The Application of Advanced Imaging Techniques for the Assessment of Paediatric Chest Disease

Dr Thomas Robert Semple FRCR, MBBS, BSc(hons)
CID 01301019

National Heart and Lung Institute, Imperial College London

Thesis Submission for the award of MD(res)
With unlimited thanks to Katriina, my wife, for her support throughout; my supervisors for their on-going support and encouragement and to Dr Catherine Owens for the inspiration to choose to follow a career in paediatric imaging.
Declaration of Originality

I declare that the work contained within this thesis is my own or is appropriately referenced.

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**Abstract**

**Introduction** –

Cystic fibrosis (CF) and primary ciliary dyskinesia (PCD) both result in chronic suppurative lung disease with significant resulting morbidity and early mortality. Many clinical and academic groups advocate biennial or even annual CT surveillance from as early as 2 years of age, but new therapies and increasing life expectancy lead to concerns over the use of repeated CT imaging. There are many recent studies showing promise of MRI for structural lung imaging MRI based measures of lung function. Both CF and PCD result in multisystem disease and whilst much of the morbidity results from lung disease, monitoring of extrathoracic disease is likely also relevant.

**Aims and objectives** –

1) To set up a clinically feasible, multisystem (lung, sinonasal and upper abdominal visceral) quantitative MRI examination for the investigation and follow up of CSLD

2) To evaluate novel imaging biomarkers of CF and PCD disease severity
Hypotheses –

1) Combined structural and quantitative MRI assessment of the thorax can provide comparable information to CT such that follow up imaging via CT could be replaced with MRI.

2) Quantitative MR measures of ventilation correlate with established clinical measures of ventilation (LCI and FEV$_1$) and provide additional spatial information.

3) A multisystem MRI assessment can provide new extra-thoracic imaging biomarkers of CF and PCD disease severity whilst being better tolerated by patients than current multimodality imaging follow up.

Methods –

People with CF or PCD referred for clinically indicated lung CT were prospectively recruited to undergo MR imaging of the lungs, liver and paranasal sinuses.

Structural lung imaging was optimised for speed of acquisition using T2 BLADE imaging, in axial and coronal plane, during breath holds rather than more conventional respiratory triggering. Images were scored by two observers using the Eichinger scoring system and compared to CT structural scores using the CFCT scoring system.
Lung T1 mapping was performed via free breathing IR-HASTE and T1 and T2 mapping performed via breath hold ufbSSFP imaging.

Functional lung imaging was performed via pre and post hyperoxygenation ufbSSFP T1 mapping, free breathing dynamic oxygen enhanced IR-HASTE imaging (OE-MRI) and non-contrast ufbSSFP-based matrix pencil decomposition imaging of ventilation and pulmonary perfusion.

Lung T1 maps included the superior portion of the liver enabling simultaneous liver T1 mapping.

A multiparametric paranasal sinus protocol was devised containing structural (T1 and T2 TSE), susceptibility and diffusion weighted sequences for the calculation of sinus volume, mucus volume and mucosal volume, presence or absence of artefact associated with infective micro-organisms and calculation of mucus and mucosal diffusion.

Participant tolerability of MR imaging assessed via a bespoke questionnaire, completed before and after both CT and MR imaging.

Multiple breath wash-out testing was performed on the day of the MRI and spirometry, antibiotic usage, abdominal ultrasound and sheer wave elastography collected retrospectively from the electronic patient record.
Results –

22 participants were recruited, all of whom completed the hour-long MRI protocol. The median age was 14 years (range 6 – 35).

2-plane structural lung imaging was acquired in a total of 2 minutes 4 seconds with only a single participant reporting difficulties with the required breath holds. Interclass Correlation Coefficients of interobserver variability in MRI scores were comparable to CT (0.877-0.965 compared to 0.877-0.989 respectively) suggesting good image quality with strong correlation between MR and CT component scores (bronchiectasis/bronchial wall thickening r=0.828,p<0.001; mucus plugging r=0.812, p<0.001; parenchymal score r=0.564 – 0.729, p<0.001 – 0.006).

Median lung T1 did not correlate with clinical markers of disease severity, but median lung T2 demonstrated strong correlation with CT bronchial wall thickening (r=-0.655, p=0.001) and LCI2.5 (r=-0.540, p=0.046), most likely representing a surrogate of pulmonary perfusion (most pulmonary T2 signal likely originates from the pulmonary blood pool).

Significant ufbSSFP enhancement was demonstrated post hyperoxygenation, but the degree of enhancement did not correlate significantly with clinical measures of disease severity. There was, however, very strong correlations between matrix pencil decomposition ventilation fraction and LCI2.5 (r=0.831, p=0.001) and CFCT scores (r= up to 0.731, p=<0.001).
Significant correlation was also demonstrated between measures of ventilation heterogeneity (oxygen wash-out time skew and kurtosis) and both LCl_{2.5} (r=0.591, p=0.013) and CFCT component scores (r= up to 0.718, p<0.001).

Liver T1 values did not correlate with evidence of liver disease on liver function tests or ultrasound imaging, but interpretation was severely limited by the very small number of recruits with CF liver disease.

Sinus imaging was the last part of the protocol with failed analysis in only one patient from too much motion (a 6 year old). Association was demonstrated between exacerbation frequency and opacification of maxillary sinuses by mucusa (p=0.074), between CT hyperinflation score and increasing levels of mucus susceptibility artefact (0=0.028), between exacerbation frequency, CT bronchial wall thickening and mucus plugging and increased sinus mucus diffusion (r=0.581, p=0.048, r=0.744, p=0.006 and r=0.633, p=0.019 respectively) and between CT hyperinflation, bronchiectasis and bronchial wall thickening scores and increased sinus mucosal diffusion (r=-0.847, p=0.016; r=-0.542, p=0.017 and r=-0.427, p=0.069 respectively).

A third of recruits stated that they would opt for MR imaging over CT imaging in the future and whilst 41% reported difficulties staying still for
the MRI, respiratory image post processing was successful in all participants, with no parts of the MRI studies repeated.

**Conclusion –**

Multisystem lung, liver and sinus MRI is feasible, well tolerated by people with CF or PCD, down to the age of 6 years, and provides gross structural imaging of sufficient quality to replace CT for lung imaging surveillance. Furthermore, the addition of functional lung imaging provides quantitative outputs which correlate well with clinically established lung function tests with the benefit of spatially localised lung function and additional quantitative measures of relevant extrapulmonary disease, within a single ionising radiation free examination. The data from this study have supported funding for future work addressing short, medium and long-term repeatability and longitudinal trends both in times of disease stability and over the course of an infective exacerbation.
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Glossary

3D FLASH  Fast Low Angle Shot
ABPA  Allergic Bronchopulmonary Aspergillosis
Abx  Antibiotics
ADC  Apparent Diffusion Coefficient
ASL  Arterial Spin Labelling
ATS  American Thoracic Society
AU  Arbitrary Units
BEIR  Biological Effects of Ionizing Radiation Committee
BMI  Body Mass Index
BWT  Bronchial Wall Thickening
Bx  Bronchiectasis
BxBWT  Combined Bronchiectasis and bronchial wall thickening
c-AMP  cyclic adenosine monophosphate
CCC  Concordance Correlation Coefficient
CF  Cystic Fibrosis
CFCT Scoring  A Semiquantitative CT scoring system specifically designed for cystic fibrosis imaging
CFLD  Cystic Fibrosis Liver Disease
CFQ-R RSS  Cystic Fibrosis Questionnaire-Revised Respiratory Symptoms Scale
CFSPID  Cystic Fibrosis Screen Positive Indeterminate Diagnosis
CFTR  Cystic Fibrosis transmembrane conductance regulator
CI  Confidence Interval
COPD  Chronic Obstructive Pulmonary Disease
CSF (spaces)  Cerebrospinal Fluid
CSLD  Chronic Suppurative Lung Disease
CT  Computed Tomography
DIOS  Distal Intestinal Obstruction Syndrome
DLP  Dose Length Product
DNA  Deoxyribonucleic acid
DWI  Diffusion weight imaging
ECG  Electrocardiogram
Eichinger scoring  A semiquantitative visual scoring system specifically designed for CF imaging via MRI
EPR  Electronic patient record
ERS  European Respiratory Society
Exhalyzer D  A multiple breath washout system using exhaled nitrogen as a tracer gas during the inhalation of 100% oxygen
FEV$_1$  Forced expiratory volume in 1 second
FLASH  A high speed dual source spiral CT mode designed to limit motion artefact in cardiac and respiratory imaging
Fourier decomposition  A mathematical process enabling the separation of two superimposed signals, in this case used to isolate respiratory and pulmonary perfusion signals
FRC  Functional residual capacity
FVC  Forced vital capacity
HASTE  Half-Fourier Acquisition Single shot Turbo spin Echo
HCC  Hepatocellular carcinoma
HRCT  High resolution computed tomography
HU  Hounsfield Units
ICC  Intraclass Correlation Coefficient
ILD  Interstitial Lung Disease
Image registration  The process of aligning images. Used in conjunction with "non-rigid" meaning each image is deformed to allow dynamic assessment of signal change by removing or at least accounting for lung motion
IQR  Inter-Quartile-Range
IR-HASTE  Inverse recovery half Fourier acquisition turbo spin echo
IR(ME)R  Ionising Radiation in Medical Examinations Regulations
ISHAK score  A liver fibrosis staging system
IV  Intravenous
LCI 2.5  Lung Clearance Index
LLL  Left Lower Lobe
LUL  Left Upper Lobe
Matrix Pencil  A newer form of Fourier Decomposition imaging (see above)
Decomposition  enabling formation of better quality, less noisy ventilation and perfusion images based on lung motion and changes in blood volume throughout the cardiac cycle
MBW test  Multiple breath wash-out testing (used to calculate LCI)
METAVIR score  An ultrasound sheer wave elastography based staging system for liver fibrosis
MOLLI  Modified Look-Locker Inversion Recovery - the sequence most T1 mapping is based on across multiple organ systems
MP  Mucus plugging
MP perfusion  Matrix Pencil Perfusion imaging
MP ventilation  Matrix Pencil Ventilation imaging
MR  Magnetic Resonance
MRI  Magnetic Resonance Imaging
Non-rigid image registration  Described above - deformation of images such that, in this case, respiratory motion can be removed from a series of images
NPV  Negative predictive value
NSIP  Non-Specific Interstitial Pneumonia
NTM  Non-Tuberculous Mycobacteria
OE-MRI  Oxygen Enhanced MRI
OR  Odds Ratio
PACS  Picture Archiving and Communications System
PCD  Primary Ciliary Dyskinesia
PD  Proton Density
Phase scout  A method of respiratory triggering used in MRI to replace respiratory belts and liver dome scouts
PO  Per Oral
pO2  Partial pressure of oxygen
PPV  Positive predictive value
PRAGMA-CF  Perth-Rotterdam Annotated Grid Morphometric Analysis - a form of computer assisted semi-quantitative visual scoring of CT images specifically designed for cystic fibrosis imaging

PROPELLER  Periodically Rotated Overlapping Parallel Lines with Enhanced Reconstruction

RLL  Right Lower Lobe
RML  Right Middle Lobe
ROI  Region of interest
RR  Relative Risk
RUL  Right Upper Lobe
Sheer wave  A form of ultrasound based elastography - measuring liver stiffness through calculating sound transmission velocity - used to grade liver fibrosis non-invasively

ShMOLLI  Shortened Modified Look-Locker Inversion - a short version of the MOLLI technique often used for T1 mapping

SPECT/CT  Single positron emission computed tomography coupled to conventional x-ray computed tomography

STIR  Short Tau Inversion Recovery
T (as in 1.5T or 3T MRI)  Tesla

T1 Mapping  Determining T1 relaxation in each voxel of an imaged section of tissue
T1 TSE  T1 weighted Turbo spin echo
T1 VIBE  T1 weighted Volume Interpolated Breath-hold Examination
T2 BLADE  T2 weighted radial acquisition MRI
T2 HASTE  T2 weighted Half Fourier Acquisition Turbo Spin Echo
T2 Mapping/signal etc  Determining T2 relaxation in each voxel of imaged section of tissue
T2 TSE  T2 weighted Turbo Spin Echo
TE  Echo time
TR  Repetition time
ufbSSFP  ultrafast balanced Steady State Free Procession - a non-proprietary MR sequence developed by our collaborators in Basel

UIP  Usual Interstitial Pneumonia
UTE  Ultra-short Echo Time
VDP  Ventilation Defect Percentage
VIBE  Volume Interpolated Breath hold Examination
VIPS  Ventilation Inflammation Perfusion and Structure - a multiparametric lung imaging MRI protocol under investigation by a network of lung MRI centres

Voxel  3D pixel
VQ  Ventilation:perfusion ratio
ZTE  Zero Echo Time
Chapter 1 – Introduction, hypotheses and aims

1.1 Cystic Fibrosis

Cystic fibrosis (CF) is caused by mutations on chromosome 7, in the gene encoding the CF transmembrane conductance regulator (CFTR) protein. CFTR acts as a cyclic adenosine monophosphate (c-AMP) regulated chloride and bicarbonate channel, which controls salt and water movement, into and out of epithelial cells throughout the body [1,2]. Disease-causing mutations in CFTR result in abnormally thick secretions in various organs. These secretions lead to a number of pathologies, most significantly sinopulmonary disease (airway infection and resulting inflammation with subsequent small and large airways disease, nasal polyposis and chronic rhinosinusitis) and gastrointestinal disease (recurrent pancreatitis, pancreatic insufficiency and resulting malabsorption, chronic hepatic disease and intestinal problems such as meconium ileus and distal intestinal obstruction syndrome)[3,4].

