Original Article

Regional ventilation in cystic fibrosis measured by electrical impedance tomography☆

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Abstract

Background: The feasibility of electrical impedance tomography (EIT) as an alternative examination tool in cystic fibrosis (CF) was examined. Methods: 14 CF patients and 14 healthy volunteers were studied. Spirometry and EIT measurements were performed simultaneously. The global inhomogeneity (GI) index was applied to assess the degree of ventilation homogeneity at different levels of maximum inspiratory volume. Ratios of maximum expiratory flow at 25% and 75% of vital capacity (MEF25/MEF75) were calculated for both global lung and regional areas in EIT images. Results: Significant differences among GI values at various lung volumes were found in CF patients (P<0.01) but not in healthy subjects. Global MEF25/MEF75 measured with spirometry and with EIT were highly correlated for all subjects (r²=0.69, P<0.01). Significant difference in global MEF25/MEF75 was found between CF patients and healthy volunteers with both spirometer (CF: 0.15±0.09; healthy: 0.46±0.15; P<0.001) and EIT (CF: 0.14±0.09; healthy: 0.42±0.08; P<0.001). Regional airway obstruction was identified in the MEF25/MEF75 maps in CF patients. Conclusions: Compared to the global parameters provided by spirometry, EIT is able to deliver both global and regional information to assess the airway obstruction in CF patients.

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Keywords: Cystic fibrosis; Electrical impedance tomography; Lung function test; Ventilation homogeneity

1. Background

Cystic fibrosis (CF) is an inherited, chronic disease that mainly affects the lungs and the digestive system. It is caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene [1]. Unfortunately, there is still no cure for CF and it tends to increase in severity over time [2]. Despite improved treatments, CF patients only have a mean survival time of 37 years [3]. The alteration of lung structure and small airways leads to flow reduction during inspiration and expiration [4,5]. A spirometer measures global parameters such as forced expiratory volume in 1 second (FEV₁) and maximum expiratory flow at 25%, 50% and 75% of vital capacity (MEF₂₅, MEF₅₀, MEF₇₅) from which the degree of airway obstruction can be implied. However, information on regional ventilation cannot be captured with these global parameters. In order to recognize an exacerbation early and more precisely, imaging techniques such as conventional radiography and computed tomography (CT) are employed. CT is considered a gold standard for assessment of aeration in injured lungs [6]. Unfortunately, due to high radiation exposure, CT is inadequate for long term monitoring of disease progression.

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Multibreath inert gas washout technique (MBWT) was proposed to evaluate ventilation inhomogeneity in CF patients, [7,8]. Though this technique is more sensitive than FEV₁ and MEF₂₅ in early diagnosis of CF, it is not able to detect regional changes in early CF lung disease. This is due to the fact the both MBWT and spirometry are assessed at the mouth of the patients which represents the last end of the airways. Therefore, any detection of regional changes in early CF lung disease might be masked by the inevitable dilution of regional air flow from all lung sites. A direct, radiation-free assessment of regional lung ventilation might therefore demonstrate additional information in early CF lung disease or during exacerbations.

Electrical impedance tomography (EIT) is a noninvasive, radiation-free imaging technique which can monitor regional lung ventilation and tidal volume distribution by measuring the electrical potentials at the chest wall surface. The rationale is that changes in regional air content and regional blood volume modify the electrical impedance of lung tissue [9,10]. The reliability of EIT has already been confirmed by comparison with different conventional methods including CT and pneumotachography [11-13]. Applications of EIT have been proposed in subjects without lung disease [14-16] and in patients with mild, moderate, and severe lung diseases [17-19] to assess the ventilation distribution or even guiding respiratory therapies. However, there exists no EIT study in CF patients up to now. The aim of this pilot study was to examine the feasibility of EIT as an alternative clinical examination tool for CF patients. In order to be an alternative clinical tool, EIT should be able to deliver: 1) reliable information comparable with spirometry; 2) additional information about the lung dynamics and ventilation distribution (information gain). In the present study, we compared the EIT findings with spirometry according to these two criteria.

2. Material and methods

2.1. Protocol and measurement

A total of 14 CF patients (CF group: 6 male, 8 female; age 34±9 years; height 166±9 cm; weight 56±8 kg (mean±SD)) and 14 lung healthy volunteers (control group: 8 male, 6 female; age 28±7 years; height 171±10 cm; weight 71±20 kg (mean±SD)) were studied prospectively. Exclusion criteria included age <18 years, pregnancy and lactation period, and any contraindication to the use of EIT (pacemaker, automatic implantable cardioverter defibrillator, and implantable pumps). An additional exclusion criterion for the control group was history or clinical signs of lung disease. The study was approved by the Ethics Committee of the University of Munich. Written informed consent was obtained from all patients and healthy subjects prior to the study.

