Evaluation of pulmonary disease using static lung volumes in primary ciliary dyskinesia

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ABSTRACT

Background In primary ciliary dyskinesia (PCD) lung damage is usually evaluated by high-resolution CT (HRCT).

Objective To evaluate whether HRCT abnormalities and Pseudomonas aeruginosa infection were better predicted by spirometry or plethysmography.

Methods A cross-sectional study performed in consecutive patients with PCD who underwent sputum culture, spirometry, plethysmography and HRCT within 48 h. Principal component analysis and soft computing were used for data evaluation.

Results Fifty patients (26 children) were studied. P aeruginosa infection was found in 40% of the patients and bronchiectasis in 88%. There was a correlation between infection with P aeruginosa and extent of bronchiectasis (p = 0.009; r = 0.367) and air-trapping (p = 0.03; r = 0.315). Moreover, there was an association between infection with P aeruginosa and residual volume (RV) values >150% (p = 0.04) and RV/total lung capacity (TLC) ratio >140% (p = 0.001), but not between infection with P aeruginosa and forced expiratory volume in 1 s (FEV1) <80%, or forced expiratory flow between 75% and 70% (EF75–70%) or when expressed as z scores z <0.451, and RV/TLC (p = 0.002; r = 0.513) or when expressed as z scores (p = 0.002; r = 0.451 and p < 0.001, r = 0.536 respectively). Principal component analysis on plethysmographic but not on spirometry data allowed recognition of different severities of focal air trapping, atelectasis and extent of bronchiectasis.

Conclusions Plethysmography better predicts HRCT abnormalities than spirometry. Whether it might be a useful test to define populations of patients with PCD who should or should not have HRCT scans requires further longitudinal studies.

INTRODUCTION

In primary ciliary dyskinesia (PCD), abnormal motility of respiratory cilia and impaired mucociliary clearance result in recurrent infections of the airways, eventually causing permanent parenchymal damage, and progressive decline in lung function.

Chest high-resolution CT (HRCT) has become the method of choice to evaluate structural airway changes, and is used in a number of chronic respiratory diseases including PCD. However, there is no evidence that regular CT scans affect outcome in PCD and the potential lifetime cumulative radiation exposure should be considered.

PCD guidelines suggest that lung function should be evaluated at every visit in cooperative children since it has been shown that the severity of structural abnormalities may correlate with impairment in forced expiratory volume in 1 s (FEV1). However, a decreased FEV1 is not indicative of the site of airway obstruction and, as in cystic fibrosis, there are preliminary suggestions that PCD is characterised by marked peripheral airway dysfunction. Since small airways obstruction may lead to air trapping and to a consequent increase in residual volume (RV) and RV/TLC ratio, we hypothesised that raised functional residual capacity (FRC) made by plethysmography (FRCpleth), and RV and/or RV/TLC ratio, indirect calculated estimates of pulmonary hyperinflation and lung restriction respectively, may be more sensitive than spirometry to structural changes as shown by HRCT in PCD. The aim of the study was to determine the

Key messages

What is the key question?

Do lung volume measurements predict lung damage better than spirometry in patients with primary ciliary dyskinesia?

What is the bottom line?

Raised residual volume and residual volume/total lung capacity ratio are associated with Pseudomonas aeruginosa infection and with lung damage shown by high-resolution CT.

Why read on?

The evaluation of static volumes by plethysmography seems to be an underappreciated method for the follow-up of children with primary ciliary dyskinesia; early identification of deterioration in such parameters could result in a more adequate treatment of the disease and in research of eventual unhealthy attitudes of the patients.
correlations between HRCT abnormalities and dynamic or static lung function parameters in patients with PCD to assess their potential use as clinical monitoring tools in PCD.12

MATERIALS AND METHODS

Subjects

Between March 2008 and May 2010, we enrolled all consecutively newly diagnosed patients with PCD aged ≥6 years followed up in the Department of Paediatrics of the University of Pisa. PCD was diagnosed on standard criteria.1 We obtained sputum, cough swab or pharyngeal aspirate cultures, spirometry, body plethysmography and a HRCT of the chest. A sputum culture was collected, preferably by expectoration. Pharyngeal aspirate was obtained in uncooperative children after an overnight fast using a disposable catheter connected to a mucus extractor inserted into the mouth to a depth of 7–10 cm and drawn back while applying gentle suction.