1.1.1 Mutation classes

Over 2000 mutations in CFTR have been identified to date, with the well-known Phe508del representing the most common disease-causing CFTR mutation in the UK and USA (around 90% of people with CF have one or two copies of Phe508del)[3,5]. To further understanding and direct therapy, mutations are grouped into classes according to their molecular result.
Class I mutations are non-sense mutations resulting in either no CFTR synthesis or low levels of truncated CFTR. Class II mutations include folding or maturation defects, again resulting in minimal plasma membrane CFTR (this group includes the Phe508del mutation). Class III mutations are referred to as “gating defects”. Whilst CFTR reaches the plasma membrane limited channel opening results in non-function of the CFTR ion channel. This class includes the G551D mutation (now known as Gly551Asp). Class IV mutations result in reduced chloride conductance. Abnormal splicing is termed a class V mutation with reduced numbers of CFTR proteins at the plasma membrane and class VI mutations result in decreased cell surface CFTR stability. Class I – III mutations result in no (Class I) or minimal (Class II and III) CFTR function and cause the classic CF phenotype described above[4].

1.1.2 Advances in therapy and survival -

When first described in 1938, CF was almost uniformly fatal in early childhood [6], but now, significant advances have led people with cystic fibrosis to survive well into adulthood. According to the most recent summary from the UK Cystic Fibrosis Registry, median survival for a person born in the UK with CF is currently at least 49.1 years [7]. Thanks to newborn screening programs, the vast majority of people with CF in the UK are now diagnosed in infancy with subsequent increases in survival [8,9], better lung function at age 15 years [10] and better nutritional status [11,12].
Airway clearance is a mainstay of CF therapy, with inhaled DNase, hypertonic saline and/or mannitol added to thin secretions. Although there is evidence of reduced rate of pulmonary exacerbations [13] and improved lung function [14,15] comparative trials of varying approaches to airway clearance are generally lacking and are limited by relatively blunt outcome measures such as spirometry [4,16].

Recurrent infection has been clearly linked to declines in lung function with infection by *Pseudomonas aeruginosa, Staphylococcus aureus* and *Aspergillus* particularly common [17–19]. Use of inhaled tobramycin is now commonplace in the treatment of chronic *Pseudomonas aeruginosa*, with associated improvements in lung function and reduced exacerbation frequency [20], but non-tuberculous mycobacterial infection is a growing concern. For example *Mycobacterium abscessus* is linked to significant declines in lung function, is difficult to treat, often requiring prolonged repeated courses of antibiotics and is a contraindication to lung transplantation [21,22].

Whilst airways clearance and prompt treatment of infective exacerbations is clearly of on-going importance, the recent emergence of small molecule therapies is promising a paradigm shift in CF care in the 21st century. Ivacaftor (Kalydeco®) is a CFTR potentiator which increases the time the CFTR channel remains open. It was initially tested in Class III gating mutations (most commonly G551D) [23]. Ivacaftor has been shown to significantly improve forced expiratory volume in 1 second (FEV₁), reduce
sweat chloride concentration, improve quality of life scores, decrease the frequency of pulmonary exacerbations, increase weight gain and improve markers of pancreatic exocrine function in children [24–26] but only targets mutations resulting in cell surface CFTR. Ivacaftor can, however, be combined, as so-called ‘double’ therapy as Lumacaftor/Ivacaftor (Orkambi®) or tezacaftor/ivacaftor (Symkevi®), with a ‘corrector’ molecule which alters misfolded CFTR protein and improves its trafficking to the cell surface such that Phe508del mutations can be treated. Addition of Lumacaftor to Ivacaftor resulted in modestly improved FEV\textsubscript{1} and a 33% reduction in pulmonary exacerbation rate[27–29] with a reduction of number of days on antibiotics from 14.9 to 5.8 in a retrospective observational study by Diab-Caceres etc al. [30] a 55% reduction in hospitalisations in a cohort study by Feng et al [31] and a 20.7% increase in quality of life year scores [32] Triple therapy with Elexacaftor/Tezacaftor/Ivacaftor (Kaftrio ®) extends treatment to those with minimal function CFTR mutations and demonstrates better results in Phe508del homozygous patients than Lumacaftor/Ivacaftor [33–35].

1.1.3 Multiple breath washout testing -

Interventional trials in CF, including trials of small molecule therapies have largely relied on rather noisy outcome measures such as spirometry, exacerbation frequency, quality of life questionnaires (CFQ-R) and BMI [35]. As the CF population becomes healthier, with far more difficult to detect disease until a more advanced age, the need for more sensitive testing becomes more apparent. One such method is multiple breath washout
testing. First described in 1952 as a two-phase test measuring the wash in and washout phases of an inert gas, it is often now performed as a single-phase washout test and can be performed using endogenous (e.g. nitrogen) or exogenous (e.g. SF₆) tracer gas [36]. The test begins in room air. The concentration of exhaled nitrogen is then continuously measured, alongside exhaled volume, as the subject breathes 100% oxygen. As the 100% oxygen is breathed in it replaces the nitrogen in the patients lungs. The test is finished when the concentration of exhaled nitrogen reaches and arbitrary 2.5% of the starting concentration. The number of lung volume turnovers required to reach this 2.5% target is the key output of this test - the lung clearance index (LCI) and reflects ventilation homogeneity – the worse the airways disease, the more heterogeneous the ventilation and the higher the LCI [37].

It is well known that spirometry is relatively insensitive to structural lung disease with one study demonstrating increasing bronchiectasis on serial CT despite stable or even improving spirometry in 27/119 patients and structural lung disease frequently demonstrated on CT in those with normal spirometry [38]. LCI, however, is far more sensitive, having been found to be elevated in 85-94% of school age children with CF with abnormalities on CT [39]. In children and young adults (6-26 years of age) with normal spirometry but abnormal CT, LCI had a positive predictive value for structural lung disease of 88%, but a low negative predictive value of between 44% and 63% [40,41]. Age plays a key role in diagnostic accuracy in CF with far more subtle disease in infants requiring far more sensitive tests. AREST CF showed correlation between LCI and air-trapping on CT in
infants, but no significant correlation with bronchiectasis. By preschool and school age, LCI’s positive predictive value for bronchiectasis on CT reaches 85% with a negative predictive value of 55% [42,43]. A key weakness of LCI is its ability only to read-out from communicating airways. If an airway is completely obstructed, the lung distal to the obstruction does not contribute to exhaled gas and forms a blind-spot. This is particularly important in follow up studies, where it is possible that a significant improvement in airways disease results in aeration of previously unventilated lung segments and subsequently a paradoxical ‘worsening’ of LCI compared to baseline, despite successful treatment.

1.2 Primary Ciliary Dyskinesia

There are more than 35 known inherited ciliopathies, but prevalence is low at around one in 10-20,000 globally. Most primary (often known as syndromic) ciliopathies do not have mutations associated with diseased motile cilia, but when motile cilia are affected respiratory disease may result [44]. Primary ciliary “dyskinesia” (PCD) is a term applied to a group of, mostly autosomal recessive, disorders of ciliary structure, that results in abnormal or absent ciliary motion. In much the same way that abnormally thick secretions cause multisystem disease in cystic fibrosis, abnormal ciliary function in PCD results in failure of normal mucociliary clearance leading to lower lobe predominant bronchiectasis, chronic rhinosinusitis, otitis media, male and female sub-fertility and increases the incidence of
ectopic pregnancy. Dysfunctional nodal cilia in embryonic life result in disorders of organ situs in approximately 48% of PCD patients[45,46].

Although more common in certain ethnic groups and small communities, the very low incidence PCD means that its optimal therapy is much less well established than that of cystic fibrosis, with studies often including a small number of PCD patients within a group of people with ‘non-CF bronchiectasis’. Most therapeutic pathways for PCD are, therefore, taken directly from CF care [47,48]. Airways clearance is considered a ‘pillar’ of PCD therapy [48,49] and much like CF, infections such as H influenza, S pneumonia, S aureus, M catarrhalis and P aeruginosa play an important role in pulmonary health decline with trials of long term azithromycin showing significant reductions in exacerbation frequency [47,50,51].

1.3 Imaging lung disease in CF and PCD

1.3.1 Chest Radiography
Chest radiographs are cheap, reproducible, readily available and require minimal radiation exposure. The mucus plugs and resulting alveolar over-distension (air-trapping), collapse / consolidation, bronchial wall thickening and bronchiectasis commonly found in patients with CF and PCD, are demonstrated as nodular or mottled shadows, hyperinflation with flattening of the diaphragmatic contours, confluent opacification, linear shadows or ring shadows respectively[52].
A number of scoring systems have been developed allowing the conversion of visual radiographic appearances into a numeric score to facilitate longitudinal follow up studies, more strictly define acute pulmonary exacerbations and for short-term evaluation of treatment efficacy during times of acute exacerbation. Many of these scoring systems integrate radiographic scores with measures of general activity, nutritional status, physical assessment, pulmonary function tests, sputum culture results and other non-imaging information [53]. Examples of scoring systems utilising radiographic findings include the Scwachman-Kulczycki[54], Chrispin-Norman[52], Brasfield (Birmingham)[55], Wisconsin[56] and Northern[57] scores.

The Chrispin-Norman score, for example, assigns scores for chest configuration (sternal bowing, diaphragmatic depression and spinal kyphosis) and quadrant-based scores for “bronchial line shadows”, “mottled shadows”, “ring shadows” and “large shadows” (lobar or segmental collapse / consolidation). These are all scored as 0 (not present), 1 (present, but not marked) or 2 (marked).

These scoring systems have been shown to be reproducible (a head to head comparison study reported ICCs of 0.84 for Shwachman-Kulczychi, 0.84 for Chrispin-Norman, 0.84 for adjusted Chrispin-Norman, 0.82 for Brasfield, 0.80 for Wisconsin and 0.76 for Northern) and to correlate with relevant clinical features (see table below, adapted from S. Terheggen-Lagro et al 2003)[53,58–60].
<table>
<thead>
<tr>
<th></th>
<th>Shwachman-Kulczycki</th>
<th>Chrispin-Norman</th>
<th>Adjusted Chrispin-Norman</th>
<th>Brasfield</th>
<th>Wisconsin</th>
<th>Northern</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEV₁ (%predicted)</strong></td>
<td>0.73**</td>
<td>-0.77**</td>
<td>-0.78**</td>
<td>0.72**</td>
<td>-0.72**</td>
<td>-0.72**</td>
</tr>
<tr>
<td><strong>FVC (%predicted)</strong></td>
<td>0.74**</td>
<td>-0.73**</td>
<td>-0.74**</td>
<td>0.69**</td>
<td>-0.69**</td>
<td>-0.72**</td>
</tr>
<tr>
<td><strong>Exacerbations</strong></td>
<td>-0.68**</td>
<td>0.71**</td>
<td>0.69**</td>
<td>-0.69**</td>
<td>0.73**</td>
<td>0.71**</td>
</tr>
</tbody>
</table>

Pearson's correlation coefficients from S Terheggen-Lagro et al, 2003

**p<0.01

As reproducible as these scores have been shown to be, as with spirometry and LCI, the increasing availability and lower radiation doses of modern CT technology has led to plain radiographic scoring being largely superseded by more sensitive CT scoring systems.

1.3.2 Computed Tomography (CT) -

The thin, three-dimensional cross-sectional images produced via CT provide a far higher sensitivity and specificity for the features of both CF and PCD described above[61]. The ability to resolve/differentiate individual elements of disease such as bronchiectasis and bronchial wall thickening, has led to numerous CT-specific scoring systems, several of which remain commonly used imaging biomarkers in current-day imaging research.
1.3.2.1 CFCT scoring

The CF-CT score, based on the Brody score, divides the lungs into 6 lobes, with the lingula counted as a lobe is its own right. Each lobe is assigned scores for bronchiectasis, bronchial wall thickening, mucus plugging, parenchymal disease (atelectasis / consolidation, bullae and cysts, ground glass) and “air-trapping” (the low attenuation attributed to combined trapped air and reduced local perfusion). Multipliers are then applied according to the severity and extent (central vs. peripheral) of each finding and scores presented either individually as disease component scores or added together to provide composite summary scores[62].

Studies have linked both composite and component scores with clinical outcomes. Tepper et al found each point increase in bronchiectasis score was associated with a 10% increase in the number of pulmonary exacerbations in the following year and correlated with symptoms reported via the CFQ-R questionnaire [63]. CT scores (particularly bronchiectasis component scores) change over time and have been found to be more sensitive to decline than spirometry[64] and response of bronchial wall thickness and mucus plugging component scores to treatment of respiratory exacerbation has been demonstrated[65]. The combination of CFCT scores and quantitative CT scores have been shown to predict disease progression with parenchymal abnormalities and total lung score at baseline and progression of bronchiectasis over one year predictive of worsening bronchiectasis at 2 years post baseline in a group of school aged children with CF [66]. These findings highlight both the relevance of
structural-functional relationships in CF and the potential of structural imaging-derived biomarkers as intermediate or surrogate end points for use in CF trials.

