventional spirometric bronchodilator reversibility test-
ing, it is recommended to assess the effect after 10–15 min (31,
33). It was interesting to observe that EIT identified the 
induced lung function changes at earlier times as well. Al-
though the degree of volumetric and flow changes determined 
from the forced expiration maneuver increased with the post-
bronchodilator examination time, the effects were mostly de-
tectable already at 5 min in the responder group. The improve-
ments in expiration times $t_{75}$ and $t_{90}$ were most pronounced 5

Fig. 9. Histograms of pixel times required to exhale 90% ($t_{90}$) of pixel forced vital capacity (mean values ± SE) in patients with a significant (A–D) and an absent 
spirometric response to reversibility testing (E–H). The values were determined 5 min before (A and E) and 5 (B and F), 10 (C and G), and 20 min (D and H) 
after the bronchodilator inhalation. Black dotted lines show the mean center expiration times. *$P < 0.05$; ***$P < 0.001$. 

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min after the bronchodilator inhalation; also the VT distribution improved promptly. This early detectability of postbronchodilator changes was also seen in the pooled EIT data analysis.

The capability of EIT to identify the presence of the bronchodilator response from the tidal breathing phase is an interesting finding. This might become a relevant feature of EIT-based PFT because it could potentially eliminate the necessity of performing the forced full expiration maneuver. This maneuver and the lung function measures derived from it are effort dependent. Therefore, patients with low compliance or noncooperating patients like small children might benefit from EIT because it could potentially eliminate the necessity of performing the forced full expiration maneuver. This maneuver and the lung function measures derived from it are effort dependent. Therefore, patients with low compliance or noncooperating patients like small children might benefit from EIT if it is confirmed that lung function can be sufficiently characterized from tidal breathing alone. Already our previous EIT study showed that COPD patients could be discriminated from healthy subjects on the basis of spatial distribution of VT (50).

In our present study, the EIT examinations were performed in patients using a mouthpiece because of the simultaneous reference spirometry examinations. However, EIT does not require the use of a mouthpiece. Thus, patients’ lung function can be examined under more natural conditions with unchanged respiratory system mechanics than with a mouthpiece. EIT-based PFT might be carried out easier without a mouthpiece in specific patient groups, like pediatric patients.

A certain disadvantage of EIT is its relatively low spatial resolution associated with the measuring principle of this method. Compared with established radiological tomographic methods like CT or MRI, EIT images offer a clearly lower resolution; however, as shown in this and other previous studies, the resolution is sufficient for obtaining reliable functional information. The full characterization of pulmonary disease pathophysiology requires not only anatomical but also functional information (23).

Besides EIT, functional information on lung ventilation distribution can also be obtained by methods like MRI using hyperpolarized gases. However, this functional imaging approach is mostly used only under experimental conditions in specialized laboratories at high costs. EIT offers the advantage of independency on examination site and special gas mixtures, as well as low examination costs and the possibility of continuous assessment of regional lung ventilation.

Our study is one of the pioneering studies on the use of EIT in COPD patients during PFT. We acknowledge that it exhibits limitations. One limitation is that the study design did not allow us to reliably examine the question how the disease severity impacted the EIT findings. Our study population consisted of patients with mostly severe and no mild COPD and was not adequate for that type of analysis. This issue needs to be addressed in further studies with a proper study design for that aim, taking all COPD stages and different phenotypes into account.

Another limitation is that, corresponding to the current clinical practice, we only studied the patients during one reversibility testing session (albeit repeatedly). It has been established in a large patient cohort that the bronchodilator responsiveness is an unstable phenotypic characteristic in COPD (1). However, since the reproducibility of EIT findings has been confirmed in several studies (15, 38, 51), EIT can be expected to produce reliable estimates of ventilation distribution during repeated examinations in COPD patients as well.

EIT determines gas volume changes in a three-dimensional section of the chest. These changes and the corresponding EIT findings are related with the global lung volume changes, as shown by using spirometry in healthy adult patients (8), preterm infants (46), and adult patients with acute lung injury (18). However, they do not merely duplicate the spirometry findings,
which only trace the summed-up volume changes in the whole chest. EIT provides additional data that allow the assessment of regional ventilation distribution. For instance, the global FEV1/FVC ratio determined by spirometry was not significantly affected by the bronchodilator; however, the regional EIT-derived FEV1/FVC was affected and improved significantly.

In our study, the overall dose of 200 μg salbutamol was administered during the reversibility testing. This dose corresponded with the standard procedure used in the PFT laboratory where the study was carried out and to the national guidelines. The same dose was used in large clinical trials studying the bronchodilator responsiveness, like the BOLD study with more than 10,000 patients (44). However, several recent publications, such as the updated GOLD 2016 document, recommend only a single dose of 400 μg of the short-acting β2 agonist.

Finally, we would like to point out that, owing to our expertise, the application of 16 single electrodes on the chest of the studied patients did not take long and was acceptable in the setting of a clinical study. However, the potential routine clinical use would require the use of electrode belts or strips and an automated online analysis of PFT-specific parameters.

In summary, the findings of our study imply that, in addition to the already recognized potential use of EIT in monitoring critically ill patients undergoing ventilator therapy, other patient groups could benefit from EIT monitoring as well. The assessment of spatial and temporal distribution of regional ventilation by EIT in patients with chronic lung diseases, like COPD, asthma, and cystic fibrosis, could provide new regional information in addition to the global lung function information provided by conventional methods. This might advance patient phenotyping, improve the monitoring of natural disease history and pharmacological and nonpharmacological treatment, and increase the prognostic value of PFT regarding clinical outcomes.

GRANTS

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

B.V., P.Z., N.W., and I.F. conception and design of research; B.V. and I.F. interpreted results of experiments; B.V. and I.F. drafted manuscript; B.V., Z.Z., P.Z., N.W., and I.F. approved final version of manuscript; I.F. prepared figures.

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