Ventilation and perfusion assessed by functional MRI in children with CF: reproducibility in comparison to lung function

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Abstract

Background: Chronic lung diseases such as cystic fibrosis (CF) can be monitored by imaging and lung function modalities. Magnetic resonance imaging (MRI) techniques such as matrix pencil (MP) decomposition allows for evaluation of regional impairment of fractional ventilation (RFV) and relative perfusion (RQ). However, reproducibility of MP MRI outcomes in children with CF is unknown. We examined short-term variability of ventilation and perfusion impairment from MP MRI and compared this to lung function outcomes.

Method: Twenty-three CF and 12 healthy school-aged children underwent MRI and lung function tests on the same day on two occasions 24 h apart. Global ventilation inhomogeneity was assessed by the lung clearance index (LCI) from nitrogen-multiple breath washout (N2-MBW) technique. Intra-class coefficient (ICC), percentage change, and Bland-Altman limits of agreement were evaluated to assess reproducibility.

Results: Sixty-nine measurements from MP MRI and N2-MBW were performed. The ICC between two visits for RFV, RQ and LCI ranged between 0.60 and 0.90 in individuals with CF and healthy controls. In individuals with CF, percentage of change between the visits was 0.02% for RFV, −1.11% for RQ and 2.91% for LCI and limits of agreement between visits were −4.3% and 3.9% for RFV, −4.4% and 3.7% for RQ, and −2.6 and 3.0 for LCI.

Conclusions: Functional imaging is reproducible and short-term changes in RFV and RQ greater than ±4.4% can be considered clinical meaningful. Very good short-term reproducibility, and easy application without the need for breathing maneuvers or contrast agent, makes MP MRI a promising surveillance method for CF.

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Keywords: Functional magnetic resonance imaging; Lung function measurements; Reproducibility

1. Introduction

Chronic airway infection, inflammation, and mucus plugging can lead to irreversible bronchiectatic lung damage in children with Cystic Fibrosis (CF), despite a lack of respiratory symptoms and spirometry indices within the normal range [1]. The implementation of newborn screening in many countries has meant that CF can now be detected in the first weeks of a child’s life. In addition, developments in medical care of
patients with CF has increased life expectancy [2]. As a result, patients with CF now often live beyond the third decade and have only mild lung function impairment during childhood [3,4]. This requires the development of sensitive and reproducible tools to assess early changes in disease severity or treatment response. Imaging and lung function modalities allow for close monitoring of early CF disease [5–8]. Lung function tests such as spirometry and nitrogen multiple breath washout (N2-MBW) provide information on lung function impairment. Spirometry has been traditionally used to assess airflow limitation from central large airways in established lung impairment. Spirometry has been traditionally used to assess airflow limitation from central large airways in established lung disease [9–11]. In comparison, N2-MBW is more sensitive to assess small airway impairment in early stages of disease. However, lung function techniques do not directly assess the regional location or extent of structural and functional impairment in the lung [12].

High-resolution computed tomography (HR-CT) or magnetic resonance imaging (MRI) scans can detect regional structural and functional changes in the lung [13–18]. The main advantage of functional MRI-based techniques is the lack of exposure to ionizing radiation [19–21]. In addition, recently developed techniques for functional assessment of the lung known as matrix pencil decomposition (MP) MRI does not require the administration of intravenous contrast-agents or breathing maneuvers during the examination [22]. MP MRI allows for the evaluation of regional functional impairment of the lung including fractional ventilation (RFV) and relative perfusion (RQ). In a previous study, we demonstrated a strong correlation between functional indices from the MRI and the lung clearance index (LCI), a global marker of ventilation inhomogeneity, from the N2-MBW [23]. A central criticism of the novel functional MRI methodology is the lack of longitudinal studies assessing the reliability, i.e. natural variability of RFV and RQ. We examined short-term (two measurements within 24 h) reproducibility of RFV and RQ in healthy and CF children. Secondary aims were to relate reproducibility of RFV and RQ to reproducibility of lung clearance index from N2-MBW and to confirm feasibility and the correlation between MRI and lung function.