All subjects were seated during the complete measurement. After a stabilization period of 2 min, they were asked to breathe in as deep and exhale as hard as possible for three times at the spirometer (MasterLab, Inc. Carefusion, Höchberg, Germany), according to standard spirometry guidelines from the American Thoracic Society and European Respiratory Society [20]. This process was repeated once for every subject.

An EIT electrode belt with 16 electrodes was placed around the thorax in the fifth intercostal space and one reference electrode was placed at the patients’ abdomen (EIT Evaluation KIT 2, Dräger Medical, Lübeck, Germany). After applying electrical alternating currents (50 kHz, 5 mA peak-to-peak) in a sequential rotating process and measuring the resulting surface potential differences between neighboring electrode pairs, EIT images (each consisting of 32 × 32 pixels) were generated with a reconstruction algorithm based on a modified ‘finite element model’ [21]. EIT images were continuously measured at 20 Hz during lung function test.

2.2. Data evaluation

A so-called global inhomogeneity (GI) index based on EIT was recently introduced by our group to quantify the tidal volume distribution within the lung [16,22]. In the present study, the GI index was slightly modified to evaluate the inhomogeneity degree at 25%, 50%, 75% and 100% of maximum inspiratory volume. For every forced inspiration, four difference images, which represented the respective differences of impedance between 25%, 50%, 75%, 100% of maximum inspiratory volume and inspiration begin (0%), were generated. Lung regions in EIT images were defined using the LAE method [23]. The median value of the pixels in the lung area was calculated for each difference image. The GI index was defined as the sum of the absolute differences between the median value and every pixel value, which was normalized with the sum of the impedance values within the lung area:

\[
GI = \frac{\sum_{x,y=\text{lung}} |DI_{xy} - \text{Median}(DI_{\text{lung}})|}{\sum_{x,y=\text{lung}} DI_{xy}}
\] (1)

where \(DI\) is the value of the differential impedance in the difference images; \(DI_{xy}\) denotes the pixel in the identified lung area; \(DI_{\text{lung}}\) are all pixels in the lung area under observation. The GI index values at the levels of 25%, 50%, 75%, and 100% are denoted as \(GI_{25}\), \(GI_{50}\), \(GI_{75}\) and \(GI_{100}\), respectively. Coefficient of variation for within-subject GI was calculated for both groups to assess the repeatability.

The total relative impedance values (\(I_{\text{rel}}\)) are proportional to inspiratory and expiratory volumes [13], derivatives of \(I_{\text{rel}}\) (\(I'_{\text{rel}}\)) are considered to be proportional to inspiratory and expiratory flows. Since EIT delivers only relative impedance values, a direct comparison with spirometric parameters is not possible. Therefore, the ratios of maximum expiratory flows at 25% and 75% of vital capacity (MEF₂₅/MEF₇₅) during forced expiration were calculated both for the global sum of impedance values, and for every pixel of lung regions in the EIT images. MEF₂₅/MEF₇₅ values derived from EIT were compared to that obtained from spirometry tests for validation.
2.3. Statistical analysis

Data analysis was performed using MATLAB 7.2 (The MathWorks Inc., Natick, MA, USA). The Lilliefors test was used for normality testing. For not normally distributed data, results were expressed as median (interquartile range) or lower and upper quartiles. Kruskal–Wallis test was performed to compare GI_{25}, GI_{50}, GI_{75} and GI_{100}. Post-hoc paired comparisons were performed with the paired-sample Wilcoxon signed rank test and the significant levels were corrected using the Holm’s sequential Bonferroni method for multiple comparisons. Data are reported when a ≥ 20% difference existed between variables. In case of normal distribution, results were expressed as mean values±SD. Global \( \frac{MEF_{25}}{MEF_{75}} \) values in CF patients and healthy subjects were compared with an unpaired \( t \)-test. A \( P \) value <0.05 was considered statistically significant. The frequency distribution of regional \( \frac{MEF_{25}}{MEF_{75}} \) was described with histograms.

3. Results

All subjects were able to complete the procedure. The data evaluation described in the last section was performed on all measurements. Figs. 1 and 2 show the difference images of a healthy volunteer and a CF patient at different preselected lung volume levels of the forced breathing cycle. Air distribution is similar at all levels in the healthy subject (Fig. 1) while more air is distributed to the right dorsal regions of the CF patient compared to the right ventral regions at 25% and 50% of the maximum inspiratory volume (Fig. 2). Ventilation distribution becomes more homogeneous at higher inspiratory volume levels in this patient, which indicates that the airways are partially obstructed leading to a delay in air distribution. However, the difference between the healthy subject and the CF patient is not obvious when only comparing the EIT images.