Whilst global (whole lung) summary scores show high levels of reproducibility (reported ICCs from 0.74-0.98), individual component scores, particularly scores for bronchial wall thickening and “air-trapping”, have considerably poorer reported reproducibility (ICCs of 0.4-0.61 and <0.4 respectively)[67]. As described by Calder et al, two reviewers can assign identical composite scores to a set of images whilst disagreeing on every single individual component, thus making the reporting of composite scores and their variability potentially meaningless[62]. Clearly the need for objective measures of disease severity will never be completely met by scoring systems based solely on visual assessment.

1.3.2.2 PRAGMA scoring

PRAGMA-CF – The Perth-Rotterdam Annotated Grid Morphometric Analysis method is an alternative approach to the semiquantitative visual scoring method of CFCT. Ten equally-spaced sections of a chest CT are overlaid with a grid and the presence of specific features of disease within each cell of the grid is labelled by a trained observer at a core-lab. Each cell gains a single label via a hierarchical system with bronchiectasis the highest priority feature, followed by mucous plugging, bronchial wall thickening, atelectasis and then normal lung. Features can then be quantified as present within a percentage of the total number of annotated cells. Trapped air is then
separately annotated on expiratory scan sections. This scoring system has been shown to be reproducible with intraobserver ICCs of 0.928-0.960 and interobserver ICCs of 0.851-0.938 for all features [68]. PRAGMA bronchiectasis scores correlate well with CFCT bronchiectasis scores and manual airway measurements on CT [69] and, at one year of age can predict progression of structural lung disease at 3 years (Pearsons 0.44, p=0.016) [68]. It is also sensitive to change in disease state with significant increases in disease extent and bronchiectasis extent following *P aeruginosa* infection [70].

1.3.2.1 Quantitative CT

Application of computational analysis and the relatively recent move from interrupted (interspaced) high resolution computed tomography (HRCT) to volume acquisitions (i.e. no gaps between sections) has lead to the development of a number of new, semi-automated, quantitative imaging techniques, with the potential to remove some of the issues surrounding reproducibility of visual scoring systems. E DeBoer et al used a computer algorithm to count bronchi and to quantify low attenuation regions as a percentage of lung area on interspaced CT sections. They found that the number of airways demonstrated and the extent of low attenuation on expiratory sections were significantly greater in children with CF than in matched controls. Peripheral airway counts correlated positively with bronchiectasis component Brody scores and negatively with lung function measures[71]. More advanced 3D methods have been employed using volumetric CT acquisitions in studies of many airways diseases, most
notably COPD and asthma. The 3D data allows curved reconstruction of the bronchial tree along centre lines, such that more accurate measurements of bronchial wall thickness and luminal area can be made “in-plane” with the bronchus, rather than at a tangent. Visualisation of the airways ‘in plane’ allows accurate measurement of inner and outer airway diameter and wall thickness, with measurement of the diameter of the adjacent pulmonary artery for normalisation and definition of airways dilatation – bronchiectasis [69,72]. Low attenuation areas can also be expressed as a percentage volume of computed whole lung volume, again leading to a potentially more accurate quantitative measure of abnormal lung [73]. Similar methods have been shown to identify and quantify bronchiectasis in PCD, but to date, no correlation of these quantitative CT outputs with other clinical measures of disease severity or progression has been investigated in PCD [74].

When intending to produce quantitative measures, such as airway diameter and wall thickness, from structural imaging tests, standardisation of imaging technique is essential. Studies have shown significant differences in measurements of airway diameter and wall thickness between paired inspiratory and expiratory CT scans in the same patients[72]. As a result, there have been significant efforts to introduce spirometer guidance of respiratory phase at the time of CT acquisition in children deemed old enough to comply (generally those over 5 years of age)[75].
It should also be noted that the sensitivity and specificity of all imaging techniques (and indeed all tests imaging or otherwise), quantitative or semiquantitative, are heavily dependent on the population to which it is applied. Thia et al. screened 65 infants with CT at one year of age following CF diagnosis via newborn screening. With the exception of air-trapping scores, they found the reproducibility of Brody2 scores (similar to CFCT scoring) in this population was so poor that CT screening at this age was deemed to be inappropriate (interobserver kappa values of 0.2 – 0.49) the same is likely to be true when applying automated techniques to populations with very mild disease, with the additional problem of increased motion artefacts and uncontrolled respiratory phase in infants and young children with CF [76].

1.3.2.2 Ionising Radiation in CT and cancer risk

Children are widely considered to be more sensitive to ionising radiation than adults, with rapid cell turnover throughout growth / development and longer lifespans in which to develop a secondary malignancy [77–79]. However, there are conflicting publications in the medical literature variably reporting no association between CT scanning and future cancer risk [80,81] or significant increases in the incidence of cancers, particularly leukaemia and brain cancers in people exposed to ionising radiation in the form of CT scanning during childhood [82,83].

It is worth mentioning that the radiation dose a patient receives during a CT scan is not measurable. Instead, it is estimated based on measurements from phantoms scanned as part of quality assurance programs.
Representative measures of dose such as volume CT dose index (CTDI\text{vol}) and dose length product (DLP) are helpful guides of individual patient exposures, but more accurate estimates of patient doses are via mathematical modelling (Monte Carlo modelling) based on anthropomorphic phantoms. Organs exposed as part of a set scan protocol (for example a chest CT would include thymus, breast tissue, heart, upper liver etc in addition to the lungs) are assigned tissue-weighting factors used to convert blunt measures of absorbed dose into an equivalent and then effective dose, the latter being used to assess resulting patient risk. These tissue-weighting factors are regularly updated in a report from the Biological Effects of Ionizing Radiation (BEIR) Committee, based on the most up to date studies [84]. Early data concerning the risk of ionising radiation exposure comes largely from retrospective studies of people exposed to very high levels of ionizing radiation (nuclear fallout from the bombs dropped on Hiroshima and Nagasaki and numerous nuclear accidents such as the Chernobyl reactor meltdown) many of which also resulted in significant exposures to non-radioactive, but significant environmental pollutants which may play a part in subsequent cancer induction. There is no doubt that at high doses, ionising radiation exposure has a linear relationship with cancer risk, however at the low doses encountered in diagnostic medical practice, this relationship is far more controversial. Historically, risk from higher dose exposures was extrapolated to lower doses (the so-called 'Linear No Threshold' model of risk) but several studies of populations exposed to high natural background levels suggest there may actually be a protective effect of low dose
exposures (so called radiation hormesis)[85]. As such, the ‘true’ risk of diagnostic radiology exposures to ionising radiation remains a topic of debate and active research.

There are several techniques which examine the effect of ionising radiation on tissues, both in vitro and in vivo, summarised in a review by Jánosiková et al [86]. Dicentric chromosome assays quantify the levels of aberrant chromosomes containing two centromeres, formed subsequent to DNA breakages with inappropriate repair resulting in one chromosome with two centromeres (dicentric) and one with no centromere (acentric). A small study demonstrated significantly higher levels of dicentric chromosomal aberrations in the peripheral lymphocytes of young children (0.4 – 9 years) following CT than levels seen in teenagers (10-15 years) following CT supporting the notion that young children are more radiosensitive [87]. Age dependant radiosensitivity was also demonstrated via this method by Gomolka et al [88]. Micronuclei assays demonstrate chromosomal loss and breakage in the form of small clusters of genetic material formed from fragments of damaged chromosomes, which appear as small spheres staining in the same manner as cell nuclei (hence the term ‘micronuclei’) [86]. Human studies have shown increased frequency of micronuclei in peripheral blood lymphocytes predicts the risk of future cancers [24 and 25]. Numbers of micronuclei have been found to increase after medical ionising radiation procedures in children with congenital heart disease, once a median threshold lifetime cumulative effective dose of 7.7 mSv is reached [89]. The importance of cumulative dose is supported by a study demonstrating no change in micronuclei within the reticulocytes of infants
2 hours before and 48 hours after their 1st CT, but significant increases in micronuclei within those with a history of prior CT scans [90].

Whilst the ionising radiation dose associated with diagnostic CT has decreased over the past decade, and low dose protocols have been implemented specifically for patients requiring frequent follow up examinations, concern persists regarding the risk of repeated CT examinations in inducing malignancy. A particularly thorough study conducted by Berrington de González et al modelled organ specific radiation exposure from a cystic fibrosis-specific low-dose follow-up CT protocol and applied the Biological Effects of Ionising Radiation (BEIR) VII radiation risk models to calculate the increase in risk of malignancy resulting from an annual CT follow-up program. Assuming a median survival of 36 years, the risk increase was 0.02% in male patients and 0.07% in female patients (the increased risk in females relating to irradiation of breast tissue). However, given the increasing longevity of CF patients, they also investigated the associated risk at a median survival of 50 years (a median survival now reached) and found the risk increased to 0.08% in males and 0.46% in females. Whilst there are many ways of reducing radiation exposure (starting monitoring from age 18 once the per scan risk drops, scanning every other year, dropping the dose parameters (mA and kV) of each scan), an increased risk may persist, particularly in females where breast tissue is directly within the radiation beam during chest CT examinations. Under the UK’s Ionising Radiation in Medical Examinations Regulations (IR(ME)R), each CT scan needs to be clinically
justified, and as Berrington de Gonzalez et al state “routine monitoring [via
CT] should not be recommended until it is demonstrated that it results in a
benefit that will outweigh these risks”[91]. The first publication of the
impact of imaging on CF care was published very recently, by the Perth-
Rotterdam group, in September 2019. Thirty-six clinical vignettes were
shown to a group of CF physicians, with or without accompanying imaging
by CT and radiography. The exercise was then repeated after 10 weeks, to
avoid recall bias, with inversion of the groups such that each vignette was
assessed both with and without imaging. The impact of the imaging was
then assessed by asking whether the physician would recommend changes
in antibiotic therapy, mucociliary clearance techniques, other medications
such as steroids or antifungals, bronchoscopy, blood tests and sputum
cultures. The authors found that chest radiography was associated with
significant increases in the use of inhaled antibiotics (risk ratio 1.28,
p=0.04) but no other significant therapy change. CT was associated
significant increases in antifungal therapy (risk ratio 2.75, p=0.04), induced
sputum samples for NTM (1.25, p=0.02) and admission for IV antibiotics
and bronchoscopy (1.38, p=0.03) [92]. The authors quite reasonably
conclude that CT has more of an impact on therapy choice than radiography,
but go on to state in their highlights section that ‘this study offers support
for the use of biennial CT in monitoring of cystic fibrosis”. This ignores
remaining questions, most significantly whether these interventions based
on imaging would have any clinical benefit, rather than resulting in
clinically unnecessary intervention. There is a well-known saying in
medicine that we “treat the patient, not the x-ray” or in this case the CT.
Furthermore, the vignettes only assessed single time-point imaging and this study offers no information on the benefit of serial imaging non-targeted follow up imaging over any time period. Given the findings of basic science studies of increased risk from the cumulative doses of repeated imaging as opposed to single CT studies, the UK’s approach of not using CT as a screening test in this young population and using imaging only to answer specific clinical questions seems justified.

In addition to concerns of the risk of induced malignancy following repeated medical exposures to ionising radiation, as people with CF live longer into adulthood it is becoming apparent that the background incidence of certain malignancies, particularly colorectal cancers, is elevated in people with CFTR mutations [93–97]. In large cohort studies, the mean age at cancer diagnosis has been found to be 40.4 years in people with CF, compared 64.2 and 54.8 years in males and females with a single copy of mutated CFTR (i.e. carriers). Furthermore, down-regulation of CFTR has been reported in primary tumours of the intestinal tract [98,99], liver (HCC) [100,101], lung [102,103] and nasopharynx [104] amongst others [101,105–107] suggesting CFTR is not just an ion channel but has complex interactions with tumour suppression mechanisms[108]. Mouse studies have even shown that single or double knockout of CFTR results in higher levels of small intestinal and colonic malignancies compared to wild type mice [99]. These studies further emphasise the need to rationalise ionising radiation exposures in CF care to conditions where a clear benefit is evident.
1.3.3 Magnetic Resonance Imaging (MRI)

As a result of the potential increase in cancer induction risk from repeated CT examinations, there has been considerable research into the application of non-ionising radiation dependent imaging techniques in the examination and follow up of patients with cystic fibrosis and, more recently primary ciliary dyskinesia.