Informed consent was obtained from adult patients or from the parents of children. The study protocol was approved by the local Hospital Ethical Committee.

Ciliary motion analysis and ultrastructural studies

Samples were obtained from the inferior turbinate using a cytology brush (Microvasive, Milford, Massachusetts, USA) for immediate light microscopy, transmission electron microscopy and cell cultures.13 Ciliary morphology, motion pattern, beat frequency, ultrastructural studies and ciliary activity after ciliogenesis in culture were evaluated.14–16 Ciliary motion analysis, ultrastructural assessment and cultures were performed by different operators each one blind to the results obtained by the others.

Lung function

All lung function testing (Master Screen Body equipment; Jaeger, Wuerzburg, Germany) was performed by experienced doctors (MP, MDC) utilising standard American Thoracic Society methodology,17 18 FEV1, forced vital capacity (FVC), forced expiratory flow between 25% and 75% of FVC (FEF25–75%), FRCPleth, RV, TLC, RV/TLC and parameters of airway mechanics including airway resistance (Raw), specific airway resistance (sRaw) and effective specific resistance (sReff) were expressed as percentage of predicted and z scores values.19 For plethysmography in each patient we obtained at least three reproducible manoeuvres. To be accepted, single inspiratory manoeuvres needed to have yielded virtually superimposed X–Y plots, and values of FRCPleth had to be within 5% of each other.20

Lung function studies were all performed on the same day, within 2 days of the HRCT.

CT scanning of chest

In all patients chest HRCT was performed using the same scanner (Multislice CT; General Electric Medical Systems, Milwaukee, Michigan, USA). Slices (1 mm thick) were obtained with 10 mm spacing (100–120 kV, 80–150 mA), in the supine position. All images were evaluated by the same radiologist (DC) who was blinded to the clinical data and scored using a modified Bhalla system,21 which includes severity of bronchiectasis (score 0–3) and extent of bronchiectasis (score 0–3), mucous plugging (score 0–3), peribronchial thickening (score 0–3), parenchymal abnormalities, such as atelectasis (score 0–3) and focal air-trapping (score 0–3). Bronchiectasis was identified according to standard criteria.22 Thus, a severity class (from 1 to 3) for total lung impairment was obtained (class of severity 1 for total score of 0–6, class 2 for total score of 7–12, class 3 for total score of 13–18).

Soft computing analysis of data

Data were analysed with soft computing methodologies. Basic elements of soft computing and the application of intelligent control have been recently introduced.23 The soft computing-based modelling approach was applied to either flow-volume data or body plethysmography or both to develop a model predictive of chest HRCT scores. The model was identified by means of a self-organising artificial neural network (ANN). ANNs are mathematical models in which distributed adaptable parameters are modified through a learning process according to real data. Kohonen self-organising map (KSOM) predictive models were identified to classify chest HRCT scores, (total lung impairment, severity of bronchiectasis, extent of bronchiectasis, peribronchial thickening, mucous plugging, atelectasis, focal air-trapping), starting from flow-volume parameters (FEV1, FVC, FEV1/FVC, FEF25–75%), body plethysmography data (FRCPleth, RV, TLC, RV/TLC) and parameters of airway mechanics (Raw, sRaw, sReff). To check the generalisation capability of the neural network, a 10-fold cross-validation process was carried out. In this work, we fixed a 5×5 neurons KSOM with the parameters ω (T) = 0.8 and a training of 5000 epochs, which allowed us to obtain the best performance of the model. Further details on KSOM ANNs are reported in the supplementary material online.

Statistical analyses

The principal component analysis (PCA) methodology was applied to display data. PCA is a mathematical linear transformation aimed at reducing the dimensionality of (number of variables in) a dataset to a manageable level while retaining as much as possible of the variance present in the original dataset.24 Data from correlated groups of variables are used to calculate a smaller number of uncorrelated variables (principal components) to simplify further analyses. We used the eigenvalue decomposition24 to obtain the first three principal components in our dataset (denoted Y1, Y2 and Y3) which are associated with 99% of the variance.

There are no data in the published literature to inform a power calculation, so the sample size was opportunistic. Baseline variables were expressed as group mean ± SD or as median and IQR when the variables were non-normally distributed. Moreover, to allow comparison of observations from different normal distributions, all lung function data were expressed as SD (z) scores.25 Z-score transformation was carried out by using the equation $z = (x - μ)/σ$, where $x$ is the raw score or observation to be standardised, $μ$ is the mean of the reference population, and $σ$ is the SD of the reference population. Differences between means and distributions were evaluated by the two-tailed Student t test.

