PROGRESSION OF LUNG DISEASE ON COMPUTED TOMOGRAPHY AND PULMONARY FUNCTION TESTS IN CHILDREN AND ADULTS WITH CYSTIC FIBROSIS

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Key words: Cystic Fibrosis, Tomography X-Ray Computed, Pulmonary Function Tests, Bronchiectasis, Lung structure.

Running title: CT worsens faster than lung function in children and adults with CF

What this paper adds: Peripheral bronchiectasis CT-score in adults and composite CT-score in children with CF worsened faster than PFTs. A marked discrepancy between changes in CT-score and PFTs was seen, with CT-scores worsening more frequently than PFTs in children and adults. Peripheral bronchiectasis CT-scoring may be helpful in the clinical monitoring of CF-patients.

ABSTRACT

Background: In a single centre study structural lung abnormalities on computed tomography (CT) scans worsened in children with cystic fibrosis (CF) who had on average stable pulmonary function tests (PFTs). The aims of this study were to compare the ability of CT-scores and PFTs to detect changes in CF lung disease in children and adults.

Methods: CT scans and PFTs were retrospectively studied in a cohort of CF-patients aged 5 to 52 years for whom 2 or 3 CT scans at 3-year intervals were available in combination with PFTs (FEV1, FVC, FEV1/FVC, MEF25, MEF50, RV, TLC and RV/TLC). All CT scans were scored by two observers. PFTs were expressed as percentage predicted and Z-score.

Results: Of 119 patients included, 92 patients had two and 24 had three CT scans. CT (composite and components) scores and PFTs both worsened significantly (p<0.02). Peripheral bronchiectasis worsened by 1.7% per year in children (p<0.0001) and by 1.5% per year in adults (p<0.0001). Bronchiectasis worsened in 68 of 92 patients relative to 54 of 92 for FEV1 and it worsened in 27 patients with stable or improving FEV1. CT-score and its components and PFTs showed similar worsening rates for adults and children (p>0.09).

Conclusion: Peripheral bronchiectasis CT-score worsens faster and more frequently than PFTs in children and adults with CF, which demonstrates that PFTs and CT measure different aspects of CF lung disease. Our data support previous findings that peripheral bronchiectasis CT-score has an added value to PFTs in monitoring CF lung disease.
INTRODUCTION

Patients with cystic fibrosis (CF) show progressive worsening in lung structure and function due to chronic infection and inflammation (1-3). Pulmonary function tests (PFTs) are considered the gold standard for monitoring changes in CF lung disease (2). It was found, however, that functional changes can be preceded by structural changes detected on computed tomography (CT) scans (4-8). CT scoring systems can quantify structural abnormalities in CF in a reproducible fashion (5, 9-13). A recent study in children from a single CF centre demonstrated that structural lung abnormalities as evaluated with composite CT-scores worsened while PFTs remained stable or improved over a two-year interval. In addition, the component CT-scores for only bronchiectasis and mucous plugging worsened significantly and irreversibly (6).

The aims of this study were to compare the ability of CT-scores and PFTs to detect changes in CF lung disease in a different cohort of children and in adults. We hypothesized firstly that on average CT-scores and PFTs would show worsening in adults with equal rate of worsening, and secondly that in concordance with previous findings in children CT-scores on average would show worsening whereas PFTs would remain stable.

METHODS

Study population

Since 1997, the West Swedish CF centre (Gothenburg, Sweden) has added CT scans to PFTs in the annual check up for patients aged 5 years and older. The first CT scan was done when a patient obtained reliable PFT results, and CT scans were repeated every third year after. Annual check up was postponed if exacerbation was evidenced by change in antibiotics regimen necessitated by acute worsening of CF lung disease. Therefore, CT scans and PFTs were performed only when patients were clinically stable. We included all routine CT scans up to April 2004. Patients were diagnosed as having CF when they had a positive sweat test and/or 2 known CF mutations. The cohort was divided in subjects ≤18 years at first scan (children) and >18 years (adults). Pancreatic status and prevalence of chronic Pseudomonas aeruginosa infection were assessed at first CT. Chronic Pseudomonas infection was defined as sputum or nasopharyngeal cultures positive for Pseudomonas at 2 or more occasions in 6 months. In all subjects cultures had been obtained monthly. The ethical review board of the West Swedish CF centre approved this retrospective study.

