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Research letter

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Feasibility of unsedated lung MRI in young children with cystic fibrosis

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Take home message: Lung MRI could serve as a sensitive surveillance method in young childhood. We found that unsedated lung MRI is feasible in young children with cystic fibrosis. Feasibility increases with age and was comparable with lung function tests.

INTRODUCTION

Chronic lung disease leads to morbidity and mortality in patients with cystic fibrosis (CF) [1]. Computed tomography imaging of the lung has revealed that lung disease starts early in life and progresses during childhood [2]. Early detection and treatment of lung damage are essential to improve the prognosis and quality of life of individuals with CF [3]. Therefore, non-invasive surveillance methods are needed to monitor lung disease throughout life.

Advancements in the last decade have made magnetic resonance imaging (MRI) a promising technique to assess lung structure and function, especially in the pediatric setting. MRI is a radiation-free imaging technique that can be used for repeated assessments of lung structure throughout life [4]. Furthermore, functional proton lung imaging through Matrix Pencil (MP) MRI can be used to simultaneously assess regional perfusion and ventilation defects without contrast agents or breathing manoeuvres [5, 6].

Historically, young patients received sedation, which increased the procedure duration and potential for adverse events. Data on MRI feasibility in children have either reported on children older than six years or children younger than six years under sedation [7]. This study aimed to investigate the feasibility of unsedated lung MRI and compare the success rates to those of spirometry and nitrogen multiple breath washout (N2-MBW) in young children with CF.

METHODS

This was a prospective, observational, single-centre study at the University Children's Hospital of Bern, Switzerland. Children with CF diagnosed following new-born screening from nine centres all over Switzerland were enrolled in the Swiss CF Infant Lung-Development (SCILD) cohort and invited to participate in a study visit in early childhood. The SCILD study protocol has been published previously [8].

Participants underwent N2-MBW, fractional exhaled nitric oxide, spirometry, body plethysmography, prick test, sweat test, oropharyngeal swab, and finally functional and structural MRI on the same day, in that order. Only N2-MBW, spirometry, and MRI data are considered in this letter.

N2-MBW was performed (Spiroware 3.3.1, Exhalyzer D; Eco Medics, Duernten, Switzerland) according to consensus [9]. Quality control and re-analysis were performed as previously described [10]. Spirometry (Jaeger MasterScreen; CareFusion, Hochberg, Germany) was performed and quality controlled according to guidelines [11].

Families were provided with MRI preparation materials, consisting of child-friendly videos, showing the positioning in the bore and scanning protocol, to allow families to playfully mimic the MRI experience at home. All children were attempting an MRI scan for the first time. Most children had previously been exposed to lung function testing (100% for spirometry, 54% for MBW). MRI was performed on a 1.5T whole-body scanner (MAGNETOM Aera; Siemens Healthineers, Erlangen, Germany). No sedation was applied. Parents and caregivers could accompany the child into the scanner cabin. Functional scans consisted of free-breathing multi-slice acquisitions [5, 12]. Following functional imaging, a local lung MRI protocol was used [6]. Structural sequences consisted of respiratory triggered coronal, T2-weighted fast spin-echo with fat saturation and steady-state gradient echo sequence and 3D T1/T2-weighted ultra-fast steady state free precession. Coronal and transverse T2-weighted single-shot fast spin-echo was performed as multi-breath-hold in patients older than 5 years or during free breathing in younger patients. In children older than 5 years, an axial T1-weighted spoiled gradient echo sequence was also performed during breath-hold manoeuvres. No contrast agent was applied. An experienced pediatric radiologist rated image quality per sequence on a 5-point Likert scale (1-no diagnostic quality; 2- low quality to 5-excellent quality), overall movement (5-no movement), and counted the number of repeated sequences.

The primary outcome was test feasibility defined as the number of acceptable tests divided by the number of attempted tests. For spirometry, we examined tests with acceptable FEV_t (FEV_1 or $FEV_{0.75}$) only and acceptable FEV_t and FVC separately. For MBW, we include tests with an acceptable lung clearance index (LCI). We examined feasibility of structural and functional MRI separately, to account for children stopping the procedure after completing

the functional sequences. For functional MRI, an acceptable test was defined as a completed scanning protocol and diagnostic image quality suitable for post-processing (Matrix pencil decomposition) [12]. For structural MRI, an acceptable test was defined as a completed scanning protocol and diagnostic image quality suitable for analysis with a dedicated disease severity score [13].

