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Research article

Non-contrast enhanced magnetic resonance imaging detects mosaic signal intensity in early cystic fibrosis lung disease

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ABSTRACT

Objectives: To determine if morphological non-contrast enhanced magnetic resonance imaging (MRI) of the lung is sensitive to detect mosaic signal intensity in infants and preschool children with cystic fibrosis (CF).
Materials and methods: 50 infant and preschool CF patients (mean age 3.5 ± 1.4y, range 0–6y) routinely underwent morphological (T2-weighted turbo-spin echo sequence with half-Fourier acquisition, HASTE) and contrast-enhanced 4D perfusion MRI (gradient echo sequence with parallel imaging and echo sharing, TWIST). MRI studies were independently scored by two readers blinded for patient age and clinical data (experienced Reader 1 = R1, inexperienced Reader 2 = R2). The extent of lung parenchyma signal abnormalities on HASTE was rated for each lobe from 0 (normal), 1 (< 50% of lobe affected) to 2 (≥50% of lobe affected). Perfusion MRI was rated according to the previously established MRI score, and served as the standard of reference.
Results: Inter-method agreement between MRI mosaic score and perfusion score was moderate with κ = 0.58 (confidence interval 0.45–0.71) for R1, and with κ = 0.59 (0.46–0.72) for R2. Bland-Altman analysis revealed a slight tendency of the mosaic score to underestimate perfusion abnormalities with a score bias of 0.48 for R1 and 0.46 for R2. Inter-reader agreement for mosaic score was substantial with κ = 0.71 (0.62–0.79), and a low bias of 0.02.
Conclusions: This study demonstrates that non-contrast enhanced MRI reliably detects mosaic signal intensity in infants and preschool children with CF, reflecting pulmonary blood volume distribution. It may thus be used as a surrogate for perfusion MRI if contrast material is contra-indicated or alternative techniques are not available.

1. Introduction

In chronic obstructive lung diseases such as cystic fibrosis (CF) [1–3] the phenomenon of mosaic perfusion of lung parenchyma detected by computed tomography (CT) reflecting blood redistribution caused by airway obstruction (so-called hypoxic pulmonary vasoconstriction) is well known [4–6]. Recently, we demonstrated that morpho-functional magnetic resonance imaging (MRI) is able to depict characteristic changes of lung structure and perfusion already in infants and preschool children with CF [7–10]. In early CF lung disease, perfusion impairment is thought to occur due to small airways mucus obstruction that may not be detected by morphological imaging directly due to the small size of the peripheral airways. MRI is an important diagnostic parameter in monitoring CF lung disease to detect and surveil lung abnormalities and prevent life-limiting structural damage. One advantage is clearly that MRI is radiation-free in contrast to all other imaging modalities (CT, radiography). Further, lung perfusion can be directly depicted and quantified by four-dimensional (4D) perfusion

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MRI, which requires the i.v. injection of Gadolinium-based contrast material [6,8,11]. The latter, however, may be contra-indicated in some patients, e.g. with impaired renal function, and in addition there are still controversies about the deposition of Gadolinium in the brain after injection of some contrast materials although the clinical significance remains unknown [12,13]. It is well-known that lung signal on MRI is dependent on inflation level but also on pulmonary blood volume [14–16]. However, in contrast to chest CT, the phenomenon of mosaic perfusion in CF has not been studied systematically with MRI. Thus, limited data exists on the changes in lung parenchymal signal on MRI in infants in preschool children with CF in relationship to pulmonary blood volume distribution. In infants and preschool children, the tissue density of normal lung parenchyma is much higher than in adults thus improving conditions for the detection of signal from the lungs with MRI [17]. Recently, Bauman et al. showed that signal changes of the lung on balanced steady-state free precession (bSSFP) sequences induced by the pulsatile inflow of blood can be used to calculate perfusion maps indicating that non-contrast enhanced MRI may be sufficient to detect perfusion abnormalities [18]. This technique requires acquisition times around 2 min per image slice and dedicated post-processing, and is not yet available in clinical routine. It is known that T2-weighted fast spin echo sequences with half-Fourier acquisition (HASTE) deliver a robust signal of the normal lung. We hypothesized that mosaic signal intensity may be sensitively detected by a navigated HASTE sequence triggered to expiration. To test this hypothesis we developed a novel mosaic signal intensity score based on HASTE acquisitions, and validated this score against the previously established 4D perfusion MRI score in 50 infants and preschool children with CF [7,11]. A novel MRI mosaic score adjunct to the previously established MRI score could deliver important information on lung perfusion without using contrast material even in newborn and infant CF patients.