1.3.3.1 Structural / Morphological MR imaging -

Initial attempts at assessment of the pulmonary parenchyma via MR were hindered by the inherent low proton density of aerated lung and the rapid signal decay caused by magnetic susceptibility effects at air-tissue interfaces. More recent advances in MR hardware and software (stronger gradients, multichannel coils and acceleration and parallel imaging techniques) have led to improved visualisation of pulmonary structures[109]. An early CF MRI study by Puderbach et al. compared a conventional MR sequence (HASTE – Half-Fourier Acquisition Single shot Turbo spin Echo) with CT using a modified version of the Bhalla score. The lower spatial resolution of MR did not allow assessment of mosaic attenuation, so this component was not scored on either modality. Comparison of global modified Bhalla scores between MR and CT yielded a Pearson correlation coefficient of 0.80 (p 0.0001) with median pulmonary segment-based component score concordance varying from 79% for mucus plugging (range 63-97%), to 97% for collapse/consolidation. The median segment-based concordance for bronchiectasis score was 80% with better concordance in the upper lobes due to the effect of cardiac motion on the
lungs bases[110]. Other conventional MRI sequences have been studied, but more recent studies regarding structural lung imaging via MRI, have focused on respiratory and pulse gated radial acquisitions and non-proprietary (and therefore not widely available) ultra-short and zero echo time (UTE and ZTE respectively) sequences [111–113].

Radial acquisitions (eg. PROPELLER – Periodically Rotated Overlapping ParallEL Lines with Enhanced Reconstruction, Philips) are less sensitive to respiratory motion than Cartesian reconstruction methods. Although these sequences have been shown to be less sensitive to the changes of CF than CT (sensitivity 0.33 using CT as the reference standard), the high reproducibility of scoring these images (ICC 0.79 by CF-MR, vs 0.85 for CT by CF-CT) and wide availability of the sequences on clinical MRI systems has led to their proposed use as a non-ionising radiation alternate to CT for short term follow up of airways disease[114].

Whilst the spatial resolution of MR somewhat limits its use in primary structural analysis, there are many functional and quantitative MR techniques available with considerable promise in the investigation and follow up of chronic airways disease. Small airways occlusion (by mucus plugs, bronchial wall thickening etc) is a prominent feature of both CF and PCD and, as such, CT scoring systems ascribe a separate score for mosaic attenuation as an imaging surrogate for small airways disease. It is well known that areas of poorly aerated lung are subjected to reflex hypoxic vasoconstriction and it is likely that the combination of trapped air and
reduced blood volume accounts for the mosaic appearance on CT. In MR imaging, this phenomenon can be analysed via dynamic post-contrast perfusion imaging directly assessing reduced regional lung perfusion, albeit with the disadvantage of requiring the administration of IV contrast media and the resultant risk of renal complications and potential for accumulation of gadolinium [115].

As in CT, MRI-based semi-quantitative visual scoring systems have been proposed either taken directly from CT scores [116], modified from CT scores (e.g. modified Bhalla score) [117] or designed specifically for MRI (e.g. Eichinger score) [118]. Eichinger et al designed an MR-specific scoring system for semiquantitative visual assessment of CF lung disease. Structural imaging via T1 VIBE (volume interpolated breath-hold examination) or T1 TSE (turbospin echo) and ECG gated T2 HASTE (Half Fourier single shot turbo spin echo) are combined with perfusion assessment via a time-resolved 3D FLASH (fast low angle shot). In contrast to the CFCT scoring system, Eichinger et al combined the bronchiectasis/bronchial wall thickening scores into a single score, as the spatial resolution of MRI was felt to be inadequate to distinguish one from the other. Separate scores for mucus plugging, abscesses/sacculations, consolidation, pleural effusion or thickening (termed “special findings”) and perfusion defects are also assigned scores, all at a lobar level, with solely extent-based scores of 0 (absent), 1 (present and involving <50% of the lobe) or 2 (present and involving >50% of the lobe) (i.e. no accounting for feature severity). These
scores can be summed to provide a global assessment or summary score[118].

Eichinger scores have been shown to be reproducible, with intraobserver CCC (concordance correlation coefficient) of 0.94 – 0.98 and interobserver CCC of 0.97 in a group of CF patients across a very wide age group (0.5 – 42 years) and disease severity.

Midterm scan-scan reproducibility of Eichinger structural scores has also been shown at one month in 15 people with CF during a period of disease stability with between test ICCs of 0.98, 0.82 and 0.96 for summary morphology scores, perfusion scores and global summary scores respectively [119].

1.3.3.2 Quantitative MR Imaging -

Whilst structural imaging via MR is clearly possible and can be useful both in research and clinical settings through the use of qualitative and semi-quantitative visual assessment, it is perhaps the newer quantitative imaging methods possible via MRI that justify on-going work in the application of MR to the investigation of pulmonary disease.

MR signal from the lung originates from water molecules in two states – fixed (within the pulmonary interstitial tissues) and dissolved (mostly within the blood of the pulmonary circulation). In normal healthy individuals, the majority of signal will originate from the free water of the pulmonary circulation, but in pathological states with an increase in parenchymal tissue, e.g. in pulmonary fibrosis, the fixed water will have an
abnormally increased effect on pulmonary T1 relaxation[120]. The value of the lung's native T1 (T1₀ – the T1 relaxation time in normoxic conditions) is therefore a potentially useful quantitative marker of lung pathology in its own right. This imaging biomarker has been investigated in a number of respiratory conditions including CF, COPD, asthma, pulmonary fibrosis and lung allograft dysfunction[121–126].

**1.3.3.3 Functional Lung MR Imaging**

In addition to structural imaging of the lungs, MRI is well placed to provide functional imaging of the respiratory system.

Whilst in conventional contrast enhanced MRI, images are acquired at one or two set time points following contrast media administration, it is possible to image more frequently creating a time-resolved series (essentially a video) during contrast administration. In this way perfusion dynamics can be assessed either visually, or semiautomatically via the drawing of regions of interest and the formation of enhancement curves [127,128]. Dynamic contrast enhanced MRI in a group of children with CF (median age 3 years) demonstrated perfusion defects, even in areas of structurally normal appearing lung with longer ‘time to peak’ enhancement measures compared to age matched children with non-CF diagnoses and increased peak enhancement in areas of consolidation. These children were imaged under general anaesthetic with resultant atelectasis, but times to peak enhancement in areas of atelectatic lung were found to be identical to time to peak in non-atelectatic lung, whilst time to peak enhancement in areas of pathologic consolidation were found to be reduced[129]. It is also
possible to image pulmonary perfusion via MRI, without the use of injected contrast media. This is particularly important when moving from a non-contrast CT led approach to CF imaging without the need for vascular access in small children toward MRI-based imaging. There are several non-contrast perfusion techniques including arterial spin labelling and Fourier decomposition (the latter is discussed later in this chapter). In arterial spin labelling, a radiofrequency pulse is used to ‘tag’ a cross sectional area of blood with vascular signal provided by the inflow of non-tagged blood into the imaged volume. Subtraction imaging can then provide a quantitative map of lung perfusion [130]. Arterial spin labelling (ASL) -based measures of whole lung perfusion have been shown to be reduced in children with CF compared to normal controls, particularly within the upper lobe and has been shown to correlate with FEV₁ (r=0.84, p<0.0001) [131].

1.3.3.3.1 Ventilation MRI

Ventilation scintigraphy has been suggested as an imaging modality capable of providing useful data in infants and children with CF who are too young for accurate assessment via spirometry and other forms of lung function testing. A study at the Royal Brompton demonstrated ventilation scintigraphy defects in one in eight children too young to undergo conventional lung function testing, despite normal plain chest radiographs showed: that ventilation defects at baseline predicted FEV₁ at 7 years of age (r=0.4, p=0.042); that ventilation defect extent correlated with Brasfield and Shwachman scores (r= -0.46 and -0.31 respectively, p<0.5 and <0.001 respectively); and that new defects detected on follow up scintigraphy
coincided with new cultures of significant microorganisms (*P. aeruginosa*) [132].

A further key area of development in functional lung MRI is ventilation imaging. Ventilation scintigraphy is performed via direct spatial localisation of a tracer gas (Krypton-81m). There are several options for ‘tracer’ gases directly visible via MR imaging. Ventilation MRI was first performed back in the 1970s [133] using fluorinated gases which have a high gyromagnetic ratio and multiple $^{19}$F nuclei per molecule, contributing to the MR signal. Imaging with these gases (for example SF$_6$ – also used in multiple breath washout testing, C$_3$F$_8$, C$_2$F$_6$ and CF$_4$) allows quantification of wash in and wash out times, but has considerably lower resolution than more modern ventilation imaging techniques [134–139].

Far better signal and resolution can be achieved via the hyperpolarisation of gases for MR imaging.

Noble gases (generally He or Xe) can be hyperpolarised via spin-exchange optical pumping. Rubidium is vaporised with a high power laser with circular polarisation, in a chamber containing the noble gas aligning the rubidium within a magnetic field. Interactions between the rubidium and noble gas transfer spin to the noble gas atoms, aligning them with the magnetic field and rendering the gas hyperpolarised [134]. The hyperpolarised gas can then be imaged in a number of different ways. Static imaging involves a breath hold of 5-20 seconds during which time a single image of gas distribution is acquired, much like the images traditionally obtained via krypton scintigraphy. Ventilation defects can be
quantified as present in a percentage of lung voxels (ventilation defect percentage – VDP) [140–142]. In children with cystic fibrosis, this method has been shown to demonstrate ventilation defects not detectable via CT or LCI and to show response after 4 weeks of treatment with Ivacaftor [141,143].

Dynamic imaging can be obtained either in a single breath hold, demonstrating collateral ventilation, or over multiple breaths, demonstrating slowly filling ventilation defects and gas trapping [144–149]. In addition to spatial localisation of gas, effects of gradient pulses on phase coherence and Larmor frequency of the gas allows diffusion and ultimately the size of airspaces to be calculated. This has been used to quantify lung destruction in COPD [150] and even to measure alveolar growth in teenagers born prematurely, demonstrating on-going lung growth, reversing the previously held belief that premature birth resulted in cessation of alveolarisation [151].

Xenon diffuses through alveolar membranes changing its Larmor frequency as it shifts from gaseous form to a free dissolved form within the pulmonary tissues and blood plasma and then again when bound to haemoglobin. This change in Larmor frequency allows spatially localised quantification of gaseous exchange and has huge potential to expand our knowledge of pulmonary physiology, both in disease and in health [152–154].

Hyperpolarised gases provide an ideal contrast medium for ventilation imaging via MR, with the signal originating from the gas itself as a direct measure of ventilation and an impressive tool kit of different quantitative
techniques. However, the equipment and highly specialised physics support required to run a hyperpolarized MRI service limits the technique to a handful of research centres worldwide. There are, however, several more recently developed ventilation MR imaging techniques which may be more widely applicable. Medical oxygen is cheap and readily available and in its dissolved state, is weakly paramagnetic. As such, oxygen induces shortening of T1 relaxation. This T1 shortening effect can be used to produce MR-based ventilation images. First, the native T1 relaxation time of lung tissue is quantified in 21% oxygen (bottled medical air) via the measurement of T1 signal decay following differing pre-polarisation pulses (pre-oxygen T1 mapping). The T1 mapping sequence is then repeated whilst the patient breaths 100% oxygen via a tight fitting mask (oxygen “wash in”), during equilibrium, and once the gas supply has been switched back to medical air (oxygen “wash out”). Whilst not immediately visible, the small changes in regional T1 can be plotted to provide regional or whole lung measures of oxygen wash in and wash out time, and the changes in signal intensity can be modelled to provide regional measures of pO2 [120].

As stated above, the signal measured from the lung by conventional proton MRI originates from protons in both bound (parenchymal matrix) and free (pulmonary blood) states. Rather than providing direct measurement of gas location (as is the case in hyperpolarised gas imaging), the signal changes measured following oxygen administration relate to shortening of T1 of regions of the lung and its blood pool in the immediate vicinity of the increased oxygen concentration. Since the majority of water (and therefore
protons) within the lungs is within the pulmonary circulation, the majority of this signal enhancement relates to paramagnetic effects on the pulmonary blood volume. The signal enhancement measured following the administration of 100% oxygen is, therefore, a composite measure of ventilation (delivery of 100% oxygen via the large and small airways), alveolar diffusion (the ability of the delivered 100% oxygen to cross the alveolar membrane to reach the pulmonary blood pool) and pulmonary perfusion (the delivery of blood to the alveolar membrane where it can encounter, and therefore be effected by, the inhaled 100% oxygen).

Abnormalities in any of these processes may result in abnormal oxygen enhancement on MRI[120]. As with any method of MR imaging there are significant differences in acquisition technique from vendor to vendor, centre to centre and scanner to scanner, but forms of oxygen enhanced MR have been shown to produce ventilation defect percentage (VDP) values which demonstrate similar correlation with spirometry to hyperpolarised He MR (r=-0.66 vs r=-0.75 respectively, p=<0.001 for both) and demonstrated similar repeatability at 1-2 week intervals in 25 people with CF [155].

Another promising MR technique, Fourier decomposition imaging (and a recently developed more advanced version - matrix pencil decomposition imaging), is capable of creating maps of both ventilation and perfusion without the use of medical gasses or injected contrast media. Time-resolved signal is acquired continuously during free breathing and the signal Fourier transformed to separate the spectra at respiratory and cardiac frequencies,
enabling the formation of ventilation-weighted and perfusion-weighted images (essentially using the degree of regional lung motion as a surrogate for ventilation and degree of regional increase in pulmonary blood volume during systole as a surrogate for pulmonary perfusion) [156]. This technique has been validated against SPECT/CT, hyperpolarised He MR and dynamic contrast enhanced MR imaging [157–159] and in CF resulting perfusion and ventilation defect percentages correlate strongly with LCI (r=0.76 and r= 0.85 for perfusion and ventilation respectively, p=<0.0001) [160].