Lung structure

Lung structure was evaluated using CT scans. For children a single detector CT scanner (Philips LX, Philips Medical Systems, Best, Netherlands) was used from 1997 to 1999, and a multi-detector row (4 or 8 rows of detectors) CT scanner after 1999 (General Electric light speed ultra, GE Medical Systems, Milwaukee, WI). Scans were obtained using a beam current of 120 mA, an exposure time of 0.5 sec and a beam potential of 120 kV from lung apex to base at 15 mm intervals using 1.25 mm thick slices. For adults a PQ 6000 scanner (Picker International Inc., Highland Heights, OH) was used throughout the study period. Scans were obtained using a beam current of 160 mA, a 1 sec exposure time (160 mAs) and a beam potential of 120 kV from lung apex to lung base at 10 mm intervals using 1.5 mm thick slices.

All scans were reconstructed with a high-spatial frequency algorithm (bone), printed (window width 1400 Hounsfield Unit, window level –400 Hounsfield Unit), blinded to date and patient identification and scored in random order by two independent experienced observers using an adapted scoring system recently developed by Brody et al (13). This scoring system evaluates the 5 lung lobes and the lingula as a sixth lobe for severity and extent of central and peripheral bronchiectasis, extent of central and peripheral mucous plugging, severity and extent of central and peripheral airway wall thickening, extent of
opacities (atelectasis or consolidations) and extent of cysts and bullae. Hyperinflation (gas trapping) was excluded from scoring since not all scans had expiratory images and mosaic perfusion was scored instead. Ground glass pattern was not scored in this study. The maximum composite CT-score without air trapping and ground glass pattern and with mosaic perfusion was 180 (13). In addition, component CT-scores were calculated by adding the component scores from the 6 lobes. Maximal component scores for central bronchiectasis, peripheral bronchiectasis, central mucus, peripheral mucus, central airway wall thickening, peripheral airway wall thickening, opacities, mosaic perfusion and cysts or bullae were 18. For statistical analysis the average composite CT-score and component CT-scores of both observers were expressed on a 0-100 scale (percentage of maximum possible score).

Lung function

Conventional PFTs were done using a dry rolling seal spirometer (MasterLab, Jaeger, Würzburg, Germany). Forced vital capacity (FVC), forced expiratory volume in the first sec (FEV₁), mid expiratory flow at 25% and 50% of VC (MEF₂₅ and MEF₅₀), residual volume (RV) and total lung capacity (TLC) were expressed as percentage of predicted values and as Z-scores. The ratio between FEV₁ and FVC and between RV and TLC was calculated and expressed as a percentage, as percent predicted and as a Z-score. For children, prediction equations developed by Quanjer and colleagues (14) were used for FEV₁ and FVC and prediction equations developed by Zapletal and colleagues (15) were used for MEF₂₅, MEF₅₀, RV and TLC. For adults prediction equations from the European Respiratory Society (16) were used for all parameters. Spirometry (FEV₁, FVC, MEF₂₅ and MEF₅₀) was done in all patients at each annual check-up. Plethysmography (RV and TLC) was done in 106 out of 119 (89%), 81 out of 92 (88%) and 21 out of 24 (88%) of the patients at the first, second and third check-up, respectively.

Statistical analysis

Interobserver agreement of composite and component CT-scores was calculated using intraclass correlation coefficients. An intraclass correlation coefficient >0.8 represents good agreement. Systematic errors in component scores were detected using Bland and Altman plots that express the difference between two observers as a function of their mean (17). Descriptive statistics for children and adults were calculated for the time of the baseline CT scan. Annual changes in composite CT-score, component CT-scores and PFTs over time were evaluated separately for children and adults using repeated measurements analysis of variance (RMANOVA). This analysis includes all measurements in the patients with one, two or three evaluations. Because distributions of MEF₂₅ (Z-score) and MEF₅₀ (Z-score) were not normal, we used percent predicted values transformed to a 10logaritmic scale for analysis of MEF₂₅ and MEF₅₀. For all other PFTs we found it more adequate to use Z-scores as these account for variability of test scores. A positive slope (annual change value) for CT score, RV, TLC and RV/TLC and a negative value for other PFTs indicates worsening of disease. In addition we calculated numbers of patients who remained stable, improved or who worsened for both CT and PFTs measurements. We also recorded discrepancies between changes in composite CT-score, peripheral bronchiectasis CT-score and FEV₁. Data are expressed as mean [SD] or as mean [SE], and p<0.05 was considered significant.