To examine the impact of age on feasibility for each test, we performed logistic regression analysis with robust standard errors and calculated point estimates and 95% confidence intervals. Statistical analysis was performed in Stata 17 (StataCorp, College Station, TX, USA).

RESULTS

Thirty children with cystic fibrosis (57% female) were recruited at 4 years (median [range]: 4.0 years [3.3 to 4.7]) and 52 (48% female) were recruited at 6 years (6.5 years [5.3 to 7.8]). Overall feasibility was 72% for functional MRI, 71% for structural MRI, 84% for LCI, 84% for FEV_t and 54% for FEV_t and FVC. In the children aged 3 to 4.9 years feasibility was 33% for functional MRI, 33% for structural MRI, 80% for LCI, 90% for FEV_t and 30% for FEV_t and FVC. In the children aged 5 to 7 years feasibility was 96% for functional MRI, 94% for structural MRI, 86% for LCI, 81% for FEV_t and 65% for FEV_t and FVC. The feasibility for functional and structural MRI was significantly lower in younger children, particularly those aged 3-4 years, compared with the older age group (5-7 years). Results from the logistic regression are shown in Figure 1.

Twenty-two children refused to attempt the MRI protocol before lying in the scanner. All children who attempted the MRI completed the full scanning protocol, except one child who stopped the structural MRI scan after an acceptable functional scan. As MRI technicians were allowed to repeat single sequences, adapt field of view and number of slices for standard product sequences there were no scans corrupted by incomplete coverage of the lung or artefacts. Children who completed the scan achieved good quality imaging data. All children attempted the MBW and spirometry measurements and unacceptable tests were due to inadequate test quality.

The total MRI scan duration was 25.1 (±4.6) minutes. The functional scans took 7.9 (±1.8) minutes and structural scans took 17.2 (±3.7) minutes. In fifteen examinations, one or more sequences had to be repeated (average 1.7 repeated sequences). The MRI scans had little movement artefact and were deemed high quality by the radiologist, with an average of 4.2

points on a 5-point Likert scale. The highest quality scans were the T2-weighted single-shot fast spin-echo (mean ± SD: 4.0 ±0.7) and steady-state gradient echo (4.0 ±0.5) sequences. The T1-weighted spoiled gradient echo sequence was successfully performed in all children over the age of 5 years but had the lowest image quality (2.9 ±0.6).

DISCUSSION

This is the largest study to report MRI feasibility in unsedated, MRI-naive young children with CF. Our data indicates that lung MRI is feasible in young children without the need for sedation and has a similar success rate to spirometry and the MBW technique in children from 5 years of age onwards. In children younger than 5 years, unsedated MRI remains challenging.

There have been limited studies examining the feasibility of lung MRI in unsedated young children. In a pilot study of seven infants and children younger than 4 years of age, free-breathing helium-3 hyperpolarized MRI was feasible in all subjects [14], however limited worldwide supply of helium-3 has driven the field towards xenon-129 MRI, which requires breath holds maneouvres that are challenging in young children [15]. Imaging of non-sedated infants has also been shown to be possible via feed-and-swaddle approaches [16]. Generally, studies examining feasibility of lung MRI have either performed the scans in sedated children, excluded children younger than seven years, or excluded children incapable of performing a 16-s breath-hold [7, 17]. Our data indicate that high quality lung MRI images are possible in unsedated young children. Feasibility increased with age, with higher feasibility in children aged 5-7 years, compared with 3-4 years.

MRI feasibility in our study was primarily reduced by the child refusing to attempt the scan, whereas feasibility in lung function was mostly impaired by poor test quality. These data indicate that home preparation and MRI familiarization resources may be important to achieve higher success rates. Once in the scanner, all except one child were able to complete the full protocol and achieve good quality images.

These data are encouraging for the use of lung MRI for routine application in a paediatric outpatient setting. Scan durations fit within the time-efficient workflows of a modern radiology department. The MP-MRI technique can be performed using standard MRI scanners, with no specialized equipment or personnel, and without the need for intravenous

contrast agents or complicated breath manoeuvres, making it attractive for surveillance of young children.