1.3.3.4 Multiparametric Pulmonary MR Protocols –

As the new techniques introduced above mature, preliminary work examining the use of combinations of these techniques has begun. A protocol currently under investigation at centres in Rotterdam, Perth, Sheffield and Hannover uses Fourier decomposition, diffusion weighted imaging, dynamic post contrast enhancement and HASTE (half Fourier acquisition single shot turbo spin echo) sequences to quantify ventilation, inflammation, perfusion and structural (abbreviated to “VIPS”) abnormalities in cystic fibrosis patients [161].
1.4 Sinus Disease and its Imaging in CF and PCD

1.4.1 Sinus Disease in CF and its Link with Pulmonary Function

The mucosal surface of the nose and paranasal sinuses is very similar to that of the lower airways, but with the added problems of a weaker immune response and low antibiotic bioavailability[162]. This provides an environment where bacteria can adapt and evolve antibiotic resistance before migrating to the lungs, initially causing intermittent infection, but eventually chronic infection with difficult, if not impossible, to eradicate well-adapted organisms[163]. Studies comparing the genotypes of P. aeruginosa from the paranasal sinuses and lungs of chronically colonised CF patients have shown both bacterial colonies to be identical, further enforcing the hypothesis that these infections may originate in, and seed from, the paranasal sinuses[163]. Chronic pulmonary colonisation with P. aeruginosa is associated with lower baseline percent-predicted FEV1 and accelerated decline[164,165]. Eradication of P. aeruginosa, A. xylosoxidans and B. cepacia from the paranasal sinuses of CF patients, via sinus surgery followed by nasal irrigation and topical antibiotics, has been shown to correlate with a reduced frequency of positive lower airway cultures, an increase in non-colonised patients of 150% and a improvement in quality of life[163].

Berkhout et al demonstrated an increased incidence of rhinosinusitis in an adult cystic fibrosis cohort of 62.5% compared to 10.9% in the general population[166], with polyps present in 25% (compared to 2.5% in the
general population) [167]. They also showed that the severity of sinus disease is worse in those with class I-III CFTR mutations compared to those with class IV-V mutations.

### 1.4.2 Sinus Disease in PCD -

The mechanical decrease in mucociliary clearance seen in primary ciliary dyskinesia (as opposed to the decreased clearance related to increased mucus viscosity in cystic fibrosis) results in very similar sinus disease to that seen in CF, with chronic rhinosinusitis almost ubiquitous in PCD patients [168][169]. Similar to CF, sinus hypoplasia can also be present [170].

PCD is additionally associated with chronic otitis media with effusion, affecting up to 80% of patients under 12 years of age [171].

### 1.4.3 Imaging Sinus Disease and Image-based Disease Severity Scoring -

#### 1.4.3.1 Computed tomography (CT)

In the chronic rhinosinusitis of CF and PCD, CT demonstrates mucosal thickening with or without polyposis often causing obstruction of the osteometal complex, sinus fluid levels, and osteitis/neoosteogenesis [172][173,174]. Similar to the visual scores applied to various lung diseases, there are scoring systems for the semi-quantitative evaluation of sinus disease in CF.


1.4.3.2 Lund-Mackay Score

Although originally developed in the 1980s as a combined symptom-, radiologic- and endoscopy-based assessment of rhinosinusitis severity, it is the imaging portion of the Lund-Mackay score that has continued to be implemented clinically[175,176].

The paranasal sinuses are divided into 6 portions – the maxillary, anterior ethmoid, posterior ethmoid, sphenoid and frontal sinuses and the osteomeatal complex, with each side (right and left) assessed separately. Each sinus is assigned a score of 0 – 2 (0 for completely clear, 1 for partly opacified or 2 for completely opacified). The osteomeatal complex is given a binary score of 0 (unobstructed) or 2 (obstructed). The maximum score (i.e. complete opacification of all 5 sinuses and the osteomeatal complex) is, therefore, 12 for each side and 24 in total[177]. The mean Lund-Mackay score obtained in cohort of patients imaged for non-sinus related pathology was 4.3 with a minimum score of 4 suggested by some as a prerequisite for sinus surgery[178].

This imaging score has been found to be reproducible[179] and to correlate with both disease extent and symptom severity in non-CF rhinosinusitis[176].

As non-aeration of the paranasal sinuses is a normal finding in young children and underdevelopment of the sinuses has been demonstrated in adults homozygous for the delta F508 mutation, a modified Lund-MacKay
score has been developed, with the total score divided by the number of aerated sinuses present to give a per sinus score[180,181].

Berkhout et al investigated the prevalence of these features in children and found significantly higher Lund-MacKay scores, even in 0-2 year olds, compared to age matched healthy controls. There was lateral bulging of the lateral nasal wall throughout their population, but less osteitis / neo-osteogenesis in younger children[182].

In a cohort of 202 paediatric cystic fibrosis patients studied by Gergin et al. each patient underwent an average of 4.2 sinus CTs over an average 6.2-year period. 14 individuals in this cohort underwent 10 sinus CTs each, at 1-year intervals. Despite this level of follow up, no significant post-operative change in Lund-Mackay score was demonstrated[183]. Although the high spatial resolution of CT makes it the ideal cross-sectional imaging modality for the delineation of the osteomeatal complex, the ionising radiation burden of repeated examinations is concerning.

1.4.3.3 Magnetic Resonance Imaging (MRI)

Although less able than CT to demonstrate the osteitis/neo-osteogenesis of chronic rhinosinusitis, MR is better able to differentiate mucosal thickening from fluid or infective material within the sinus. Furthermore, Eggesbo et al describe a “black-hole sign” of STIR (short Tau inversion recovery) signal void (susceptibility artefact) hypothesised to be caused by the paramagnetic properties of certain infectious organisms[184]. *P. aeruginosa*
produces two high affinity ferric iron binding transferrin class proteins; pyoverdine and pyochyline, known as siderophores[185]. *S. aureus* also produces a siderophore – aureocholine[186]. Eggesbo et al found an association of sinus material returning low / no STIR signal with *P. aeruginosa*, *S. aureus* and to a lesser degree *Candida albicans*, *S. maltophilia*, *E. aerogenes* and *H. influenza*[184]. Although not present in any of the patients examined by Eggesbo et al, Aspergillus is also known to contain paramagnetic elements and has been associated with similar T2 signal voids on lung MRI[187].

Kristo et al used a modified version of the Lund-MacKay CT score to examine the incidence of sinus disease in 4 – 7 year old children with lower respiratory tract infections with follow up MR 2 weeks later. At presentation, 68% of patients demonstrated major sinus abnormalities (defined as 1-2 thirds opacification of the sinuses or the presence of air-fluid levels), the majority demonstrating mucosal oedema. The children followed up at 2 weeks demonstrated significant improvement in MR sinus scores, although the scores did not correlate with a simple symptom score[188].

A study of 12 CF patients with G551D CFTR mutations, who underwent sinus CT before and following 1 year of uninterrupted treatment with Ivacaftor, demonstrated significant improvement in CT sinus disease score in 11 patients. The remaining patient, with no improvement, had no sinus disease prior to Ivacaftor treatment, no sinus disease following treatment
and was the only patient not colonised with *P. aeruginosa* or *S. aureus*[189]. These studies suggest a possible role for use of sinus imaging outputs as further surrogate markers of treatment response in CF trials, indeed Graham et al used serial sinus MRI to show the efficacy of maxillary sinus aminoglycoside lavage in increasing maxillary sinus aeration with positive results (improvement in sinus aeration scores at 10, 30, 60, 120 and 180 days post baseline) [190]. Recently, Sommerburg et al demonstrated that MR assessment of features of chronic rhinosinusitus is possible in children from birth to 6 years of age (albeit with the requirement of sedation) and demonstrates significant differences in the prevalence of mucosal swelling, mucopyoceles and polyps between infants and children with CF and those with images for other reasons[191].
1.5 Hypotheses

1) Combined structural and quantitative MRI assessment of the thorax can provide comparable information to CT such that follow up imaging via CT could be replaced with MRI.

2) Quantitative MR measures of ventilation correlate with established clinical measures of ventilation (LCI and FEV₁) and provide additional spatial information.

3) A multisystem MRI assessment can provide new extra-thoracic imaging biomarkers of CF and PCD disease severity whilst being better tolerated by patients than current multimodality imaging follow up.

1.6 Aims and Objectives

1) To set up a clinically feasible, multisystem (lung, sinonasal and upper abdominal visceral) quantitative MRI examination for the investigation and follow up of CSLD

2) To evaluate novel imaging biomarkers of CF and PCD disease severity

This will require the prospective recruitment of people with CF or PCD referred for CT imaging, the comparison of CT imaging findings to MRI
findings, post processing of MR images for the production of quantitative measures of lung disease and lung function, post processing of liver and sinus imaging for the production of quantitative imaging measures of liver and sinus disease severity and collection of clinically established markers of CF and PCD disease severity for comparison. Clinical markers of severity will include spirometry, multiple breath washout measures, frequency of courses of antibiotics (exacerbation frequency), liver function tests and liver and spleen ultrasound measures including sheer wave elastography of the liver (a non-invasive measure of liver fibrosis).
Chapter 2 - Methods

2.1 Funding and Ethical Approval –

This study was funded by a pump-priming grant from the Royal College of Radiologists. Ethical approval was granted by the Leeds, Bradford NHS research and ethics committee (REC) and the NHS Health Research Authority (HRA) (REC reference number 16/YH/0351). Written informed consent was sought from all Gillick-competent participants and from those with parental responsibility for non-Gillick competent participants. Assent was obtained from all participating non-Gillick competent children.

2.2 Study Design and Recruitment –

This study was a prospective cross-sectional cohort trial with subjects recruited from outpatient clinics and inpatient admissions at The Royal Brompton Hospital, London. Sample size was determined by funding and availability of the clinical MRI scanner.

The entrance criteria were as follows:

1. Established diagnosis of cystic fibrosis or primary ciliary dyskinesia (as per international guidelines, with sweat chloride and genetics for CF[192] and a combination of genetics and nasal brushings for immunofluorescence, transmission electron microscopy, and high speed video light microscopy for PCD[193])
2. Age over 6 years (no upper age limit)

3. Pre-established *clinical* need for chest CT examination

4. No contraindication to MRI.

Exclusion criteria were lack of consent, contraindication to MRI (non-MRI safe implantable medical device etc.) and non-availability of the MR scanner in the time frame required for clinical CT.

**2.3 Statistics** -

SPSS v.25 (IBM Corp) was used throughout. Normally distributed data (normality determined via Kolmogorov-Smirnov test) was expressed via mean, standard deviation and range with correlation of continuous variables via Pearson's correlation and independent sample t-test and categorical data via Chi square or Fisher’s exact test. Non-normally distributed data was expressed via median, interquartile range and range with correlation of continuous variables via Spearman’s rank and Kruskal-Wallis and categorical data via Chi-squared.

**2.4 Lung Function and Other Clinical Measures of Disease Status**

Multiple breath wash-out testing was performed on the day of the MRI examination, on the main Royal Brompton Hospital (RBH) campus, either immediately before travel to Wimpole Street for the MRI or immediately after the MRI scan on travelling back to the main RBH campus. All tests
were performed by one of two specialist respiratory physiologists, both of whom form part of the Royal Brompton and Imperial College London’s LCI reference laboratory, using an Exhalyzer D (Ecomedics AG, Switzerland) following the standard operating procedure published by Jensen et al[194] and the consensus statement from ERS and ATS [195]. The Exhalyzer D uses inhaled oxygen and measures exhaled CO2, oxygen and Argon, using their concentrations to calculate exhaled nitrogen concentration. Nitrogen is then the tracer gas for multiple breath washout testing.

Data was acquired using Spiroware (Ecomedics AG, Switzerland) version 3.1.6 and later analysed on version 3.2.1 Following calibration, measurements were repeated 3 times for each participant with tests accepted when the co-efficient of variation of LCI and FRC was below 10% (and repeated if not) and mean values of the three accepted tests were used for subsequent analyses (as per Jensen et al [196]).

An LCI of 7.91 is considered to be the upper limit of normal (at least for those aged 6 to 18 years, beyond this MBW is rarely used)[197].

Spirometry results from the 6 months preceding imaging were retrieved from the electronic patient record and converted to percentage predicted values using an online calculator available at http://glistastransfer.org.au/calcs/spiro.html. As the numbers of spirometry results over this time period varied widely from patient to patient (those with more measurements likely to have more significant, less stable disease, and therefore be attending clinic more frequently), whilst summary measures (median values) are reported in the patient background.
information section (chapter 3), only single measurement output (most contemporaneous, best and worst) test results within the 6 month period were used to assess relationships between imaging and spirometry.

Clinic letters were used to check for genotype and history of known liver and/or pancreatic dysfunction and clinic letters, admissions and pharmacy data used to count the total number of IV and oral antibiotic courses (as an inpatient or outpatient, including home IV antibiotic administration) taken in the 6 month period preceding imaging. It is, of course, possible that antibiotics were prescribed at a local hospital or GP level and not mentioned in CF clinic letters or communications stored on the electronic health record and although thought to be unlikely or at least a minor contributor of error, this is none the less, a limitation of this study that is worth noting.