Information on regional ventilation distribution was extracted by calculating the GI index. The median (interquartile range) coefficient of variation for within-subject GI was 6.2 (2.0)% for CF patients and 5.2 (3.0)% for healthy volunteers. In Fig. 3, the GI index at different lung volume levels during forced inspiration are depicted and compared in both CF and control groups. Significantly different GI values at various lung volume levels were found in the CF group (from GI_{25} to GI_{100}: 0.49 (0.25), 0.38 (0.14), 0.36 (0.12) and 0.34 (0.09), median (interquartile range); \( P <0.01 \)) but not in the control group (from GI_{25} to GI_{100}: 0.39 (0.07), 0.35 (0.04), 0.35 (0.03) and 0.35 (0.03)). Further, GI_{25} was 20% greater than GI_{100} in CF patients (relative to GI_{100}, \( P <0.01 \)).

Global flow-volume curves from one CF patient with spirometry and EIT (top), together with regional flow-volume curves with EIT (bottom) were plotted exemplarily in Fig. 4. Shape of regional flow-volume curves differed from that of the global ones. Spirometric parameters from CF patients and healthy volunteers were compared in Table 1. \( \frac{MEF_{25}}{MEF_{75}} \) values measured with spirometer and with EIT were highly correlated for all 28 subjects (\( r^2 =0.69, P <0.01 \)). Significant difference in \( \frac{MEF_{25}}{MEF_{75}} \) was found between CF group and control group with both spirometer (CF group: 0.15±0.09; control group: 0.46±0.15; \( P <0.001 \)) and EIT (CF group: 0.14±0.09; control group 0.42±0.08; \( P <0.001 \)).

Fig. 1. Difference images of one subject with healthy lungs at (a) 25%, (b) 50%, (c) 75% and (d) 100% of maximum inspiratory volume (difference to 0%). Color bars indicate the magnitude of relative impedance values in each pixel.
Regional $\text{MEF}_{25}/\text{MEF}_{75}$ was calculated for every pixel in the lung areas of the EIT images. Typical results in a healthy subject (Fig. 5, left) and a CF patient (Fig. 5, right) are plotted in two images with a resolution of 32×32 pixels. Note that the pixel values do not represent the relative impedance values as in an EIT image.

The normalized frequency distribution of regional $\text{MEF}_{25}/\text{MEF}_{75}$ is plotted in Fig. 6. The patients in the CF group have lower regional $\text{MEF}_{25}/\text{MEF}_{75}$ and the ratio is mainly distributed from 0.06 to 0.21. Less than 25% of pixels (median) have a regional $\text{MEF}_{25}/\text{MEF}_{75}$ larger than 0.24, while over 80% of pixels (median) of subjects in the control group have a ratio larger than 0.3.

4. Discussion

In the present pilot study, we found EIT being feasible to capture ventilation inhomogeneity and regional obstructions in CF patients. The decrease of GI index during forced inspiration in CF patients indicates a more homogeneous ventilation distribution with increasing inspiration time. A $\text{MEF}_{25}/\text{MEF}_{75}$ map calculated with relative impedance values visualizes regional obstructions.

Spirometry has been used for lung function testing in patients with obstructive airway diseases for a long time. It is a useful low-cost tool without need of radiation exposure when compared to chest radiography and CT. However, it measures only global parameters and may be influenced by multiple factors, e.g., cooperation of patients. Examination with CT delivers detailed information about lung aeration in CF patients. The frequent use of CT is, however, not suitable for patients. A technique is therefore warranted which provides more regional information than lung function tests and is less invasive than CT, so that it can be frequently applied. Although EIT is noninvasive and has been proved to be reliable, applications of EIT in patients with CF are still missing. Hence, a new application of EIT was attempted in the present study, which
may be of benefit in the diagnosis of disease progression with additional dynamic and regional information.