One weakness of this study is the lack of systematic feedback from patients and caregivers. Additional preparation with a mock scanner could be undertaken, as this has been shown to increase success rates [18]. However, this was not possible in our study as participants were travelling from external centres. Participants in our study also completed multiple assessments before attempting the MRI scan and the order of testing was not randomized. As a result, the feasibility of lung MRI may be under-estimated in our study. In addition, recently published 3D MRI sequences that allow for increased spatial resolution, were not available at the commencement of our study in 2018 [19].

To conclude, unsedated lung MRI is feasible in young children with CF from the age of 5 years onwards. Feasibility increases with age and is comparable to lung function testing. Functional and structural imaging is possible through free-breathing proton MRI without the need for contrast agents or maximal breathing manoeuvres.

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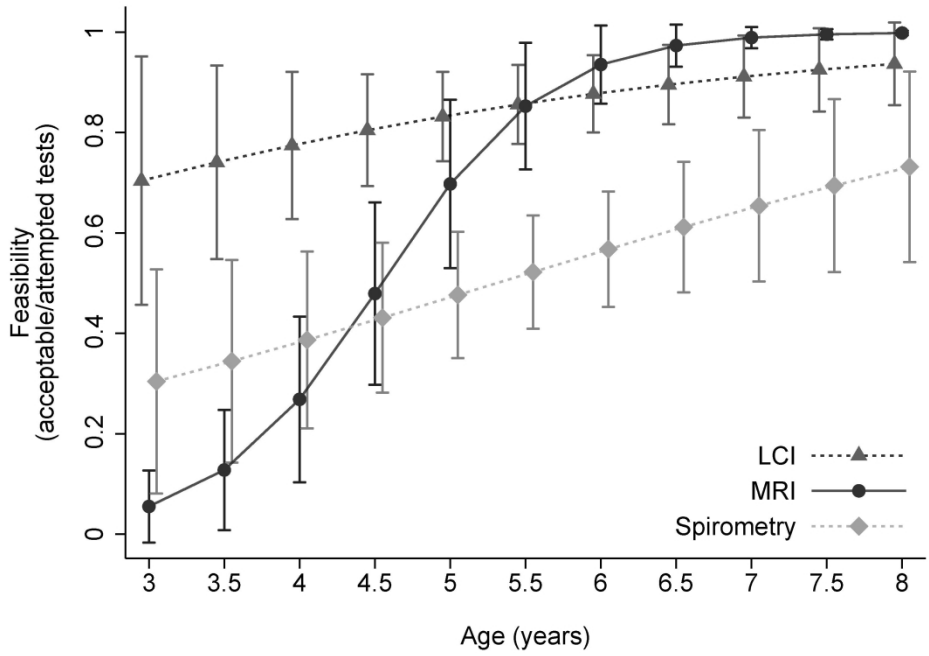
Conflict of Interest: Alexander Moeller reports lecture fees from and participation in advisory boards at Vertex inc, outside the submitted work. Philipp Latzin reports grants and lecture honoraria from, and participation on advisory board at Vertex and Vifor; lecture honoraria from OM Pharma; participation on advisory boards at Polyphor, Santhera (DMC), OM Pharma, Sanofi Aventis; outside the submitted work. Kathryn Ramsey participated on the Global Lung Initiative MBW Task Force, outside the submitted work. All other authors have nothing to disclose.

FIGURE

Figure 1: Predicted probability of test feasibility by years of age for MRI, LCI and spirometry as estimated from logistic regression. Predicted probability of a successful test is depending on age and increases over time. Solid and dotted lines represent fitted values from logistic regression, with marginal point estimates and whiskers represent 95% confidence intervals. Probability for MRI is given for structural MRI; Spirometry is given for successful FEV_1 and FVC.

LCI: Lung clearance index; FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity.


Feasibility
(acceptable/attempted tests)
0
0.2
0.4
0.6
0.8
1
3
3.5
4
4.5
5
5.5
6
6.5
7
7.5
8
Age (years)
LCI
MRI
Spirometry

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