The Royal Brompton’s Picture Archiving and Communication System (PACS) was used to identify abdominal ultrasound examinations prior to the research MRI and note made of results of liver elastography (sheer wave velocity and corresponding ISHAK and METAVIR scores[198] obtained using a GE LogiQ E10) and craniocaudal splenic length[199] as evidence of hepatic fibrosis and portal hypertension respectively.

2.5 Imaging -

2.5.1 Computed tomography (CT)

Non-contrast CTs of the thorax were performed on a Siemens Definition Flash (Siemens, Forchhiem, Germany) acquired at a full inspiratory breath
hold, using a specific low dose, high pitch (FLASH) thoracic CT protocol with separate adult and paediatric protocols (paediatric was defined as below 16 years of age and the same protocol used for older patients <50kg in weight).

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<tr>
<td>Qref mAs</td>
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<td>Care kV</td>
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<td>Reconstruction kernel</td>
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The low dose protocols used in our CF population use the same tube voltage as our other protocols (used mainly for ILD imaging), but with a significantly lower quality reference tube current values (Qref mAs) (mAs has a linear relationship with resulting patient dose). For example the adult ILD protocol uses a Qref mAs of 110 compared to 30 for the low dose protocol and the 11-50kg paediatric ILD protocol a Qref mAs of 130, compared to 80. The result of the low dose protocol is a noisier acquisition, but with significantly reduced resulting ionising radiation exposure.

Images were reviewed on a dedicated PACS workstation using AGFA IMPAX v6.6.1.1527.

The CFCT scoring system was chosen based on prior experience (TS has used this scoring system previously) and on the preference of the radiology team based on differences between CFCT and PRAGMA-CF. As discussed in the introduction chapter, PRAGMA CF uses a grid superimposed on only 10
of approximately 150-350 transverse sections, thus ignoring 97-98% of the available data. Furthermore, each cell within the grid can only be assigned a single label, i.e. if there is bronchiectasis, the presence of any other feature is completely ignored. In order to examine correlation between CT and MR findings it was felt that a more comprehensive scoring system was required. A training session was completed by two post completion of clinical training (CCT) thoracic imaging fellows (TS and BR) with 7 and 5 years thoracic CT experience, using educational resources from Erasmus MC describing CFCT scoring[200]. This was followed by 2 training rounds with images from a prior study. Each training round consisted of 6 different image sets (ie. 12 in total), each scored blindly with subsequent in-depth discussion of discrepancies in scores. Semi-quantitative visual scoring of the study cohort was then performed using CFCT. Reviewers were blinded to each other’s scores to enable calculation of inter-observer variability via kappa and ICC values. A subsequent un-blinded second read was used to discuss discrepancies in individual scores. The use of consensus scoring has fallen out of favour in radiological research, as there is a potential in cases of discrepancy to reach a “consensus” on which neither observer agrees. For this reason TS’s scores were used for correlation with clinical measures and MRI and were only updated in the case of missed findings highlighted at second read (TS has used CFCT scoring in previous trials and the discussion was used to establish a ground truth – essentially hierarchical consensus scoring).
Quantification of low attenuation lung was via the Pulmo3D package in Siemens Syngo.Via (software version VB30A_HF06). Several thresholds of ‘abnormal’ lung attenuation were used. Two commonly used thresholds from emphysema imaging (-950HU and -910HU) and one designed specifically for this study forming a patient specific threshold. The -950 and -910 thresholds have been used extensively in COPD literature and are derived from comparative studies of CT and histology from explanted lung [201,202]. The uses of further quantitative CT techniques in emphysema has recently been reviewed extensively (Kauczor et al 2019 being a particularly good example[203]). The patient specific ‘bespoke’ threshold method was designed to produce a measure equivalent to the CFCT hyperinflation score, but with a more granular numeric output and less possibility of interobserver variability. The threshold was calculated by placing a 1cm diameter circular region of interest (ROI) in an area of visually “normal” appearing lung by a single observer. The threshold level was set at the median HU value within this ROI minus 2 standard deviations. Abnormally low attenuation lung was quantified as volume of abnormality as a percentage of segmented lung volume either on an individual voxel basis or based on volumes of adjacent abnormally low attenuation voxels summing to at least 187mm\(^3\) (the largest default cluster size available in the Pulmo3D package). The cluster-based analysis reduces the effect of random image noise on voxel attenuation, calculating low attenuation ‘regions’ rather than individually low attenuation voxels. This method requires further validation with assessment of inter- and intra-observer variability along with specific assessment of the effect of
spirometry controlled acquisition as it is likely to be far more significantly affected by small variations in respiratory phase than visual scores. This output was included in this thesis as an experimental method of CT quantification and given the interesting results now forms part of on-going CF imaging research at The Royal Brompton Hospital which does not form part of this thesis.

2.5.2 Structural Pulmonary MRI

All MRI was performed on a 1.5T MR system (Siemens Aera) using the body transmit coils and a combination of spine, 16 channel body flex and head coils.

The MRI protocol was influenced by a number of different factors. The oxygen-enhanced and matrix pencil decomposition sequences were set up by Bioxydyn Ltd and the MR research team from University Hospital Basel, respectively, so their acquisition times were set. These are further discussed below. The structural lung imaging was initially influenced by the review article of Biederer et al which describes a well-established multipurpose structural lung disease MRI protocol used in University Hospital Schleswig-Holstein, set up with and endorsed by Siemens Healthcare [204]. They use breath hold T2 BLADE images for lung nodule imaging, the smallest feature with a specific protocol within their review. As this sequence is also extensively used in clinical paediatric imaging this was chosen as our sequence of choice. We designed the full protocol to not exceed one hour of scanning time, to ensure the best chance of a complete protocol in all participants right down to 6 years of age and as such,
respiratory triggered sequences were not even considered for inclusion. Biederer et al advise 8 mm thick sections, but healthy volunteer scans at the time of our protocol set up showed better demonstration of the central airways at a thickness of 6 mm with easily achievable breath holds. These six millimetre thick T2 BLADE images were acquired both in axial and coronal planes (see table below) for morphologic analysis. These were acquired during 3 full inspiratory breath holds (3 concatenations) of 14 seconds each, with a manually determined break of around 10 seconds between breath-holds for recovery (i.e. 1 minute 2 seconds for axial imaging followed by 1 minute 2 seconds for coronal imaging). The full protocol details are below (size was judged subjectively by the radiographer at the time of the scan based on height weight and appearance).

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<th>Small patient</th>
<th>Average patient</th>
<th>Large patient</th>
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Again, images were reviewed on a dedicated PACS workstation using AGFA IMPAX v6.6.1.1527. A training round with images from a prior study was completed with semi-quantitative visual scoring by two observers (post CCT thoracic radiology fellows – TS and JB) with 7 and 6 years thoracic imaging experience. This was performed using the Eichinger semiquantitative visual scoring system[118]. This scoring system was chosen as it was specifically designed for MRI scoring, complete with a
combined measure of bronchiectasis and bronchial wall thickening as we completely agree with the assertion of Eichinger et al. that MRI is not capable of the resolution required to reliably discern one feature from the other. Using this system allows more granular assessment of the degree of bronchial dilatation vs bronchial wall thickness required to give adequate signal on MRI. 2 rounds of scoring, of 6 patients each round, were completed initially blinded and then with discussion of any points of discrepancy. Scoring of the study MR images was then performed in a single sitting. Reviewers were blinded to the CT findings and MR scoring was performed 6 months prior to CT scoring to eliminate the possibility of influence of the CTs on MRI analysis and of recall bias in the reviewer who scored both sets of imaging (TS). As for CT scoring, reviewers were initially blinded to each other’s scores with a subsequent un-blinded second-read. Interobserver variability was expressed via Kappa values or interclass correlation coefficients as appropriate, and values from TS’s scores used for correlation with CT scores with scores only updated if a finding was missed (i.e. hierarchical consensus).

2.5.3 Quantitative Lung MRI

2.5.3.1 Mapping Techniques

T1 relaxation times were quantified via 2 different techniques. The inversion recovery HASTE (IR-HASTE – Half-Fourier acquisition single shot turbo-spin echo) technique of Professor G Parker[121] consists of repeated 10 mm thick acquisitions in 6 coronal positions at differing inversion times
For each inversion time, multiple images are acquired at each slice position during free breathing over a period of 5 minutes, with subsequent image registration and calculation of T1 maps. The ufbSSFP (ultrafast balanced steady-state free precession) sequence from Professor O Bieri[205] is capable of simultaneously forming maps of not just T1, but also T2 relaxation times and proton density (PD). Images are acquired as single 10 mm thick coronal slices during a 9-second inspiratory breath hold. Six coronal ufbSSFP sections were matched in position to the 6 IR-HASTE mapping slice positions. The IR-HASTE and ufbSSFP images were acquired whilst the subject was breathing bottled medical air via a non-rebreathe mask.

The lungs were automatically segmented on each map (excluding the chest wall, mediastinum and central pulmonary vasculature) and voxel values evaluated at a whole lung level as mean and standard deviation, median and interquartile range, skewness and kurtosis.

2.5.3.2. Ventilation and Pulmonary Perfusion MRI

Ventilation was examined in three ways: simple pre- and post-oxygenation T1 mapping via ufbSSFP, dynamic oxygen enhancement (IR-HASTE) and matrix decomposition imaging. The same 6 coronal ufbSSFP mapping acquisitions were repeated following 5 minutes of 100% bottled oxygen delivered via the same no-rebreathe facemask (the structural imaging was acquired during this 5 minute interval). T1 measurements post-oxygenation
were compared to those pre-oxygenation and expressed as a percentage change in T1 across the imaged portion of the lung (summation of automatically segmented portions of all 6 coronal sections). The dynamic oxygen-enhanced protocol involved 140 repetitions of six 10 mm thick coronal IR-HASTE images in the same positions as the pre-oxygenation IR-HASTE mapping slices. Initial "pre-contrast" acquisitions were taken whilst breathing bottled medical air with subsequent switching to 100% oxygen and then back to bottled air using a low flow gas blender (Inspiration Healthcare Ltd, Leicester). Resulting images were registered to eliminate respiratory motion and signal change over time fitted to curves of oxygen wash-in and wash-out[206]. Oxygen wash-in and wash-out time constants, signal intensity change and modelled regional partial pressure of oxygen were then calculated by imaging physicists at Bioxydyn Ltd (Manchester, UK).

Six further sets of coronal ufbSSFP images were obtained over a 1 minute, 15 second period of free breathing (160 images in each position – i.e. sample frequency of just over 2 frames per second) with subsequent image registration and matrix pencil decomposition (an advanced form of Fourier decomposition) of ventilation and pulmonary perfusion signals according to the method of Dr G Bauman[156]. Voxels with under 75% signal amplitude compared to the median signal amplitude were classed as ventilation or perfusion defects. Voxels under this threshold were then further divided into 3 equal bins of moderately reduced, severely reduced and absent ventilation/perfusion.
2.5.4 Novel Extra-Thoracic MR Imaging Biomarkers -

2.5.4.1 Paranasal sinuses

The paranasal sinuses were imaged using a head coil with a standard clinically implemented protocol, with parameters matched to individual patent size.

<table>
<thead>
<tr>
<th>Orientation</th>
<th>T1 TSE</th>
<th>T2 TSE</th>
<th>STIR</th>
<th>DWI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slice thickness</td>
<td>3 mm</td>
<td>3 mm</td>
<td>5 mm</td>
<td>5 mm</td>
</tr>
<tr>
<td>Aproximate acquisition time</td>
<td>2 minutes 45 seconds</td>
<td>2 minutes 15 seconds</td>
<td>1 minute 15 seconds</td>
<td>2 minutes 30 seconds</td>
</tr>
</tbody>
</table>

Mucus, mucosal thickening and susceptibility artefact were recorded as present or absent and mucus and mucosal thickening both segmented, quantified as volumes and expressed as a proportion of the total maxillary sinus volume using Terarecon’s iNtuition software (Terarecon, Durham NC) by a single observer. Regions of interest were placed within the maxillary sinus mucus on ADC maps from the DWI series, avoiding areas of artefact and adjacent mucosa, using the open-source Horos medical imaging viewer (version 2.2.0). Separate regions of interest were placed in the maxillary sinus mucosa avoiding any adjacent mucus or bone. Voxel data from these regions of interest were imported into ImageJ (version 1.49v NIH, USA) and the ‘Display Pixel Values’ Macro used to export individual voxel ADC values. These values were copied and pasted into Microsoft Excel and simple descriptive statistical outputs calculated (mean, standard deviation, median, quartiles (10th, 25th, 75th and 90th), mode, skew and kurtosis.
2.5.4.2 Liver Mapping

There are many well-validated methods of mapping liver T1 values, in use both in research and clinical settings, but the length of time already spent on the scanner for lung structure and functional imaging precluded the addition of these methods to the protocol. Instead we used the pre-oxygenation lung T1 maps to investigate the potential use of the included portion of the liver. Whilst imaging the whole of the liver would be preferable, CF liver disease is generally a diffuse process and simultaneous mapping of the liver and lungs presents the opportunity to investigate the use of the limited portion of liver included in lung imaging for a further quantitative output. It is important to realise that these acquisitions have not been optimised for liver imaging, but our hope is that the portion of the liver imaged as part of lung T1 mapping provides liver T1 values as a “free” by-product of lung mapping. The superior portion of the liver is included in both of the pre-oxygenation coronal lung mapping sequences (both ufbSSFP and IR-HASTE). Six regions of interest of 1cm diameter were placed throughout the liver parenchyma, avoiding any hepatic vasculature, and median voxel values recorded as liver T1. Resulting measures of T1 and T2 relaxation time were compared to the presence or absence of liver disease as per the patients electronic record and against quantitative ultrasound measures of liver fibrosis from sheer wave elastography, measured as part of clinical care using a GE LogiQ E10.
2.6 Patient Experience –

A bespoke questionnaire was given to each subject with questions to be answered before any imaging, after the CT and after the MRI. The questionnaire is included in the appendix, but briefly includes questions covering prior experience of CT and MR imaging, pre-existing concerns of either test, length of each examination, noise and difficulty remaining still, ease of required breath holding manoeuvres and any claustrophobia.