RESULTS

Study population

We included scans of 119 CF-patients, 72 children and 47 adults at the time of first scan. Two scans were available for 92 patients (53 children), 24 patients of whom had a third CT scan. Baseline characteristics are given in Table 1.
Table 1: Patient characteristics at baseline

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>11 [4]</td>
<td>28 [8]</td>
</tr>
<tr>
<td>Sex (male / female)</td>
<td>37/35</td>
<td>24/23</td>
</tr>
<tr>
<td>Pancreatic status (sufficient / insufficient)</td>
<td>11/61</td>
<td>14/33</td>
</tr>
<tr>
<td>Chronic Pseudomonas infection (yes / no)</td>
<td>14/58</td>
<td>18/29</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>97 [18]</td>
<td>94 [19]</td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>97 [21]</td>
<td>78 [24]</td>
</tr>
<tr>
<td>RV (% predicted)</td>
<td>98 [42]</td>
<td>126 [47]</td>
</tr>
<tr>
<td>TLC (% predicted)</td>
<td>95 [18]</td>
<td>102 [12]</td>
</tr>
<tr>
<td>MEF₅₀ (% predicted)</td>
<td>96 [34]</td>
<td>51 [30]</td>
</tr>
<tr>
<td>MEF₂₅ (% predicted)</td>
<td>84 [46]</td>
<td>41 [33]</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>88 [9]</td>
<td>70 [13]</td>
</tr>
<tr>
<td>RV/TLC (%)</td>
<td>98 [10]</td>
<td>84 [16]</td>
</tr>
<tr>
<td>Composite CT-score (points, %)</td>
<td>104 [43]</td>
<td>120 [42]</td>
</tr>
</tbody>
</table>

Data are given as mean [SD] (standard deviation)

Reproducibility of the scoring system

Intraclass correlation coefficients (r-value) between both observers for CT score were: composite 0.92; bronchiectasis 0.88; opacities 0.80; mucous plugging 0.72; airway wall thickening 0.67; bulla and cysts 0.53 and mosaic perfusion 0.27. Bland and Altman plots evidenced no systematic errors in scoring between both observers for mean bronchiectasis and bulla or cysts. While for mosaic perfusion and mucous plugging observer 1 (PdJ) scored on average systematically higher than did observer 2 (LR), for airway wall thickening observer 2 scored on average higher than did observer 1. The higher scores rated by observer 1 for mucous plugging and mosaic perfusion were more pronounced at the lower scores, but the higher score rated by observer 2 for airway wall thickening was independent of the scale. For the other component CT-scores and the composite CT-score there were no systematic differences between both observers although observer variability expressed as a percentage of the mean was larger at the lower end of the scale.

Rate of worsening of CT and PFTs for children versus adults

Table 2 shows the slopes of the RMANOVA regression equations of CT and PFTs with age, representing annual changes in CT and PFTs. Interestingly, FEV₁ worsened by 0.07 Z-score in the children (p=0.03) and FEV₁/FVC worsened by almost 0.1 Z-score per year in both children (p=0.002) and adults (p=0.02). Also MEF₂₅ and MEF₅₀ worsened in children (p=0.005 and 0.006, respectively) and adults (p=0.007 and 0.005, respectively) and RV worsened in adults (p=0.01). All other PFTs remained unchanged (p>0.07). Composite CT-scores and all components CT-scores, except mosaic perfusion score in children and adults and peripheral mucous plugging score in adults, worsened significantly over time in children (p<0.004) and adults (p<0.03). The strongest worsening rate was observed for peripheral bronchiectasis score in children (1.7% per year, p<0.0001) and for composite CT-score in adults (1.5% per year, p=0.0003). Slopes for none of the parameters differed significantly between children and adults (p>0.09), but composite CT score and RV tended to worsen faster in adults relative to children.
Table 2: Annual changes in pulmonary function test results and composite and component CT-scores in children and adults

