Cystic fibrosis (CF) in adult patients: correlation of lung function test results and pathologic lung morphology as expressed by the Brody score

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1. Cystic fibrosis (CF) is an inherited, autosomal-recessive metabolic disorder which represents one of the most common inheritable diseases among the Caucasian population in northern and middle Europe. Genetic alterations are associated with malfunction of chlorine channels in exocrine cells and glands, predominantly in the lungs and pancreases of affected patients. In the lung, CF is characterized by both pathologic alteration of lung morphology and patho-physiologic changes in lung function.

2. In clinical practice, spirometry serves to perform different lung function tests (LFTs) in CF patients. LFTs provide quantifiable test results that allow for both a cross-sectional assessment of the patient’s lung function - compared to, e.g., the general population - and a longitudinal assessment - e.g., demonstrating intrapersonal short-term changes associated with infectious exacerbation of CF, success of certain therapeutic measures, or long-term changes in the course of the disease that determine changes of medical interventions (pharmaceutical or physiotherapeutic). As technical equipment is widely available, easy to apply and to maintain, and LFTs are considered generally harmless in nature, spirometric LFTs are frequently applied in CF patients.

3. Using radiological imaging, several approaches for assessment of lung morphology can be taken: conventional chest radiography (CR), computed tomography (CT) and multi-detector-row CT (MDCT), and even MRI. Although the latter is being considered to be the least harmful procedure, the current lack of available lung imaging protocols for MRI and difficulties in interpretation due to inconsistent display of peripheral lung structures still result in inferiority to X-ray-based radiological imaging.

The superiority of CT over CR regarding the demonstration of normal and pathologic lung structures comes at the price of increased radiation exposure.

As CF patients require clinical lung imaging regularly and repetitively from an early age on, radiation dose accumulation is of great concern. Two different approaches to depicting lung morphology with high spatial resolution at reasonable radiation exposure (ALARA principle) include

- high-resolution CT (HRCT), with the acquisition of individual, incremental CT slices of 1-1.5 mm in width every 10-15 mm (i.e. leaving gaps uncovered by imaging), and

- low-dose MDCT, with coverage of the entire lung volume with a decreased tube current-time product, profiting from the already high inherent contrast between air spaces and soft tissue density matter within the lung.
4. Brody and co-workers [1] applied and validated a complex weighted scoring system for CF-specific pathologic lung morphology, offering the possibility to express structural alterations as a quantitative result.

The study was based on HRCT scans obtained in both inspiration and expiration in children of 6-10 years of age with a clinical diagnosis of CF. It demonstrated a modest but significant correlation between lung morphology scoring and spirometric LFTs, particularly including forced expiratory volume in one second (FEV1).

5. Examination conditions between children and adults vary essentially due to differences in patient compliance, lung maturation and the airspace/stroma ratio. Our retrospective study, using low-dose MDCT scans, aimed to examine if the Brody scoring system was applicable to adult CF patients and would lead to similar correlations under modified conditions.
Methods and Materials

Patients

Adult patients over the age of 18 years with a clinical diagnosis of CF were identified in the clinical and radiology information systems. CF patients who underwent both spirometric LFTs and low-dose MDCT of the chest in our institution within three days of each other between January, 2002, and January, 2008, were included in the analysis (n=36, 14 female, 22 male, age 34 +/- 8 years).

MDCT Protocol

Unenhanced MDCT of the chest was obtained in inspiration only, at a tube voltage of 120 KVp, with the lowest technically achievable tube current that would still yield diagnostic images.

Examinations performed until January, 2007, applied a 4-channel MDCT scanner, at 35 mA tube current, 0.5 s rotation time, 4x1 mm collimation, 1.75 pitch, 10 mAs effective tube current-time product per slice and 1.3 mm effective slice thickness. The protocol resulted in an average effective dose of 0.50 mSv for an adult female patient of average height and weight [2].

Examinations from February 2007 on were performed on a 64-channel MDCT scanner, at 35 mA tube current, 0.5 s rotation time, 64x0.5 mm collimation, 1.173pitch, 15 mAs effective tube current-time product per slice and 0.625 mm effective slice thickness.

MDCT images were reformatted with 3 mm slice thickness in 3 orthogonal planes and additional images of 1.0 to 1.5 mm in at least one plane and stored in an electronic picture archiving and communication system (PACS).

MDCT Evaluation

MDCT images were displayed on 1k-PACS monitors with one image per screen, window 1,600 HU and level -600 HU (lung window). Evaluation was primarily based on axial and coronal images. In cases where assigning findings to particular lung lobes was not possible, sagittal images were used additionally. All MDCT scans were evaluated by an attending radiologist with 10 years of post-residency clinical experience in chest radiology, including formal evaluation of chest scans in CF patients based on scoring systems. We applied the scoring system according to Brody et al. [2004]: it allows systematical assessment of presence, distribution, and extent of the following CF-specific alterations for each lobe of the lung, central and peripheral, regarding the lingula as the left middle lobe equivalent: bronchiectasis, mucous plugging, peribronchial thickening, parenchymal opacity, and hyperinflation.
Subscores and total score ("Brody score") are expressed numerically, ranging from 0 to 207 (possible maximum), at increments of 0.25. The Brody score increases with increasing CF-related lung structure pathology (Table 1).