Finally, each subject was asked if they were given the choice, which test (CT or MRI) they would choose for regular imaging follow up. The questionnaire was filled in by the patient themselves or, if too young to complete it alone, with the help of a parent, guardian or rarely a member of the research team.

It was not a formally validated questionnaire intended to quantifying patient impact of imaging, but used more as a source of patient involvement for the development of future MR imaging protocols – particularly opinions regarding the use and length of breath holds and the overall time taken on the scanner.
Chapter 3 – Description of Population and Disease Severity by Spirometry, Exacerbation Frequency and CT

3.1 Introduction –

The demographics and disease severity of the individuals recruited can have a marked effect on interpretation of subsequent results, for example a younger cohort should have more mild structural disease with the potential for increased interobserver variation in CFCT scores [76] and could be expected to tolerate a lengthy examination less well with more resulting motion artefacts and failed examinations. As such, this chapter describes the cohort demographics and disease severity as represented by spirometry, LCl₂₅, frequency of exacerbations and structural disease severity scores from the current gold standard CT examinations.

3.2 Methods -

Please see the methods chapter for full details.

3.3 Results -

3.3.1 Patient Age and Diagnosis –

22 patients were recruited, 12 of whom were male, with a median age of 14 years (range 6-35 years). 18 of these patients were under the age of 20 years. The patients over 20 years of age were approached following initial slow recruitment (largely due to the low number of paediatric referrals for
CT examinations) and a preliminary analysis demonstrating a predominance of very low severity disease.

Three patients had a diagnosis of PCD (two 9 year olds and a 13 year old). All other recruits had a diagnosis of CF. Of these, 5 were homozygous DF508 and 2 were pancreatic sufficient).

### 3.3.2 Spirometry –

The median interval between spirometry and MRI was 10 days (range 0-77, IQR 2-32). Four patients had spirometry on the day of the MRI (in clinic) and 12 within 10 days of the MRI.

A summary of the most contemporaneous spirometry results is below.

<table>
<thead>
<tr>
<th></th>
<th>FEV$_1$ (% predicted)</th>
<th>FVC (% predicted)</th>
<th>FEV$_1$/FVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>71</td>
<td>85</td>
<td>0.79</td>
</tr>
<tr>
<td>Minimum</td>
<td>36</td>
<td>54</td>
<td>0.35</td>
</tr>
<tr>
<td>Maximum</td>
<td>112</td>
<td>119</td>
<td>0.87</td>
</tr>
<tr>
<td>IQR</td>
<td>62-86</td>
<td>79-91</td>
<td>0.69-0.84</td>
</tr>
</tbody>
</table>
Each participant had between 1 and 12 spirometry entries on EPR in the 6 months prior to their scans (median 3.5). One participant had a single measurement 32 days prior to imaging, whilst all others had 3 or more.

Four had spirometry on the same day as imaging and the median number of days between imaging and the most contemporaneous spirometry across the cohort was 10 days.

<table>
<thead>
<tr>
<th>Highest in 6 month %FEV₁</th>
<th>Highest in 6 month %FVC</th>
<th>Highest in 6 month FEV₁/FVC</th>
<th>Median in 6 month %FEV₁</th>
<th>Median in 6 month %FVC</th>
<th>Median in 6 month FEV₁/FVC</th>
<th>Lowest in 6 month FEV₁%</th>
<th>Lowest in 6 month FVC%</th>
<th>Lowest in 6 month FEV₁/FVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>82.5</td>
<td>89.9</td>
<td>0.82</td>
<td>75.43</td>
<td>87.95</td>
<td>0.79</td>
<td>68.00</td>
<td>78.75</td>
</tr>
<tr>
<td>Min</td>
<td>41.5</td>
<td>52.3</td>
<td>0.38</td>
<td>37.2</td>
<td>53.30</td>
<td>0.35</td>
<td>36.00</td>
<td>52.30</td>
</tr>
<tr>
<td>Max</td>
<td>113.6</td>
<td>118.8</td>
<td>0.98</td>
<td>111.60</td>
<td>116.10</td>
<td>0.90</td>
<td>108.20</td>
<td>112.20</td>
</tr>
</tbody>
</table>

Highest, median, lowest and contemporaneous FEV₁/FVC values all demonstrated significant correlation with patient age, as did the lowest % predicted FVC in the 6 months preceding the MRI. The strongest correlation was with the best (highest) FEV₁/FVC in the 6 months examined. There was a weak correlation between the lowest percent predicted FVC and age, but no further significant correlation was demonstrated between other spirometric results and patient age.

<table>
<thead>
<tr>
<th>Correlation with patient age (years)</th>
<th>Best %FEV₁ in 6 month</th>
<th>Best %FVC in 6 month</th>
<th>Best FEV₁/FVC in 6 month</th>
<th>Median %FEV₁ over 6 month</th>
<th>Median %FVC over 6 month</th>
<th>Median FEV₁/FVC over 6 month</th>
<th>Lowest FEV₁% in 6 month</th>
<th>Lowest FVC% in 6 month</th>
<th>Lowest FEV₁/FVC in 6 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson correlation coefficient</td>
<td>-0.174</td>
<td>0.381</td>
<td><strong>-0.752</strong></td>
<td>-0.121</td>
<td>0.355</td>
<td><strong>-0.633</strong></td>
<td>-0.16</td>
<td>0.430</td>
<td><strong>-0.503</strong></td>
</tr>
<tr>
<td>Sig (2-tailed)</td>
<td>0.440</td>
<td>0.080</td>
<td><strong>&lt;0.001</strong></td>
<td>0.591</td>
<td>0.105</td>
<td><strong>0.002</strong></td>
<td>0.945</td>
<td><strong>0.046</strong></td>
<td>0.017</td>
</tr>
</tbody>
</table>
Simple Scatter of Contemporaneous FEV1 (% predicted) by Age at time of scans (years)

Simple Scatter of Best FEV1/FVC by Age at time of scans (years)
3.3.3 Lung Clearance Index –

Several patients declined to undergo LCI testing (most citing insufficient time, one raising concerns of cross contamination via medical equipment). 15 of the 22 patients recruited completed LCI testing, all within 2 hours of the MRI examination.

An LCI of 7.91 is considered to be the upper limit of normal (at least until the age of 18, beyond this MBW is rarely used)[197]. The median LCI₂₅ for the cohort was 11.53 (range 7.64-21.09, IQR 10.12-15.98). There was no significant correlation between LCI₂₅ and patient age (Pearson's coefficient 0.120, p=0.683), but as would be expected, there was a positive correlation between nitrogen washout time (seconds) and age (Pearson's 0.597, p=0.024).

![Simple Scatter of LCI₂₅ by Age at time of scans (years)](image-url)
3.3.4 Exacerbations -

All clinic letters, notes and other documents available on EPR were examined and any admissions for IV or outpatient courses of IV or oral antibiotics recorded over the 6-month period before the 1st imaging test (CT or MRI) as a surrogate for disease stability.

Participants recruited had between 0 and 3 admissions for IV antibiotics in the prior 6 months (median 1) and 0 – 5 ‘IV and/or PO’ courses in the preceding 6 months (median 3), see graphs below.
There was no statistically significant association between participant age and the number of antibiotic courses in the preceding 6 months.
<table>
<thead>
<tr>
<th>Correlation with Age</th>
<th>IV Abx</th>
<th>PO Abx</th>
<th>IV and PO combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson's correlation coefficient</td>
<td>0.239</td>
<td>-0.268</td>
<td>-0.076</td>
</tr>
<tr>
<td>p</td>
<td>0.284</td>
<td>0.228</td>
<td>0.736</td>
</tr>
</tbody>
</table>

Simple scatter of number of IV antibiotic courses in past 6 months by age

Simple scatter of number of IV and/or PO antibiotic courses by age
3.3.5 Disease Severity by CT -

The indication for clinical CT imaging is summarised in the table below.

<table>
<thead>
<tr>
<th>Indication for CT</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveillance (generally at transition from paediatric to adult care)</td>
<td>8</td>
</tr>
<tr>
<td>Recent infective exacerbation (generally at the end of a course of inpatient IV</td>
<td>5</td>
</tr>
<tr>
<td>antibiotics)</td>
<td></td>
</tr>
<tr>
<td>Drop in lung function with no apparent cause</td>
<td>8</td>
</tr>
<tr>
<td>Follow up of fungal chest infection</td>
<td>1</td>
</tr>
</tbody>
</table>

**3.3.5.1 Bronchiectasis Component**

Lobar bronchiectasis scores varied from 0 – 5.25 (median 0) out of a maximum possible score of 12.

<table>
<thead>
<tr>
<th>CFCT Bx score</th>
<th>RUL</th>
<th>RML</th>
<th>RLL</th>
<th>LUL</th>
<th>Lingula</th>
<th>LLL</th>
<th>Whole lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>1.5/1.63</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>1.13/1</td>
<td>4.63/5</td>
</tr>
<tr>
<td>Min</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Max</td>
<td>5.25/5.25</td>
<td>3.75/4.5</td>
<td>5.25/5.25</td>
<td>5.25/5.25</td>
<td>4.5/3.00</td>
<td>3.5/3.5</td>
<td>20.75/20.75</td>
</tr>
</tbody>
</table>

(Observer 1 [TS]/Observer 2 [BR])

The median ICC for the lobar bronchiectasis score was 0.963 (min 0.951, max 0.974). Individual ICC values for bronchiectasis score at a lobar and whole lung level are below.
<table>
<thead>
<tr>
<th>Lobe</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUL</td>
<td>0.951</td>
</tr>
<tr>
<td>RML</td>
<td>0.965</td>
</tr>
<tr>
<td>RLL</td>
<td>0.961</td>
</tr>
<tr>
<td>LUL</td>
<td>0.958</td>
</tr>
<tr>
<td>Lingula</td>
<td>0.966</td>
</tr>
<tr>
<td>LLL</td>
<td>0.974</td>
</tr>
<tr>
<td>Whole lung</td>
<td>0.989</td>
</tr>
</tbody>
</table>

Comparison of bronchiectasis component scores from observer 1 and 2 via Bland-Altman.
### 3.3.5.2 Mucus Plugging Component

Lobar mucus plugging scores varied from 0 – 6 (median 1) out of a maximum possible score of 6.

<table>
<thead>
<tr>
<th>CFCT MP score</th>
<th>RUL</th>
<th>RML</th>
<th>RLL</th>
<th>LUL</th>
<th>Lingula</th>
<th>LLL</th>
<th>Whole lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>2/2</td>
<td>1/1</td>
<td>1/1</td>
<td>1/1</td>
<td>0/0</td>
<td>1/1</td>
<td>5/5</td>
</tr>
<tr>
<td>Min</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Max</td>
<td>6/5</td>
<td>3/4</td>
<td>2/2</td>
<td>6/3</td>
<td>4/5</td>
<td>4/3</td>
<td>23/18</td>
</tr>
</tbody>
</table>

(Observer 1 [TS]/Observer 2 [BR])

The median ICC for lobar mucus plugging score was 0.963 (min 0.894, max 0.973). Individual ICC values for mucus plugging score at a lobar and whole lung level are below.

<table>
<thead>
<tr>
<th>Lobe</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUL</td>
<td>0.969</td>
</tr>
<tr>
<td>RML</td>
<td>0.966</td>
</tr>
<tr>
<td>RLL</td>
<td>0.959</td>
</tr>
<tr>
<td>LUL</td>
<td>0.894</td>
</tr>
<tr>
<td>Lingula</td>
<td>0.973</td>
</tr>
<tr>
<td>LLL</td>
<td>0.906</td>
</tr>
<tr>
<td>Whole lung</td>
<td>0.976</td>
</tr>
</tbody>
</table>
Bland-Altman plot comparing CFCT mucus plugging scores from observer 1 and 2.

### 3.3.5.3 Bronchial Wall Thickening Component

Lobar bronchial wall thickening scores varied from 0 – 4 (median 0.5) out of a maximum possible score of 9.