Correlations between continuous non-normally distributed variables were assessed using Spearman’s rank correlation coefficients. One-way analysis of variance (ANOVA) comparing the values of plethysmography indexes between the severity class for total lung impairment at HRCT was also applied. The χ² test was used to evaluate the association between Pseudomonas aeruginosa (alone or with other bacterial infection) and RV >150%, RV/TLC ratio >140% and FEV1 <80% or FEF25–75% <70% of predicted. The association between $P$ aeruginosa and FEV1/FVC <80% predicted for children and <70% predicted for adults was also evaluated. These cut-offs were selected because...
they were previously demonstrated to correlate with air-trapping on HRCT in children.26

A p value <0.05 was considered statistically significant. All statistical calculations were performed using SPSS V.18.0 for Windows (XP/Vista/7).

RESULTS

Fifty patients were studied. Twenty-six were children (19 boys and seven girls, age range 6–17 years, median 11 years; IQR 5.25) and 24 adults (nine men and 15 women, age range 18–47 years, median 30.5 years; IQR 9.5).

Infection with *P aeruginosa* (with or without other bacteria) was found in 20 (40.0%) patients, seven of whom were children (27% infected). Other organisms (*Serratia marcescens*, *Rhodococcus equi*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Enterobacter cloacae*, *Streptococcus pyogenes*, *Alcaligenes xylosoxidans*) were found in 12 (24.0%) subjects.

Results of spirometry and plethysmography expressed as per cent of predicted and as z scores are reported in table 1. HRCT Bhalla score was 0 in 3 subjects, 1 in 12, 2 in 27, and 3 in the remaining 8 subjects. Bronchiectasis was documented in 44 (88%) patients, 21 of whom were children. Bronchiectasis was present in multiple lobes in 36/44 (82%) subjects. The extent of mucous plugging, consolidation or atelectasis and air trapping) and lung function results are reported in tables 3 and 4.

![Figure 1](http://doi.org/10.1136/thoraxjnl-2011-200137)

**Figure 1** (A) Correlation between residual volume per cent predicted (% pred) and total lung impairment severity score at chest high-resolution CT (HRCT). (B) Correlation between residual volume z scores and total lung impairment severity score at chest HRCT.

Considering z scores, patient age was inversely correlated with FEV1 (p=0.058; r = −0.294), with FEV1/FVC (p=0.008; r = −0.572) and directly correlated with FVC (p=0.001; r = 0.451), with FRCpleth (p<0.001; r = 0.599), RV (p<0.001; r = 0.623), TLC (p<0.001; r = 0.646) and RV/TLC (p=0.054; r = 0.313). There was no correlation between patient age and Raw, sRaw or sReff z scores.

There was a significant correlation between infection with *P aeruginosa* and extent of bronchiectasis (p=0.009; r = 0.367) and air-trapping (p=0.03; r = 0.315). Moreover, there was a significant association between infection with *P aeruginosa* and RV values >150% (p=0.04) and RV/TLC ratio >140% (p=0.001), but not between infection with *P aeruginosa* and FEV1 <80%, or FEF25–75% <70% or FEV1/FVC <70% (<80% in children).

There were significant correlations between HRCT scores and lung function parameters. In particular, severity of the total lung impairment on chest HRCT was inversely correlated with FEV1 (p=0.02; r = −0.322), FVC (p=0.007; r = −0.376), but not with FEF25–75% or FEV1/FVC, and directly correlated with RV (p=0.003; r = 0.425) (figure 1A) and RV/TLC (p<0.001; r = 0.513) (figure 2A) per cent predicted, but not with TLC. This was confirmed with lung function z scores; severity of the total lung impairment on chest HRCT directly correlated with RV (p=0.002; r = 0.451) (figure 1B), RV/TLC (p<0.001; r = 0.536) (figure 2B) and FRCPleth (p=0.039; r = 0.505), but not with TLC. The correlations between the different HRCT parameters (severity and extent of bronchiectasis, peribronchial thickening, extent of mucus plugging, consolidation or atelectasis and air trapping) and lung function results are reported in tables 3 and 4. As can be seen there were some negative correlations between different HRCT parameters and some per cent predicted spirometry values (table 3) which disappeared when z scores were analysed (table 4). By contrast the positive correlations between severity and extent of bronchiectasis and air trapping with RV and RV/TLC were dependent on whether per cent predicted (table 3) or z scores (table 4) were used.