2. Methods

2.1. Subjects

This study was performed using annual surveillance MRI scans of infants and preschool children with CF followed in the prospective TRACK-CF cohort (clinicaltrials.gov identifier NCT02270476). The study was approved by the local ethics committee and informed written consent was obtained from the parents or legal guardians of all patients. In total, 50 infants and preschool children with CF with annual surveillance MRI were recruited for this study. Patient characteristics are summarized in Table 1. In 41 patients, the diagnosis of CF was based on clinical symptoms and 9 patients were identified by newborn screening [19]. The diagnosis of CF was confirmed by increased sweat Cl^- concentrations (≥60 mmol/l) and *CFTR* mutation analysis.

Table 1
Patient demographics.

Number of subjects	50
Age (years)	3.5 ± 1.4
Male/female	22/28
Weight (kg)	13.5 ± 3.0
Weight SDS	−1.1 ± 0.3
Height (cm)	93.5 ± 6.1
Height SDS	−1.5 ± 1.0
BMI (kg/m^2)	15.2 ± 1.5
BMI SDS	−0.7 ± 1.5
Pseudomonas positive	0

SDS = standard deviation scores for anthropomorphic data in relation to the average German population; BMI = body mass index; Pseudomonas positive is defined as chronic colonization with *Pseudomonas aeruginosa* with positive antibody status. Data are given as mean ± SD.

2.2. Chest MRI

Axial and coronary T2-weighted fast spin echo sequences with half-Fourier acquisition (HASTE) sequences and 4D first-pass perfusion imaging with a 3D gradient echo sequence with parallel imaging and echo sharing (TWIST) were acquired using a clinical 1.5T MR scanner (Magnetom Avanto, Siemens AG, Erlangen, Germany) as previously described [7,11]. The pulse sequence parameters are shown in detail in Table 2. All MRI sequences were acquired in free breathing, and patients were routinely sedated with 100 mg/kg chloral hydrate (maximum dose, 2 g/day), administered orally or rectally before the imaging procedure as described previously [11]. After initiating the 4D perfusion sequence acquisition, gadolinium-based macrocyclic contrast material was injected intra-venously by a power injector (0.1 mmol/kg body weight of Gd-DOTA [Dotarem, Guerbet, Villepinte, France]) at a rate of 2 ml/s followed by a chaser of 30 ml NaCl 0.9% at the same injection rate. Perfusion image datasets were post-processed by subtracting the baseline images without contrast from those with maximal contrast in the lung parenchyma, resulting in a single image series displaying the maximum parenchymal enhancement [6].

2.3. Image assessment

Two readers with eight (Reader 1 [R1]) and one year (Reader 2 [R2]) of experience in MRI of the lung in patients with CF independently assessed the images blinded for clinical data using the previously established dedicated morpho-functional MRI score that originally consists of six parameters: bronchiectasis/wall thickening, mucus plugging, abscesses/sacculations, consolidations, special findings, and perfusion score (based on perfusion MRI with i.v. injection of Gadolinium-based contrast material) [7,8,11]. Scoring for perfusion abnormalities on contrast-enhanced 4D perfusion MRI was performed as previously described, using the same 3-point rating scale [7,8,11]. Further, as a modification we added a novel score item, the MRI mosaic score, to the previously established MRI score. In brief, HASTE sequences were scored for mosaic signal intensity, which was defined by the presence of sharply delineated lung parenchymal signal inhomogeneities. The extent of signal inhomogeneities was rated in each lobe as 0 (normal), 1 (< 50% of the lobe involved), or 2 (≥50% of the lobe involved), similar to the other items of the MRI score (Fig. 1) [7]. Importantly, scoring for mosaic was performed at least 1 month apart and independently from the other items of the MRI score, and especially without viewing the images or scoring results of 4D perfusion MRI. Prior to this study, both readers reviewed MRI examinations of a group of 20 independent CF patients of the same age group to train scoring of mosaic signal intensity in consensus.

2.4. Statistical analysis

Data are presented as mean ± standard deviation. MRI scores were compared by the method of Bland and Altman [20], and weighted kappa (κ) scores were calculated for comparison of both methods as well as for comparison of both readers for lobar and whole-lung sum scores [21]. We employed the following previously defined levels of agreement: 0–0.20 = poor, 0.21–0.40 = fair, 0.41–0.60 = moderate, 0.61–0.80 = substantial, 0.81–1.00 = almost perfect [22]. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Mosaic signal intensity can be detected on inspiratory MRI

MRI scans of all 50 patients were of diagnostic image quality (Fig. 1). Image assessment and scoring did not exceed 5 min reading time per patient and reader. The range of the whole-lung MRI mosaic score (Table 3) was 0–12 with a mean of 3.1 ± 2.8 for R1, and