In contrast to Brody et al. [1], both parenchymal opacity and hyperinflation were assessed in inspiration, only.

**Spirometry and Lung Function Tests**

Spirometry was performed according to standardized European guidelines. At least one full LFT test cycle was completed per patient. Results were electronically calculated, documented, and stored by the spirometry system. Predicted values for the different LFTs referred to the respective standard tables of the European Coal and Steel Community (ECSC) [3].

**Correlation of MDCT and Spirometry Findings**

Linear Pearson correlation coefficients were calculated for 1-second-forced-expiratory-volume (FEV1), forced vital capacity (FVC), FEV1/FVC ratio (Tiffeneau index), peak expiratory flow (PEF), respective mean-expiratory-flow (MEF) at 50% (MEF50) and 25% (MEF25) of FVC, as dependent variables of the morphologic Brody score and its respective subscores. Linear Pearson correlation coefficients were also calculated for the respective ratios of all measured and predicted (%predicted) LFT values.
Table 1: Brody scoring system for formal evaluation of lung morphology in patients with cystic fibrosis (CF).

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Results

One patient was subsequently excluded from the analysis due to incomparability after partial lung resection. Respective median values and ranges for the Brody score (Table 1 on page 8) and for different LFTs are presented in Table 2 on page 8.

MDCT findings representing the range of different Brody scores and associated LFT results in this study are illustrated in Figures 1 to 3 (Fig. 1 on page 9, Table 3 on page 10), (Fig. 2 on page 11, Table 4 on page 11), (Fig. 3 on page 12, Table 5 on page 12).

Figure 4 graphically demonstrates the correlation between the Brody score and the Tiffeneau index %predicted ratio. Corresponding results of Brody scoring and spirometry are highlighted for the three exemplary patients. Trendlines within the graphic (Fig. 4 on page 13) that represent linear (red) and exponential (blue) fitting results appear to be close to each other, such that approximation of the relation between CF-specific lung morphology, as expressed by the Brody score, and lung function, as expressed by the Tiffeneau index %predicted ratio, by a linear fitting algorithm appeared to be warranted.

Thus, the degree of linear correlation between CF-specific lung morphology and lung function was expressed by means of the Pearson correlation coefficient (Table 6 on page 13, Table 7 on page 14).
**Table 1:** Brody scoring system for formal evaluation of lung morphology in patients with cystic fibrosis (CF).

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<table>
<thead>
<tr>
<th>Parameter</th>
<th>Meaning of Parameter</th>
<th>Median (Range)</th>
<th>Median (Range) Proportion of Predicted Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brody Score</td>
<td>patho-morphology at chest CT</td>
<td>86.00 points (19.00-176.00)</td>
<td>n/a</td>
</tr>
<tr>
<td>FEV1</td>
<td>forced expiratory volume in 1 s</td>
<td>1.97 I (0.93-4.58 I)</td>
<td>55.0% (27.7-99.4%)</td>
</tr>
<tr>
<td>FVC</td>
<td>forced vital capacity</td>
<td>3.50 I (1.81-6.01 I),</td>
<td>83.9% (37.9-118.2%)</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>Ratio of FEV1 and FVC</td>
<td>60.89% (37.35-87.23%)</td>
<td>73.1% (46.7-103.4%)</td>
</tr>
<tr>
<td>PEF</td>
<td>peak expiratory flow</td>
<td>5.33 l/s (2.74-12.28 l/s)</td>
<td>69.1% (36.2-116%)</td>
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<tr>
<td>MEF50</td>
<td>mean expiratory flow at 50% of FVC</td>
<td>1.09 l/s (0.30-4.71 l/s)</td>
<td>24.7% (7.2-83.9%)</td>
</tr>
<tr>
<td>MEF25</td>
<td>mean expiratory flow at 25% of FVC</td>
<td>0.26 l/s (0.11-1.96 l/s)</td>
<td>14.2% (4.0-82.9%)</td>
</tr>
</tbody>
</table>

*values predicted for respective gender, age, body height, and body weight, according to ECSC

**Table 2:** Respective results of MDCT lung morphology scoring and different spirometric lung function tests in 35 adult patients with cystic fibrosis

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**Fig. 1:** MDCT images of a 35-year-old male CF patient. Brody score was 42.00 points. Orange arrow marks peripheral mucous plugging.