Moreover, plethysmography indices in patients with different HRCT class severity were found to be significantly different according to one-way ANOVA (p=0.026 for FRCPleth, p=0.007 for RV and p=0.001 for RV/TLC).

Table 1 Spirometry and plethysmography parameters expressed as per cent of predicted and z scores

<table>
<thead>
<tr>
<th>Functional parameters</th>
<th>% of predicted</th>
<th>z Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>FEV1</td>
<td>31.0–136.0</td>
<td>85.3 (24.6)</td>
</tr>
<tr>
<td>FVC</td>
<td>47.0–138.0</td>
<td>93.4 (18.5)</td>
</tr>
<tr>
<td>FEF25–75</td>
<td>10.0–151.0</td>
<td>63.2 (34.4)</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>42.0–98.8</td>
<td>75.4 (13.35)</td>
</tr>
<tr>
<td>Raw</td>
<td>55.4–310.6</td>
<td>164.5 (62.9)</td>
</tr>
<tr>
<td>sRaw</td>
<td>71.0–739.2</td>
<td>289.0 (142.0)</td>
</tr>
<tr>
<td>sReff</td>
<td>64.0–680.7</td>
<td>240.6 (128.1)</td>
</tr>
<tr>
<td>FRC</td>
<td>101.2–248.0</td>
<td>159.3 (31.2)</td>
</tr>
<tr>
<td>RV</td>
<td>83.0–397.0</td>
<td>196.5 (69.4)</td>
</tr>
<tr>
<td>TLC</td>
<td>65.0–174.0</td>
<td>119.2 (16.7)</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>91.0–305.0</td>
<td>161.0 (45.6)</td>
</tr>
</tbody>
</table>

FEV1, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; Raw, airway resistance; RV, residual volume; sRaw, specific airway resistance; sReff, effective specific resistance; TLC, total lung capacity.

Table 2 Bronchiectasis distribution (%) in multiple lobes

<table>
<thead>
<tr>
<th>Lobes</th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>Middle</td>
<td>45</td>
<td>11.4*</td>
</tr>
<tr>
<td>Lower</td>
<td>84</td>
<td>70</td>
</tr>
<tr>
<td>Lingula</td>
<td>6.8*</td>
<td>16</td>
</tr>
</tbody>
</table>

*In patients with situs inversus.
Table 3 Correlation between chest high-resolution CT and functional parameters expressed as per cent of predicted normal

<table>
<thead>
<tr>
<th>HRCT parameters</th>
<th>FEV₁</th>
<th>FVC</th>
<th>FEF25–75%</th>
<th>FEV₁/FVC</th>
<th>Raw</th>
<th>sRaw</th>
<th>sReff</th>
<th>FRCpleth</th>
<th>RV</th>
<th>TLC</th>
<th>RV/TLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity of bronchiectasis</td>
<td>p&lt;0.01</td>
<td>p&lt;0.005</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>p=0.02</td>
<td>NS</td>
<td>p=0.005</td>
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<tr>
<td>r=−0.350</td>
<td>r=−0.393</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Extent of bronchiectasis</td>
<td>p&lt;0.01</td>
<td>p=0.01</td>
<td>p=0.02</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>p=0.02</td>
<td>NS</td>
<td>p=0.001</td>
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<tr>
<td>r=−0.346</td>
<td>r=−0.316</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Peribronchial thickening</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>r=0.315</td>
<td>NS</td>
<td>r=0.459</td>
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<tr>
<td>Mucus plugging</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>p=0.035</td>
<td>p=0.044</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td></td>
</tr>
<tr>
<td>Extent of atelectasis</td>
<td>NS</td>
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<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td></td>
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<tr>
<td>Consolidation or atelectasis</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Air-trapping</td>
<td>p=0.01</td>
<td>p=0.01</td>
<td>p=0.04</td>
<td>NS</td>
<td>NS</td>
<td>p=0.027</td>
<td>p=0.023</td>
<td>p=0.002</td>
<td>p=0.008</td>
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<tr>
<td>r=−0.341</td>
<td>r=−0.362</td>
<td>r=−0.291</td>
<td>NS</td>
<td>NS</td>
<td>r=0.327</td>
<td>r=0.334</td>
<td>r=0.438</td>
<td>r=0.728</td>
<td>r=0.389</td>
<td>r=0.757</td>
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</tbody>
</table>

FEF25–75%, forced expiratory flow between 25% and 75% of forced vital capacity; FEV₁, forced expiratory volume in 1 s; FRCpleth, functional residual capacity by plethysmography; FVC, forced vital capacity; HRCT, high-resolution CT; NS, non-significant; Raw, airway resistance; RV, residual volume; sRaw, specific airway resistance; sReff, effective specific resistance; TLC, total lung capacity.