<table>
<thead>
<tr>
<th>Function</th>
<th>Children</th>
<th>Adults</th>
<th>Difference between adults and children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change [SE]</td>
<td>p-value</td>
<td>Change [SE]</td>
</tr>
<tr>
<td>FVC (Z-score)</td>
<td>-0.0006 [0.031]</td>
<td>0.98</td>
<td>0.0051 [0.032]</td>
</tr>
<tr>
<td>FEV1 (Z-score)</td>
<td>-0.0734 [0.029]</td>
<td>0.03</td>
<td>-0.0397 [0.031]</td>
</tr>
<tr>
<td>RV (Z-score)</td>
<td>0.0105 [0.035]</td>
<td>0.77</td>
<td>0.1025 [0.037]</td>
</tr>
<tr>
<td>TLC (Z-score)</td>
<td>-0.0028 [0.020]</td>
<td>0.89</td>
<td>0.0294 [0.021]</td>
</tr>
<tr>
<td>MEF50 (%pred)</td>
<td>-0.0119 [0.0039]</td>
<td>0.005</td>
<td>-0.0159 [0.0053]</td>
</tr>
<tr>
<td>MEF25 (%pred)</td>
<td>-0.0133 [0.0045]</td>
<td>0.007</td>
<td>-0.0155 [0.0051]</td>
</tr>
<tr>
<td>FEV1/FVC (Z-score)</td>
<td>-0.0944 [0.026]</td>
<td>0.002</td>
<td>-0.0748 [0.030]</td>
</tr>
<tr>
<td>RV/TLC (Z-score)</td>
<td>0.0231 [0.046]</td>
<td>0.62</td>
<td>0.0763 [0.041]</td>
</tr>
<tr>
<td>Composite CT-score</td>
<td>1.007 [0.21]</td>
<td>&lt;0.0001</td>
<td>1.547 [0.24]</td>
</tr>
<tr>
<td>Central bronchiectasis</td>
<td>1.253 [0.052]</td>
<td>0.0002</td>
<td>0.978 [0.078]</td>
</tr>
<tr>
<td>Peripheral bronchiectasis</td>
<td>1.721 [0.049]</td>
<td>&lt;0.0001</td>
<td>1.521 [0.065]</td>
</tr>
<tr>
<td>Peripheral mucous plugging</td>
<td>0.652 [0.036]</td>
<td>0.004</td>
<td>0.391 [0.038]</td>
</tr>
<tr>
<td>Central airway wall thickening (AWT)</td>
<td>1.389 [0.060]</td>
<td>0.0003</td>
<td>1.076 [0.067]</td>
</tr>
<tr>
<td>Peripheral AWT</td>
<td>0.931 [0.048]</td>
<td>0.002</td>
<td>0.807 [0.053]</td>
</tr>
<tr>
<td>Opacities</td>
<td>0.733 [0.039]</td>
<td>0.002</td>
<td>0.737 [0.043]</td>
</tr>
<tr>
<td>Mosaic glass pattern</td>
<td>-0.354 [0.090]</td>
<td>0.58</td>
<td>0.264 [0.085]</td>
</tr>
</tbody>
</table>

Legend Table 2: Data were obtained using repeated measurement analysis of variance (RMANOVA). Lung structure or function = slope times age plus intercept. MEF50 and MEF25 (% predicted) were ^10log transformed. Being rare, central mucous plugging and bulla or cysts were excluded from analysis. Composite score adapted from Brody et al (13).

Discrepancies between changes in CT and PFTs

Figure 1 shows the marked discrepancies between changes in structure (composite CT-score and peripheral bronchiectasis CT-score) and changes in function (FEV1). FEV1 worsened in 31 of the 53 children (58%), and composite CT-score and peripheral bronchiectasis CT-score in 35 of 53 (66%). The findings of CT and PFTs were discordant in 29 of the 53 children (55%). In adults, FEV1 worsened in 24 of 39 (62%), composite CT-score in 34 (87%) and peripheral bronchiectasis CT-score in 33 (85%). The findings of CT and PFTs were discordant in 12 of the 39 adults (31%). Figure 2 presents the changes over the three evaluations for composite CT-score, peripheral bronchiectasis CT-score and FEV1 in the 24 patients who had 3 scans. Figure 3 gives an example of progression of structural abnormalities over 4 years despite stable lung function. From Figures 2 and 3 it is evident that in many patients (27 of 92) composite CT-score worsened while FEV1 remained stable.

DISCUSSION

The major findings of this retrospective clinical study are that both in adults and children with CF, routine CT scans detect worsening in more patients than do PFTs and at a
Firstly we hypothesized that in adults on average both CT-scores and PFTs would show worsening. However, in disagreement with our hypothesis we found that while peripheral bronchiectasis CT-score (1.52% per year) and composite CT-score (1.55% per year) worsened, most PFTs parameters including FEV₁ remained on average unchanged. In addition we showed that in one third of the adults there was discordance between the CT en PFTs changes.