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<table>
<thead>
<tr>
<th></th>
<th>predicted</th>
<th>measured</th>
<th>%predicted ratio (%)</th>
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</thead>
<tbody>
<tr>
<td>VC MAX [l]</td>
<td>5.53</td>
<td>6.01</td>
<td>108.6</td>
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<tr>
<td>FEV 1 [l]</td>
<td>4.36</td>
<td>4.34</td>
<td>99.4</td>
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<tr>
<td>FEV 1 % VC MAX [%]</td>
<td>80.91</td>
<td>72.17</td>
<td>89.2</td>
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<tr>
<td>PEF [l/s]</td>
<td>9.88</td>
<td>9.46</td>
<td>95.8</td>
</tr>
<tr>
<td>MMEF 75/25 [l/s]</td>
<td>4.75</td>
<td>3.08</td>
<td>65.0</td>
</tr>
<tr>
<td>MEF 50 [l/s]</td>
<td>5.50</td>
<td>3.96</td>
<td>72.1</td>
</tr>
<tr>
<td>MEF 25 [l/s]</td>
<td>2.53</td>
<td>1.15</td>
<td>45.4</td>
</tr>
</tbody>
</table>

**Table 3:** Lung function tests for CF patient presented in Figure 1
Fig. 2: MDCT images of a 37-year-old female CF patient. Brody score was 86.00 points. Yellow arrows mark bronchiectasis.

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Table 4: Lung function tests for CF patient presented in Figure 2

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Fig. 3: MDCT images of a 28-year-old female CF patient. Brody score was 134.50 points. Arrows mark bronchiectasis (Yellow), peribronchial thickening (green), mucous plugging (orange), ground glass opacity (red), and air space consolidation (blue).

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Table 5: Lung function tests for CF patient presented in Figure 3

<table>
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<tr>
<th></th>
<th>predicted</th>
<th>measured</th>
<th>%predicted ratio (%)</th>
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<tbody>
<tr>
<td>VC MAX [l]</td>
<td>3,61</td>
<td>2,88</td>
<td>79,6</td>
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<tr>
<td>FEV 1 [l]</td>
<td>3,16</td>
<td>1,33</td>
<td>42,1</td>
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<tr>
<td>FEV 1 % VC MAX [%]</td>
<td>83,97</td>
<td>46,28</td>
<td>55,1</td>
</tr>
<tr>
<td>PEF [l/s]</td>
<td>7,05</td>
<td>3,25</td>
<td>46,1</td>
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<tr>
<td>MMEF 75/25 [l/s]</td>
<td>4,04</td>
<td>0,45</td>
<td>11,1</td>
</tr>
<tr>
<td>MEF 50 [l/s]</td>
<td>4,48</td>
<td>0,52</td>
<td>11,7</td>
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<tr>
<td>MEF 25 [l/s]</td>
<td>2,15</td>
<td>0,19</td>
<td>8,8</td>
</tr>
</tbody>
</table>

Fig. 4: Trendlines within the graphic that represent linear (red) and exponential (blue) fitting results appear to be close to each other, such that approximation of the relation between CF-specific lung morphology, as expressed by the Brody score, and lung function, as expressed by the Tiffeneau index %predicted ratio, by a linear fitting algorithm appears to be warranted. Patients presented in Fig. 1 (green), Fig. 2 (yellow), and Fig. 3 (red) are highlighted.
Table 6: Degree of linear correlation between overall CF-specific lung morphology and lung function as expressed by the Pearson correlation coefficient in 35 adult patients with cystic fibrosis (highest correlations, only)

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Table 7: Degree of linear correlation between CF-specific lung morphology details and lung function as expressed by the Pearson correlation coefficient in 35 adult patients with cystic fibrosis (highest correlations, only)

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Conclusion

Retrospective analysis in a small, selected group of adult CF patients demonstrated moderate to modest negative linear correlation between CF-specific pathologic alterations of lung structure, as expressed by the Brody score and its different subscores, and quantitative results of different LFTs. Correlations in the adult CF patients appear to be even higher than reported by Brody and co-workers [1] for their selected group of pediatric CF. Although correlations found were far from perfect, our findings demonstrate that the Brody scoring system can be applied in adult CF patients, too.

Due to the small, selected group of adult CF patients included in this retrospective analysis, with its risk of being non-representative, and the numerous methodical deviations to the original study of Brody et al. [1] - low-dose volumetric MDCT in inspiration, potential differences in both lung morphology and lung function between children and adult CF patients - it appears difficult for the time being to attribute the differences in linear correlation to any particular of the multiple factors of potential influence.

In our analysis, correlation between the Brody score, as the weighted summary of its subscores, and individual LFTs was higher than correlation between individual subscores within the scoring system, as described by Brody and co-workers [1], and individual LFTs. This finding may reflect that, although not having been subjected to multivariate analysis in adults, the weighting applied by Brody and co-workers [1] to reflect lung morphology alterations in pediatric CF patients has at least some bearing in adult CF patients, too.

In our limited experience, peribronchial thickening, as an individual morphologic feature of CF, demonstrated the highest correlations among the different subscores of the Brody score with different LFTs. It may be argued, based on simple mechanical assumptions, that increasing peribronchial thickening decreases bronchial wall elasticity, which, in turn, would increase resistance to airflow and thus cause obstruction. However, scientific evidence to prove these assumptions is currently lacking.

Thus, further studies will have to establish the reasons that link up alterations in lung morphology and lung function in adult patients affected by CF beyond the observational and statistical level.
References


Personal Information

Parts of the work presented herein are based on results of doctoral thesis work in preparation by Marco Schmitz at the Medical Faculty, Ludwig-Maximilian-University of Munich, Germany.