2. Methods

2.1. Study design

This is a prospective, single-centre, observational study at the University Children's Hospital of Bern, Switzerland conducted between February 2016 and September 2017. Participants underwent N2-MBW, spirometry, and functional MRI scans in that order on the same day on two test occasions 24 h apart. The rationale for choosing the time interval for the measurements was based on the assumption that the nature of variability of functional outcomes from MRI resemble the nature of variability of outcomes from respiratory function tests. In general, day-to-day (within 24 h), week-to-week, and year-to-year are recommended time periods to assess variability of lung function outcomes [24]. Morphological MRI scans were performed only on test occasion 1 in order to determine the extent of structural impairment.

2.1.1. Study population

We enrolled 23 unselected children with CF across a wide age range of 6–18 years, irrespective of bacterial colonisation or antibiotic use to ensure a broad range of disease severity. Eligibility criteria included a confirmed diagnosis of CF and no requirement for supplemental oxygen therapy. Healthy controls had no history of chronic lung disease or acute respiratory infection in the four weeks prior to the investigations. Data from the healthy study participants has been partly published before [23]. The study was approved by the Ethics Committee of Bern (EKNZ 2015–326 and KEK 2017–00279). We obtained written informed consent from parents and participants if older than 14 years.

2.1.2. MRI data acquisition and evaluation

MRI scans were performed on a 1.5 Tesla whole-body MR-scanner (MAGNETOM Aera, Siemens Healthineers, Erlangen, Germany) using a 12-channel thorax and a 24-channel spine receiver coil array. Children were awake and not sedated during the scans. Parents or caregivers were allowed to accompany children in the room during imaging.

Functional lung imaging was performed using MP decomposition MRI technique (a derivative of Fourier decomposition (FD) method [25]. MP MRI relies on dynamic free-breathing ultra-fast balanced steady-state free precession (uf-bSSFP) acquisitions of lung images and provides regional ventilation and perfusion information from a single acquisition series, requiring no administration of contrast agent, as well as no further patient compliance such as repeated or prolonged breath holding [22,26]. The acquired two-dimensional time-series were processed by non-rigid image registration for compensation of respiratory motion. Subsequently, the registered images were analyzed voxel-wise using a MP decomposition of the respiratory and cardiac signal modulations used to generate fractional ventilation and perfusion maps. MP MRI allows for more robust spectral estimation of respiratory and cardiac amplitudes and eliminates the problem of truncation effects associated with the application of the fast Fourier transform used in the previous implementation based on FD.

The lungs were semi-automatically segmented using a growing region algorithm [27]. The segmentation masks were overlaid on functional maps in order to extract distributions of fractional ventilation and perfusion values for each subject. A threshold equal to 75% of the median value from each voxel distribution was used to identify regions with impaired lung function as described previously [23]. A similar threshold method was used previously in a study comparing Fourier decomposition MRI with dynamic contrast-enhanced MRI in patients with CF [28]. The primary outcomes were percentage of the lung volume with impaired fractional ventilation (RFV) and relative perfusion (RQ).

The functional MRI scans were followed by morphological scans including a breath-hold axial and coronal T2-weighted half-Fourier acquisition single-shot spin-echo (HASTE), a
navigator-triggered axial and coronal periodically rotated overlapping parallel lines with enhanced reconstruction (PROPELLER/BLADE), breath-held three-dimensional ufSSFP sequence. The sequences were chosen on the basis of published standard MR protocols for thorax examinations [29]. The assessment of the structural disease using MRI was based on a scoring system previously described by Eichinger et al. for CF patients [30].

2.1.3. Lung function testing

$N_2$-MBW was performed with an unmodified device (Exhalyzer D, Eco Medics AG, Duerten, Switzerland) according to consensus guidelines [31]. The primary outcome was the LCI, calculated as the cumulative expired volume divided by functional residual capacity, an estimate of global ventilation inhomogeneity. Spirometry (Jaeger MasterScreen, CareFusion, Hochberg, Germany) was performed after $N_2$-MBW, according to ERS/ATS guidelines [10] and the primary outcome was the forced expiratory volume in 1 s (FEV$_1$).