Our second hypothesis was that, in concordance with previous findings, CT in children on average would show worsening whereas PFTs would remain stable (6). In contrast to previous findings, however, we found that FEV₁ worsening (0.07 Z-score is approximately 1% predicted) equalled that of the component CT score The peripheral bronchiectasis CT-score nevertheless decreased 70% faster than did both the FEV₁ and the composite CT-score. In addition, the proportion of children showing decline in the peripheral bronchiectasis CT-score was larger than that showing decline in FEV₁. In more than half of the children the change in CT was discordant with the change in PFTs. The peripheral bronchiectasis CT-score worsening rate in was also larger than that of the composite CT-score.

The fact that peripheral bronchiectasis CT-score declined faster than PFTs warrants further discussion. For several reasons we feel bronchiectasis CT-score is an attractive outcome parameter, both clinically and in trials and we believe this is the abnormality that is most characteristic of CF lung disease. For the evaluation of bronchiectasis CT is considered to be the gold standard (18-21) and PFTs are considered insensitive to diagnose bronchiectasis. Bronchiectasis can be evaluated relatively easily on CT, witness the good interobserver agreement in this and other studies (5, 13) and while bronchiectasis is argued to be reversible in other diseases (22, 23), it is an irreversible feature in CF (6). Finally, we believe that airway wall thickening (related to airway inflammation), mucous plugging and consolidations all are risk factors for the development of bronchiectasis and bronchiectasis is therefore a highly relevant ‘end stage’ feature of CF lung disease. At this moment we lack a sensitive true endpoint to monitor CF lung disease. Mortality and quality of life are considered true endpoints but they are insensitive. The relationship between bronchiectasis, CT-score and mortality remains to be investigated in CF. From studies in non-CF bronchiectasis patients we do know that severity of bronchiectasis is closely correlated with quality of life (24). It is likely that the same is true for CF though other factors like pancreatic insufficiency, diabetes might obscure this correlation.

For several reasons PFTs worsened less than bronchiectasis on CT. First, PFTs have a high noise to signal ratio and Z scores or percent-predicted values are calculated using reference equations based on a large population. Second, CT can clearly demonstrate focal areas of bronchiectasis that can be scored reproducibly, whereas PFT values can fluctuate for reasons other than structural airway damage, such as viral infections and patient effort. That PFTs and CT measure different aspects of CF lung disease is also reflected by our observation that composite CT-scores worsened in a substantial number of patients with stable or improving PFTs. In addition, PFTs worsened in several patients with stable composite CT-score. This discrepancy between lung function and CT findings supports the view that both are needed to adequately determine the state of CF related lung disease and that CT provides detailed structural information that can not be obtained by PFTs or chest X radiographs. We feel strongly that this structural information helps us to tailor treatment and to reduce under or over treatment. However, to date there is no scientific proof that the use of CT improves disease outcome.

There are two possible explanations why the peripheral bronchiectasis CT scores worsened faster than the composite CT scores in the children but not in the adults. First,
reversible abnormalities, such as mucous plugging (25, 26), airway wall thickening and mosaic perfusion, might have been more reversible in the children. This would lead to less change over time in the partly reversible composite CT score in relation to the irreversible bronchiectasis CT score. Second, changes in airway wall thickening and mosaic perfusion were more subtle in the children and therefore more difficult to score. Less reproducible scoring of these abnormalities could have introduced more noise and subsequently have reduced the ability to detect disease progress in the children’s composite CT-scores.

The most likely explanation for discrepancies in PFT findings between this cohort and the previously published cohort is duration of follow-up. The latter was followed for 2 years only, the former for up to 6 years. Furthermore there might be differences between CF centres and between patient populations.

We can only speculate why composite CT-scores in the children in this study worsened similarly to PFTs. As the children in the previous study had on average more advanced disease (lower PFTs at baseline), the CT abnormalities might have been less reversible and could therefore have been scored more reproducibly as discussed previously. On the other hand, while in the present study CT images were acquired at 15 mm intervals, the previous study obtained them at 10 mm intervals. As CF airway disease starts heterogeneously, the greater interval between images is likely to have resulted in less sensitive composite CT-scores in this study.

The PFTs findings in this study warrant further consideration. First, we found a significant worsening in MEF25 and MEF50, which may be consistent with early lung disease (7). Unfortunately, MEF25 and MEF50 have a relative large standard deviation, and changes in Z-scores that we could not use in this study may not have been significant. Second, the FEV1/FVC-ratio changed significantly. Although this parameter is usually not included in the analysis of large clinical trials in CF (27-30), our findings suggest that it may be a relatively sensitive PFT measurement in CF.