Only weak or no correlations were found between the different HRCT parameters and Raw, sRaw and sReff depending on whether per cent predicted values (table 3) or z-scores (table 4) were considered.

Moreover, there was a direct correlation between the age of patients and severity of total lung impairment on chest HRCT (p=0.002; r =0.425), and severity (p=0.004; r =0.404) and extent of bronchiectasis (p<0.001; r =0.510), but not with focal air-trapping scores or other parameters.

PCA performed using the body plethysmography data is depicted in figure 3, which shows three-dimensional scatter plots of the first four principal components evaluated processing the original body plethysmography variables (FRCpleth, RV, TLC and RV/TLC ratio), after the removal of an outlier. Each scatter plot shows the differences between scores 1 and 3 for focal air-trapping (figure 3A), atelectasis (figure 3B), extent of bronchiectasis (figure 3C) and total lung impairment (figure 3D). The PCA topological study allows focal air-trapping severity, atelectasis and the extent of bronchiectasis to be visually discriminated, although the clusters overlap. The analysis does not allow severity of bronchiectasis, peribronchial thickening and mucous plugging to be discriminated. The PCA topological study of flow−volume data and of airway mechanics parameters (Raw, sRaw and sReff) does not permit any discrimination of chest HRCT scores. The PCA topological study does not identify patients with Pseudomonas aeruginosa infection. Further results obtained by KSOM models are reported in the supplementary material online.

DISCUSSION
Statement of principal findings
To our knowledge this is the largest dataset of contemporaneous spirometry, plethysmography and HRCT in patients with PCD. HRCT was performed in all patients aged 6 years or older because it is known that from this age many patients already have some degree of bronchiectasis and from this age patients can both cooperate with the procedure and be able to perform reproducible lung function testing.

We show that soft computing based on plethysmographic lung volumes, but not spirometry, is sensitive to a range of HRCT abnormalities. Reduction in lung function associated with bronchiectasis has been previously reported in patients with PCD. However, we report for the first time that FRCpleth, RV and RV/TLC ratio is associated with the severity of air trapping, atelectasis and extent of bronchiectasis and with Pseudomonas aeruginosa infection. Hence follow-up of PCD patients may be preferable with plethysmography rather than simple spirometry.

Strengths and weaknesses of the study
Our study has some strengths. First the completeness of ascertainment, since all patients performed all the tests, obviating selection bias. Second all the evaluations were done within 48 h. Third the objective analytical techniques using soft computing greatly reduces the chance of investigator bias.

Strengths and weaknesses in relation to other studies
In our study group the vast majority of adults and 80% of the children had bronchiectasis and, as previously reported, half of the adults and approximately one-third of the children had chronic Pseudomonas aeruginosa infection. The latter was associated with air-trapping, as previously documented in young children with cystic fibrosis. Focal air-trapping, which indicates small airways disease, probably starts early and our results document that static lung volume evaluation can detect this even in younger patients. This finding lends further support to the hypothesis that peripheral lung damage may be an early event in PCD.

It has recently been suggested that even the youngest patients already have irreversible lung damage and that bronchiectasis,
reduction in lung flows and increased RV and RV/TLC can be present in patients with PCD as young as <3 years. We were not able to determine this because we could not study very young children with PCD.

**Meaning of the study**

Our findings suggest that lung disease in PCD begins early and that it is better identified at least in school-aged children and adults by the finding of air-trapping or HRCT, rather than chest XR.

**Table 4 Correlations between chest high-resolution CT and functional parameters expressed as z scores**

<table>
<thead>
<tr>
<th>HRCT parameters</th>
<th>FEV₁</th>
<th>FVC</th>
<th>FEF₂₅₋₇₅%</th>
<th>FEV₁/FVC</th>
<th>Raw</th>
<th>sRaw</th>
<th>sReff</th>
<th>FRCpleth</th>
<th>RV</th>
<th>TLC</th>
<th>RV/TLC</th>
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<tbody>
<tr>
<td>Severity of bronchiectasis</td>
<td>NS</td>
<td>NS</td>
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<td>Peribronchial thickening</td>
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</table>

FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; HRCT, high-resolution CT; NS, non-significant; Raw, airway resistance; RV, residual volume; sRaw, specific airway resistance; sReff, effective specific resistance; TLC, total lung capacity.