2.1.4. Statistical analysis

We first assessed differences in MRI and lung function indices between the two study visits in healthy controls and children with CF. Continuous variables between the visits were compared with paired t-test, and differences between the groups with unpaired t-test, as appropriate. Percentage of change (differences) for each index between the visits was calculated as $(x_{\text{Visit2}}-x_{\text{Visit1}}) * 100 / x_{\text{Visit1}}$. Absolute differences were calculated with paired t-test. The agreement and reproducibility of MRI and lung function indices over two visits was assessed graphically by the Bland–Altman method and analytically by calculating intra-class correlation (ICC) coefficients [32]. With the Bland-Altman method, we calculated the upper and lower limits of agreement between visits (mean difference ± 1.96 SD of differences between visits). The ICC relates intra-subject to inter-subject variation. ICC was defined as very good (>0.80), good (0.60–0.80) and moderate (0.40–0.59) [33]. In a second step, we examined associations between functional indices from MRI and lung function. In a third step we examined associations between functional indices from MRI and lung function indices between the groups with unpaired t-test, as appropriate. Percentage of change (differences) for each index between the visits was calculated as $(x_{\text{Visit2}}-x_{\text{Visit1}}) * 100 / x_{\text{Visit1}}$. Absolute differences were calculated with paired t-test. The agreement and reproducibility of MRI and lung function indices over two visits was assessed graphically by the Bland–Altman method and analytically by calculating intra-class correlation (ICC) coefficients [32]. With the Bland-Altman method, we calculated the upper and lower limits of agreement between visits (mean difference ± 1.96 SD of differences between visits). The ICC relates intra-subject to inter-subject variation. ICC was defined as very good (>0.80), good (0.60–0.80) and moderate (0.40–0.59) [33]. In a second step, we examined associations between functional indices from MRI and lung function. In a third step we examined the association between the morphological pathologies (Eichinger score) from MRI and lung function. Uni-variate linear regression models were used to determine the association between lung function and MRI indices. P-values <.05 were considered statistically significant. Analyses were performed using Stata™ (Stata Statistical Software: Release 13. College Station, TX: StataCorp LP), Matlab (2012b, The MathWorks, Natick, MA, US) and GraphPad Prism (GraphPad Software Inc., La Jolla, CA).

3. Results

3.1. Feasibility

All 23 patients with CF and 12 healthy controls were able to perform MRI, $N_2$-MBW and spirometry at two time points. $N_2$-MBW and spirometry were feasible at both visits in all children. From the total of 70 MRI examinations, the functional MRI data were excluded in one patient due to the increased body movement at the first study visit. Functional lung MRI took on average 7 minutes (min = 6, max = 8) and morphological scans took 8 minutes (min = 5, max 21) in patients with CF.

3.1.1. Comparison between healthy and children with CF

The characteristics of the study participants are presented in Table 1. As expected, impairment of fractional ventilation (R$_{FV}$) at visit 1 was significantly higher in patients with CF (mean (SD): 30.32% (4.63)) compared with healthy controls (18.06% (4.73); p < .001). Impairment of perfusion (R$_Q$) at visit 1 was higher (27.98% (4.07)) in patients with CF compared with healthy controls (15.27% (2.34); p < .001). In addition, the LCI at visit 1 was higher in children with CF (11.72 (3.18)) compared with healthy children (6.05 (0.47); p < .001). We were able to replicate these findings at visit 2 (Tables 2 and 3).

3.1.2. Inter-visit reproducibility

The absolute difference in R$_{FV}$ between visit 1 and visit 2 was close to zero in both healthy children (mean (SD) difference: 0.46 (0.94) %) and children with CF (0.19 (0.45) %). Absolute difference in R$_Q$ between the two visits was close...
Table 2
Functional MRI imaging values of study participants at two visits.