Gustafsson et al. suggested that ventilation inhomogeneity based on multiple-breath inert gas washout may be better than lung function test in detecting early CF lung disease [8]. Compared to multibreath washout technique and CT, EIT has the advantage that it visualizes ventilation distribution with a very good temporal resolution. Differences in ventilation homogeneity between healthy volunteers and patients with critical lung disease based on EIT have previously been reported [22]. Low within-subject coefficient of variation for GI index in both groups indicates that the EIT measurements and GI calculation are highly reproducible. The degree of ventilation inhomogeneity is relatively high in CF patients because of “mucus plugging” in the small airways. Unfortunately, large inter-patient variability at low lung volume range (Fig. 3, CF25) makes it hard to distinguish CF patients from healthy subjects during tidal breathing, unlike our previous study, where healthy subjects were compared to patients with acute lung injury [22]. Due to chronic airway obstruction in CF patients, it may take longer for air to distribute within their lungs. During cycles of forced inspiration and expiration, there should be more time for air distribution. Thus, we assessed the changes of ventilation distribution with EIT during lung function tests with data recordings performed during forced breathing. As hypothesized, the EIT-based GI index demonstrated ventilation inhomogeneity at the onset of forced breathing in CF patients, while ventilation became more homogeneous during the later phases of inspiration (Figs. 2 and 3). No significant changes of ventilation over the breathing cycle were found in healthy volunteers.

\[
\text{MEF}_{25}/\text{MEF}_{75} \text{ measured by EIT was found to be highly correlated with spirometry (r=0.83). Further, regional } \text{MEF}_{25}/
\]

Table 1

<table>
<thead>
<tr>
<th>Spirometric parameters</th>
<th>CF group</th>
<th>Control group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 (%predicted)</td>
<td>59.9±21.2</td>
<td>96.2±12.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FVC (%predicted)</td>
<td>68.1±27.7</td>
<td>86.2±13.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>MEF25 (%predicted)</td>
<td>23.1±18.3</td>
<td>130.0±39.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MEF75 (%predicted)</td>
<td>52.9±30.9</td>
<td>91.8±23.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MEF25/MEF75</td>
<td>0.15±0.09</td>
<td>0.46±0.15</td>
<td>&lt;0.001</td>
</tr>
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Data are presented as mean±SD. FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; MEF25, MEF75, maximum expiratory flow at 25% or 75% of vital capacity; %predicted, measured value divided by predicted value [24] in percentage.

Fig. 4. Flow-volume curves of one CF patient, obtained from spirometry and EIT. a, b) global Flow-volume curves from spirometry and EIT, respectively. c,d) two exemplary regional Flow-volume curves from EIT. AU: arbitrary unit.
MEF75 varied in different lung areas (Figs. 5 and 6). A low MEF25/MEF75 value potentially indicates regional obstructions, which can be easily recognized in the MEF25/MEF75 map. Since CF is initially a disease of the airways that eventually progresses to parenchymal destruction and the extent of destructive process is not uniformly distributed but rather varies between lung regions [7], such regional information provided by EIT may be useful for monitoring disease progression, e.g. during onset and recovery from a pulmonary exacerbation as well as the effects of therapy.

One drawback in the current EIT devices is that they deliver only relative impedance values which do not represent exact volumes and flow rates. A direct comparison with spirometry indices such as FEV1 is therefore not possible. Hahn et al. proposed a promising technique for absolute EIT [25,26], however, this technique has to be further developed before applicable in clinical routine. In the present study, we extracted the feature MEF25/MEF75 for comparison since MEF25 is usually much lower in CF patients compared to healthy subjects [7]. A high correlation with the spirometry indicates that the MEF25/MEF75 measured with EIT is reliable and useful. In further studies, equivalent spirometry indices in EIT should be considered. Another limitation of the current EIT devices is that the measurement was taken at one cross-sectional plane that is about 40 mm thick close to the body surface and increases its thickness towards the central region of the body. Although the EIT measuring plane is much thicker than a plane in CT imaging, it cannot be observed if the destroyed lung regions are outside the measuring plane. In the present study, significant differences among various regional parameters were found between healthy volunteers and CF patients, which means that the measuring plane of EIT was well selected and represented global lung status. Reifferscheid et al. and Bikker et al. have measured ventilation distribution at two thoracic levels in healthy subjects and mechanically ventilated patients [27,28]. In clinical practice, it is feasible to perform EIT measurement at two thoracic planes when necessary, since the measurement itself is not complicated or time consuming, however, at present such measurements cannot be performed in parallel. Three dimensional EIT systems are being developed in several research groups but not yet used in a clinical setting [29,30].

In the future, 3D EIT may also be a solution for monitoring the entire lung. One limitation of this feasibility study is that only limited number of patients were recruited for examination at one time point. In further studies, the sensitivity of EIT in CF patients should be investigated. The CF patients should also be examined at different time points to verify the ability of EIT in tracking disease progression over time.

5. Conclusion

Compared to the global parameters provided by spirometry, EIT is able to deliver both global and regional information to assess the airway obstruction in CF patients. Further, EIT is able to capture the variation of ventilation homogeneity during forced respiration in CF patients. This may be helpful in early diagnosis of disease exacerbation. Based on these findings, EIT has the potential to become an additional clinical examination tool for CF patients.
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