Expectedly, the adults in this study were a selected group of long term survivors and few had severe lung disease (27 of 39 adults had a FEV1 greater or equal to 75% predicted). Accordingly, the proportion of pancreatic sufficient patients in adults was higher than that in children. Our findings might therefore not be valid for patients with end stage lung disease.

The potential negative effect of radiation exposure of repeated CT scanning remains a point of discussion and concern (31, 32). When using repetitive CT scanning it is important to keep the cumulative lifelong radiation exposure as low as possible. For this reason CT scans were performed once every three years rather than annually. We recently completed a computational modelling study to estimate the cancer mortality risk of lifelong biennial CT scanning in CF-patients (33). Based on this model this risk of our current CT protocol is estimated to be well within acceptable limits. Technical improvements are likely to further reduce radiation doses.

Our study is limited in that we did not evaluate air or gas trapping on CT scans, which is an early marker of CF lung disease (13, 34-36). Nevertheless, the sensitivity of this CT abnormality to track disease progression in CF is at present unknown, and requires further study. In addition, we did not include potentially more sensitive PFTs such as multiple breath washout tests (37). The comparison between changes in such tests and CT parameters requires further study. The rate of progression of bronchiectasis could have been influenced by allergic bronchopulmonary aspergillosis (ABPA). However, only 1 patient was classified as ABPA at the centre, treated in 1995. After a short course of oral steroids he has been doing well with stable lung function using only high dose inhaled steroids and on and off itraconazole. We are confident of not having missed any other ABPA because total IgE is included in the annual review since 1990 and all patients with high total IgE would be investigated for ABPA.
In conclusion, this study shows in adults and children with CF that routine CT scans worsened while PFTs remained unchanged or worsened less. The CT worsening was best reflected in peripheral bronchiectasis CT-score in children and in both composite CT-score and peripheral bronchiectasis CT-score in adults. Bronchiectasis can be scored reproducibly and is irreversible in CF. Our findings indicate that a composite CT-score may be less useful than a peripheral bronchiectasis CT-score since it consists of reversible and irreversible components, and not all components were scored reproducibly in this study. Therefore, by providing complimentary information to PFTs, peripheral bronchiectasis CT-score is important to monitor CF patients clinically and is expected to become an important outcome parameter in clinical studies in CF.

Figure 1: Change in FEV1 versus change in composite CT-score over 3 years in children and adults with CF
Changes in CT versus FEV1 are concordant in the left upper quadrant (both worsening in FEV1 and CT; 19 children; 23 adults) and in the right lower quadrant (both improvement in FEV1 and CT; 5 children; 4 adults). Changes in CT versus FEV1 are discordant in the left lower quadrant (worsening in FEV1 and improvement in CT; 12 children; 1 adult) and in the right upper quadrant (improvement in FEV1 and worsening in CT; 17 children; 11 adults).

Figure 2: Changes in FEV1 (a), composite-CT score (b) and peripheral bronchiectasis CT-score (c) over 6 years in 24 patients who had three evaluations
Legend Figure 1: Of the 24 patients most demonstrated a stable FEV1 over six years while the composite CT-score and the peripheral bronchiectasis CT-score (13) demonstrated the expected disease progression.

Figure 3: Worsening of irreversible structural abnormalities and improvement in lung function parameters over 4 years in a patient with cystic fibrosis
Legend Figure 2: Female CF patient, age at CT1=9.5 years (1999 I), at CT2 12.0 years (2001 II) and at CT3 13.9 years (2003 III). Composite CT scores (13) worsened from 21 to 37 to 40. FEV1 improved from 51 to 61 to 70 % predicted. FVC improved from 67 to 78 to 85 % predicted. FEV1/FVC improved from 75 to 78 to 82 %. FEF25-75 improved from 11 to 14 to 20 % predicted. Arrows in the upper three images (2aI-III) represent increase in severity of bronchiectasis and airway wall thickening in both upper lobes. Arrows in the middle three images (2bI-III) show decrease in central mucous plugging and increase in size of central bronchiectasis. Circled areas show decrease in central mucous plugging and an increase in the bronchiectatic size of the airway in the lower lobe. The circled areas in the lower three images (2cI-III) show increased number and size of peripheral bronchiectasis, although there was some motion artefact on the CT scan of 1999.

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CONFLICT OF INTEREST
PdJ, AL, LR, WH, JJ, MB and HT have no competing interest in the content of this manuscript to declare.
ETHICS
The ethical review board of Queens Silvia Children's Hospital, Gothenburg, Sweden approved this retrospective study.

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