<table>
<thead>
<tr>
<th>Healthy controls</th>
<th>Visit 1 (n = 12)</th>
<th>Visit 2 (n = 12)</th>
<th>Absolute differences mean (SD)</th>
<th>Percent change (95% CI)</th>
<th>Inter-visit ICC (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFV [%]</td>
<td>18.06 (4.73)</td>
<td>17.60 (4.59)</td>
<td>0.46 (0.94)</td>
<td>−0.72 (−11.92, 10.49)</td>
<td>0.75 (0.45, 0.92)</td>
<td>0.633</td>
</tr>
<tr>
<td>RQ [%]</td>
<td>15.27 (2.34)</td>
<td>15.96 (1.82)</td>
<td>−0.69 (0.51)</td>
<td>5.71 (−2.0, 13.42)</td>
<td>0.60 (0.24, 0.87)</td>
<td>0.203</td>
</tr>
</tbody>
</table>

Cystic Fibrosis

<table>
<thead>
<tr>
<th>Visit 1 (n = 22)</th>
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<tbody>
<tr>
<td>RFV [%]</td>
<td>30.32 (4.63)</td>
<td>30.12 (3.73)</td>
<td>0.19 (0.45)</td>
<td>0.02 (−3.73, 3.36)</td>
<td>0.87 (0.74, 0.94)</td>
</tr>
<tr>
<td>RQ [%]</td>
<td>27.98 (4.07)</td>
<td>27.63 (4.23)</td>
<td>0.35 (0.44)</td>
<td>−1.11 (−4.59, 2.37)</td>
<td>0.87 (0.73, 0.94)</td>
</tr>
</tbody>
</table>

Data is presented as mean (SD) or mean difference and 95% confidence interval (CI) or absolute values. Continuous variables between the visits were compared with paired t-test.

*One patient was excluded for the functional MRI on visit 1 and did not contribute to comparison of repeatability.

3.1.3. Correlation between MRI and lung function

In patients with CF, we found a significant association between RFV and LCI and RFV and FEV1 on both visits. Further associations are presented in Table E1. There were no correlations observed between lung function and imaging outcomes in healthy controls (data not shown). The total morphology score in patients with CF ranged from 1 to 30. We found a correlation between LCI and total morphology score at visit 1: Coefficient 1.54, 95% CI 0.72 to 2.36, p = .001, R² 0.42, r 0.65). For detailed sub-scores see Table E2. Using non-parametric statistical tests did not change our results.

Table 3
Lung function values of study participants at two visits.

<table>
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<tr>
<th>Healthy controls</th>
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<tr>
<td>N2-MBW Spirometry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCI [TO]</td>
<td>6.05 (0.47)</td>
<td>6.20 (0.61)</td>
<td>−0.15 (0.12)</td>
<td>2.50 (−1.88, 6.86)</td>
<td>0.68 (0.34, 0.89)</td>
<td>0.244</td>
</tr>
<tr>
<td>FEV₁ (% pred.)</td>
<td>101.50 (11.20)</td>
<td>99.67 (10.71)</td>
<td>1.83 (1.08)</td>
<td>−1.71 (−4.08, 0.66)</td>
<td>0.90 (0.80, 0.98)</td>
<td>0.117</td>
</tr>
<tr>
<td>FEV₁ [z-score]</td>
<td>0.14 (0.93)</td>
<td>−0.02 (0.88)</td>
<td>–</td>
<td>–</td>
<td>0.92 (0.79, 0.98)</td>
<td>0.096</td>
</tr>
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Cystic Fibrosis

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<td>LCI [TO]</td>
<td>11.72 (3.18)</td>
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<td>−0.24 (0.30)</td>
<td>2.91 (−3.0, 8.82)</td>
<td>0.90 (0.79, 0.96)</td>
</tr>
<tr>
<td>FEV₁ (% pred.)</td>
<td>79.74 (15.73)</td>
<td>78.78 (14.37)</td>
<td>0.96 (0.99)</td>
<td>−0.68 (−3.65, 2.29)</td>
<td>0.95 (0.89, 0.98)</td>
</tr>
<tr>
<td>FEV₁ [z-score]</td>
<td>−1.68 (1.30)</td>
<td>−1.76 (1.18)</td>
<td>–</td>
<td>–</td>
<td>0.95 (0.89, 0.98)</td>
</tr>
</tbody>
</table>