**Figure 3** (A) Three-dimensional scatter plots for air-trapping score 1 (triangles), 2 (circles), 3 (squares) in relation to functional residual capacity by plethysmography (FRCpleth), residual volume (RV), total lung capacity (TLC) and RV/TLC ratio. (B) Three-dimensional scatter plots for atelectasis score 1 (triangles), 2 (circles), 3 (squares) in relation to FRCpleth, RV, TLC and RV/TLC ratio. (C) Three-dimensional scatter plots for bronchiectasis extension score 1 (triangles), 2 (circles), 3 (squares) in relation to FRCpleth, RV, TLC and RV/TLC ratio. (D) Three-dimensional scatter plots for total lung impairment score 1 (triangles), 2 (circles), 3 (squares) in relation to FRCpleth, RV, TLC and RV/TLC ratio.
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spirometry. In previous studies of adults and children with PCD, total lung abnormalities and bronchiectasis severity on HRCT were shown to be related to FEV1 and FVC. Our results do not confirm this in a larger series of PCD, even when analysed using a soft computing-based modelling approach, but instead suggest that plethysmography is a much more sensitive test.

CT scanning of the chest has become a popular tool to monitor patients with cystic fibrosis, a disease that has similarities with PCD. However, no study has evaluated the impact of such monitoring on health outcomes or on clinical decision-making in patients with PCD or cystic fibrosis. Moreover, there are concerns on the uncertain use of high-tech medical imaging and on the potential harm of repeated radiological exposures, particularly in children with lifelong diseases. Consequently, careful thought is needed before requesting repeated chest CT scans. By contrast a detailed evaluation of lung volumes is only limited by the availability of the equipment, and by the ability of the technician to obtain patients’ collaboration, but this is usually not a problem in the specialist centres that should care for these patients.

Unanswered questions and future research

Even though we have not studied very young subjects, from our results it is tempting to speculate that accumulation of secretions, in the early stages of disease, may induce primarily an obstruction in terminal bronchioles which may go undetected for a long period during alveolar growth of the lung. The consequent focal air-trapping during this phase of alveolar growth might lead to impaired septation and decreased elastic recoil as has been observed in animal models. Early structural changes in the distal airways could explain why we found a lack of correlation between per cent predicted RV and RV/TLC with age, unlike for spirometry, which may reflect slower progressive, age-related damage to large airways. To confirm this hypothesis, data are required from a longitudinal study in patients with PCD from the newborn period, using age-appropriate physiological techniques.

Although our findings show the superior sensitivity of plethysmography over spirometry in detecting HRCT changes in PCD, the findings need to be validated in a second cohort of patients. It would be valuable to compare plethysmography over spirometry in detecting HRCT changes in monitoring patients with cystic fibrosis. It would be valuable to compare plethysmography over spirometry in detecting HRCT changes in monitoring patients with cystic fibrosis. It would be valuable to compare plethysmography over spirometry in detecting HRCT changes in monitoring patients with cystic fibrosis. It would be valuable to compare plethysmography over spirometry in detecting HRCT changes in monitoring patients with cystic fibrosis. It would be valuable to compare plethysmography over spirometry in detecting HRCT changes in monitoring patients with cystic fibrosis.

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Contributors

M Pifferi: contributed to study design, data evaluation and drafting and revising the submitted manuscript. He had full access to all of the data in the study and he takes full responsibility for the integrity of all of the data and the accuracy of the data analysis. A Bush: contributed to data evaluation and drafting and revising the submitted manuscript. G Poggia: contributed to data analysis and drafting and revising the submitted manuscript. D Caramella: contributed to data analysis and drafting and revising the submitted manuscript. D Di Cicco: contributed to collecting data. M Zampaglini: contributed to collecting data. F Moggi performed the statistical analysis. G Tezza: contributed to the reevaluation of all data after reviewers’ comments. P Macchia: contributed to study design. A L Boner: contributed to study design, data evaluation and drafting and revising the submitted manuscript.

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Competing interests

None declared.

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Obtained.

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