Data is presented as mean (SD) or mean 95% confidence intervals (CI). Continuous variables between the visits were compared with paired t-test.
4. Discussion

4.1. Main findings

This study comprehensively assessed short-term repeatability of functional MRI using the matrix pencil decomposition method. We found that the short-term reproducibility of functional indices of MRI is very good in children with CF and good in healthy controls. A change in RFV or RQ exceeding ±4.4% within a 24 h period can be considered greater than the biological variability in children with CF. We also confirm previously reported associations between RFV, RQ and LCI, which is an established marker of lung disease severity in CF. Furthermore, functional imaging is feasible in school-aged children and data acquisition takes on average only seven minutes to complete.

4.2. Comparison with previous studies

Imaging and lung function measurements are considered indispensable methods to monitor CF lung disease. Imaging modalities such as the MRI are increasingly used as non-ionizing techniques to monitor structural and functional changes in patients with CF [16,18,34]. Previous studies have reported good feasibility to obtain MR images even in infants and preschool children with CF [16,18]. In addition to imaging, tidal breathing lung function tests such as the MBW are feasible to perform throughout the entire pediatric age range [12,35–38]. In our study, all except for one MRI measurement were feasible even in the youngest participant who was five years of age.

As expected, functional MRI and lung function outcomes were significantly worse in children with CF compared with healthy control, which supports the findings of our previous study [23] and other studies using different proton-based MRI pulse sequences (16). One study in healthy adult volunteers assessed the reproducibility of ventilation and perfusion amplitude within 24 h using the standard FD MRI and demonstrated a high reproducibility of ventilation- and perfusion weighted images [39]. The results from the current study show that outcomes from functional MRI are robust and reproducible after 24 h in healthy children and children with CF. Pediatric studies evaluating the short-term reproducibility of MRI and lung function tests are sparse. One study examined the variability of hyperpolarized helium-3 MR images in five patients with CF over a 4 week period [40]. Another study examined the longitudinal changes over a time period of 1–2 years in 14 patient with CF [41]. Both studies showed that functional MRI indices are reproducible and sensitive to track progression of lung disease over time in children. Different
studies have reported the reproducibility of LCI measurement over months and years in patients and healthy controls [42–44]. However, reproducibility data for LCI within 24 h in healthy and children with CF only have marginal representation in the literature. One study in 77 preschool children with CF showed good reproducibility of LCI, however, the percentage change of LCI was higher than in the school age children in our study [42]. Another study showed in 25 children (13 children with CF, 12 healthy controls) that LCI measurements were reproducible in 24 h and revealed a higher reproducibility (lower variability) of LCI in children with CF compared to healthy children [38]. We also found that the reproducibility of both LCI and MRI outcomes were higher in children with CF compared with healthy controls. Higher reproducibility of functional outcomes in patients with CF versus controls has been described previously and is summarized, for example, in a recent consensus document on inert gas washout testing [31]. The reason for this is unclear. We hypothesize that disease constrains natural adaptive boundaries of physiological time constants. This has been described for different physiological outcomes and different diseases, e.g. in premature infants with bronchopulmonary dysplasia, in whom respiratory rate was overall slightly elevated but less variable as compared to term-born controls [45]. Another reason that has already been described could be the training effect, as patients with CF have LCI measurements every three months and nearly all patients with CF had performed CT scans or MRI measurements previously. On a group level, there were no systematic changes between day 1 and day 2 for LCI, RQ and RQFV, respectively. However, not surprisingly, magnitude and directions of the vectors varied stronger between healthy subjects (RQ ICC = 0.75) compared to patients with CF (RQFV ICC = 0.87, Figs. 3 and 4). While greater variability in health compared to disease groups has been described for several physiological outcomes, the higher variability in RFV in healthy controls compared to patients with CF may be also influenced by one outlier (RFV visit 1 (23%), visit 2 (14%) in our study. The magnitude of variation in this healthy subject, however, did not exceed the upper limit of normal RFV = 24.2% as described previously [23].
4.3. Clinical relevance

The MBW and functional MRI techniques represent attractive non-invasive methods to clinically monitor children with CF. While the functional outcomes from different MRI techniques (using intravenous contrast agents, inhaled hyperpolarized tracer gas or non-contrast enhanced techniques) have all been shown to correlate with lung function parameters [16,23,34,41], it is not yet known whether these outcomes can be directly compared to each other. In addition, outcomes from the MBW technique using either SF₆ or N₂ as the tracer gas may not be directly comparable due to physiological and
methodological differences [46,47]. Data on the reproducibility and clinically meaningful difference in ventilation and perfusion impairment are important and necessary for monitoring patients’ response to therapeutic interventions and identifying novel therapeutic mechanisms. Data from this study suggest that a change in RFV or RQ when measured twice within 24-h exceeding ±4.4% can be considered greater than the biological variability in healthy children and children with CF. Previous MRI studies have examined the structural and functional changes in the lung following antibiotic therapy and shown that MRI indices are responsive to therapy [18,48]. However, the study from Wielpütz et al. examined perfusion impairment in the lung by using intravenous contrast agents. The use of contrast agents should be carefully considered, especially in chronically ill children where follow up measurements are performed more frequently to monitor disease progression [49,50]. While hyperpolarized gaseous tracers such as helium-3 have shown to provide the best static and dynamic ventilation image quality [41,51], the clinical application of these techniques is impeded by limited availability and high cost of gases, hardware and trained personnel.

4.4. Strengths and limitations

This is the first study to evaluate the short-term (24 h) reproducibility of MRI and lung function measurements in healthy controls and children with CF. The study design was rigorously performed. MRI scans and lung function were feasible in children at both visits within a short time frame. The inter-visit reproducibility of MRI and N₂-MBW indices was good in both groups. In addition to ensure a broad range of lung disease severity, we did not want to select the CF patients based on disease severity. However, we acknowledge that current findings may not be extrapolated to other MRI setups or disease populations with different lung disease severity. The rather small sample size may influence, i.e. overestimate short-term variability. Healthy patients were not well aged-matched. However, as our data showed a good reproducibility in younger patients, we are not assuming that this would change in older patients. We did neither assess long-term or same-day variability of the functional MRI indices, nor did we assess variability of the structural MRI sequences. Thus, we cannot report on the variability of MRI indices over a very short or long period in healthy children and stable patients with CF. To diminish the bias of exacerbation, we excluded in a separate analysis all six patients with an exacerbation and determined no change in the inter-visit ICC. As expected, the 95% confidence intervals (95% CI) became wider possibly due to sample size. Furthermore, we used a modified Eichinger scoring system without perfusion studies from dynamic contrast-agent MRI acquisitions. Application of contrast-agent possibly also influences the evaluation of other pathologies that are represented by sub-scores of the morphology score. According to the modified Eichinger score, imaging without contrast agent application could also influence the extent of these sub-scores and the morphology score as the sum of these sub-scores.

5. Conclusion

In summary, this study demonstrates that functional MRI indices are reproducible within 24 h. Our results indicate that functional MRI could be used to non-invasively monitor the development and progression of lung disease and response to therapies in children with CF. Future studies and replication in a larger population with a wider range of disease severity will reveal if MRI indices can be used as trial end points for interventional clinical trials.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcf.2018.10.003.

Disclosures

Dr. Latzin reports personal fees from Gilead, Novartis, Polyphor, Roche, Schwabe, Vertex, Vifor and Zambon.
Otherwise, no conflicts of interest, financial or otherwise, are declared by the author(s).

Authors contributions

SN, GB, OP, CC, OB and PL designed the study concept. SN collected study data. SN, GB and ES analyzed the data. SN, GB, OP, ES, KR, FS, SY, CC, OB and PL interpreted the data. SN and GB drafted the manuscript. All authors revised the manuscript.

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