<table>
<thead>
<tr>
<th>CFCT BWT score</th>
<th>RUL</th>
<th>RML</th>
<th>RLL</th>
<th>LUL</th>
<th>Lingula</th>
<th>LLL</th>
<th>Whole lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>1.38/2</td>
<td>0/1</td>
<td>1/2</td>
<td>0/0.5</td>
<td>0/0</td>
<td>1/1</td>
<td>4.5/6.75</td>
</tr>
<tr>
<td>Min</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
</tbody>
</table>

(Observer 1 [TS]/Observer 2 [BR])
The median ICC for lobar bronchial wall thickening score was 0.900 (min 0.872, max 0.988). Individual ICC values for bronchial wall thickening score at a lobar and whole lung level are below.

<table>
<thead>
<tr>
<th>Lobe</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUL</td>
<td>0.907</td>
</tr>
<tr>
<td>RML</td>
<td>0.872</td>
</tr>
<tr>
<td>RLL</td>
<td>0.881</td>
</tr>
<tr>
<td>LUL</td>
<td>0.935</td>
</tr>
<tr>
<td>Lingula</td>
<td>0.988</td>
</tr>
<tr>
<td>LLL</td>
<td>0.892</td>
</tr>
<tr>
<td>Whole lung</td>
<td>0.973</td>
</tr>
</tbody>
</table>

Bland Altman plot comparing the bronchial wall thickening scores of observer 1 and 2.
### 3.3.5.4 Parenchymal Component

Lobar parenchymal scores varied from 0 – 3 (median 0) out of a maximum score of 9.

<table>
<thead>
<tr>
<th>CFCT Parenchymal score</th>
<th>RUL</th>
<th>RML</th>
<th>RLL</th>
<th>LUL</th>
<th>Lingula</th>
<th>LLL</th>
<th>Whole lung</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median</strong></td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>1/1</td>
</tr>
<tr>
<td><strong>Min</strong></td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td><strong>Max</strong></td>
<td>2/2</td>
<td>3/3</td>
<td>1/1</td>
<td>1/1</td>
<td>1/1</td>
<td>2/2</td>
<td>8/8</td>
</tr>
</tbody>
</table>

(Observer 1 [TS]/Observer 2 [BR])

The median ICC for lobar parenchymal score was 0.990 (min 0.945, max 1.00). Individual ICC values for parenchymal score at a lobar and whole lung level are below.

<table>
<thead>
<tr>
<th>Lobe</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUL</td>
<td>1.00</td>
</tr>
<tr>
<td>RML</td>
<td>0.979</td>
</tr>
<tr>
<td>RLL</td>
<td>1.00</td>
</tr>
<tr>
<td>LUL</td>
<td>1.00</td>
</tr>
<tr>
<td>Lingula</td>
<td>0.945</td>
</tr>
<tr>
<td>LLL</td>
<td>0.966</td>
</tr>
<tr>
<td>Whole lung</td>
<td>0.992</td>
</tr>
</tbody>
</table>
Bland-Altman plot comparing the CFCT parenchymal scores of observer 1 and 2.

3.3.5.4.1 Opacity Extent Scores (part of the parenchymal component summary score)

Lobar opacity extent scores varied from 0 – 3 (median 0) out of a maximum score of 3. This includes consolidation >1cm in diameter and collapse.

<table>
<thead>
<tr>
<th>CFCT opacity extent score</th>
<th>RUL</th>
<th>RML</th>
<th>RLL</th>
<th>LUL</th>
<th>Lingula</th>
<th>LLL</th>
<th>Whole lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>1/1</td>
</tr>
<tr>
<td>Min</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Max</td>
<td>1/1</td>
<td>3/3</td>
<td>1/1</td>
<td>3/3</td>
<td>3/3</td>
<td>1/1</td>
<td>7/7</td>
</tr>
</tbody>
</table>

(Observer 1 [TS]/Observer 2 [BR])
At a lobar level, linear weighted Kappa values were calculated rather than ICC values, as lobar opacification scores are essentially categorical rather than continuous. The median Kappa value (linear weighted) for the lobar opacification score was 0.936 (min 0.861, max 1.00). The ICC for whole lung opacification score was 0.990.

<table>
<thead>
<tr>
<th>Lobe</th>
<th>Agreement (linear weighted Kappa for lobes, ICC for whole lung)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUL</td>
<td>1.00</td>
</tr>
<tr>
<td>RML</td>
<td>0.927 (0.956 quadratic)</td>
</tr>
<tr>
<td>RLL</td>
<td>0.861 (0.861 quadratic)</td>
</tr>
<tr>
<td>LUL</td>
<td>1.00</td>
</tr>
<tr>
<td>Lingula</td>
<td>0.944 (0.971 quadratic)</td>
</tr>
<tr>
<td>LLL</td>
<td>0.904 (0.904 quadratic)</td>
</tr>
<tr>
<td>Whole lung</td>
<td>0.990</td>
</tr>
</tbody>
</table>

**3.3.5.5 Hyperinflation Component**

Lobar hyperinflation scores varied from 0 – 3 (median 1) out of a maximum score of 4.5.

<table>
<thead>
<tr>
<th>CFCT hyperinflation score</th>
<th>RUL</th>
<th>RML</th>
<th>RLL</th>
<th>LUL</th>
<th>Lingula</th>
<th>LLL</th>
<th>Whole lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>1/0</td>
<td>0/0</td>
<td>1/1</td>
<td>0.5/0.5</td>
<td>0/0</td>
<td>1/1</td>
<td>4/3</td>
</tr>
<tr>
<td>Min</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Max</td>
<td>3/3</td>
<td>1/3</td>
<td>31.5</td>
<td>3/3</td>
<td>3/1</td>
<td>3/3</td>
<td>14/14.5</td>
</tr>
</tbody>
</table>

(Observer 1 [TS]/Observer 2 [BR])

The median ICC for lobar hyperinflation score was 0.819 (min 0.625, max 0.919).
Individual ICC values for hyperinflation score at a lobar and whole lung level are below.

<table>
<thead>
<tr>
<th>Lobe</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUL</td>
<td>0.908</td>
</tr>
<tr>
<td>RML</td>
<td>0.625</td>
</tr>
<tr>
<td>RLL</td>
<td>0.801</td>
</tr>
<tr>
<td>LUL</td>
<td>0.919</td>
</tr>
<tr>
<td>Lingula</td>
<td>0.773</td>
</tr>
<tr>
<td>LLL</td>
<td>0.836</td>
</tr>
<tr>
<td>Whole lung</td>
<td>0.888</td>
</tr>
</tbody>
</table>

Bland-Altman plot comparing the CFCT scores of observer 1 and observer 2.
Figure 1 - Coronal CT reconstructions of a 16 year old boy with cystic fibrosis. a) there is upper lobe predominant bronchiectasis, bronchial wall thickening and mucus plugging. b) Narrowing the window width exaggerates the mosaic attenuation of “small airways disease” at the lung apices at the medial right lung base. The CFCT summary score in this patient was 54.8 (22.6% of the maximum possible score).

Figure 2 - Coronal CT reconstructions of a 9 year old girl with cystic fibrosis. a) Whilst there is mild left lower lobe bronchiectasis, wall thickening and atelectasis and some upper lobe mucus plugging, the predominant feature is small airways disease. The CFCT summary score in this patient was 17 (7% of the maximum possible score).
### 3.3.5.6 Summary of CT Disease Extent and Interobserver Agreement Measures

The component level median structural disease severity scores within our cohort are summarised below as whole lung totals.

<table>
<thead>
<tr>
<th>Component</th>
<th>Max possible whole lung score</th>
<th>Median whole lung score (%)</th>
<th>Min whole lung score (%)</th>
<th>Max whole lung score (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiectasis</td>
<td>72 (12x6)</td>
<td>4.63 (6.4%)/5 (6.9%)</td>
<td>0/0</td>
<td>20.75 (28.8%)/20.75 (28.8%)</td>
</tr>
<tr>
<td>Mucus plugging</td>
<td>36 (6x6)</td>
<td>5 (13.9%)/5 (13.9%)</td>
<td>0/0</td>
<td>23 (63.9%)/18 (50%)</td>
</tr>
<tr>
<td>Wall thickening</td>
<td>54 (9x6)</td>
<td>4.5 (8.3%)/6.75 (12.5%)</td>
<td>0/0</td>
<td>17 (31.5%)/18 (50%)</td>
</tr>
<tr>
<td>Parenchymal</td>
<td>54 (9x6)</td>
<td>1 (1.9%)/1 (1.9%)</td>
<td>0/0</td>
<td>8 (14.8%)/8 (14.8%)</td>
</tr>
<tr>
<td>Hyperinflation</td>
<td>27 (4.5x6)</td>
<td>4 (14.8%)/3 (11.1%)</td>
<td>0/0</td>
<td>14 (51.9%)/14.5 (53.7%)</td>
</tr>
</tbody>
</table>

(Observer 1 [TS]/Observer 2 [BR])

#### Median CFCT component scores (% maximum score)

![Median CFCT component scores chart](chart.png)
As expected for a young cohort of CF and PCD patients, small airways disease (demonstrated as mosaic attenuation on CT and assessed by the “hyperinflation” component score of the CFCT scoring system) and mucus plugging predominate within our cohort.

Although not statistically significant, there is a general trend toward higher hyperinflation scores with lower bronchiectasis scores in the younger patients within our cohort. This is demonstrated in the graph below plotting difference between hyperinflation and bronchiectasis scores by participant age.

Although at a whole lung level, interobserver variability for each component was considered very good to excellent, the least reproducible component was the hyperinflation score. (ICC from 0.4-0.6 considered moderate agreement, 0.6-0.8 good, 0.8-0.9 very good and >0.9 excellent).
<table>
<thead>
<tr>
<th>Component</th>
<th>Median lobar ICC (range)</th>
<th>Whole lung ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiectasis</td>
<td>0.963 (0.951-0.974)</td>
<td>0.989</td>
</tr>
<tr>
<td>Mucus plugging</td>
<td>0.963 (0.894-0.973)</td>
<td>0.976</td>
</tr>
<tr>
<td>Bronchial wall thickening</td>
<td>0.900 (0.872-0.988)</td>
<td>0.973</td>
</tr>
<tr>
<td>Parenchymal findings</td>
<td>0.990 (0.945-1.00)</td>
<td>0.992</td>
</tr>
<tr>
<td>Hyperinflation</td>
<td>0.819 (0.625-0.919)</td>
<td>0.888</td>
</tr>
</tbody>
</table>
### 3.3.5.7 Comparison with Other Clinical Measures:

<table>
<thead>
<tr>
<th>CT measure</th>
<th>Age</th>
<th>IV and PO antibiotic courses</th>
<th>Lowest FEV₁ (%)</th>
<th>Lowest FEV₁/FVC</th>
<th>LCI₂.₅</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole lung</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson's p</td>
<td>0.412</td>
<td>0.385</td>
<td>-0.474</td>
<td>-0.451</td>
<td>0.812</td>
</tr>
<tr>
<td></td>
<td>0.057</td>
<td>0.077</td>
<td>0.026</td>
<td>0.035</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson's p</td>
<td>0.516</td>
<td>0.005</td>
<td>-0.263</td>
<td>-0.327</td>
<td>0.789</td>
</tr>
<tr>
<td></td>
<td>0.014</td>
<td>0.981</td>
<td>0.238</td>
<td>0.138</td>
<td>0.001</td>
</tr>
<tr>
<td>Peribronchial thickening</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson's p</td>
<td>0.286</td>
<td>0.407</td>
<td>-0.290</td>
<td>-0.161</td>
<td>0.555</td>
</tr>
<tr>
<td></td>
<td>0.196</td>
<td>0.060</td>
<td>0.190</td>
<td>0.473</td>
<td>0.039</td>
</tr>
<tr>
<td>Mucus plugging</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson's p</td>
<td>0.266</td>
<td>0.291</td>
<td>-0.426</td>
<td>-0.326</td>
<td>0.723</td>
</tr>
<tr>
<td></td>
<td>0.232</td>
<td>0.188</td>
<td>0.048</td>
<td>0.139</td>
<td>0.003</td>
</tr>
<tr>
<td>Parenchymal findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson's p</td>
<td>0.177</td>
<td>0.328</td>
<td>-0.423</td>
<td>-0.663</td>
<td>0.205</td>
</tr>
<tr>
<td></td>
<td>0.432</td>
<td>0.136</td>
<td>0.050</td>
<td>0.001</td>
<td>0.482</td>
</tr>
<tr>
<td>Hyperinflation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson's p</td>
<td>0.143</td>
<td>0.642</td>
<td>-0.510</td>
<td>-0.444</td>
<td>0.599</td>
</tr>
<tr>
<td></td>
<td>0.526</td>
<td>0.001</td>
<td>0.015</td>
<td>0.038</td>
<td>0.024</td>
</tr>
</tbody>
</table>

A statistically significant association was demonstrated between age and the bronchiectasis component score, with whole lung summary score approaching statistical significance with both scores increasing with age, as expected.
The spirometry figures with the best correlation to CT scores were the lowest readings in the preceding 6 months (as opposed to the best, median or most contemporaneous readings) with statistically significant correlations between the lowest FEV\textsubscript{1} and the whole lung score and mucus plugging, parenchymal findings and hyperinflation component scores. Significant correlations were also demonstrated between the lowest FEV\textsubscript{1}/FVC and the whole lung score, parenchymal findings and hyperinflation scores. As expected, as the disease severity by CT increases, the lung function by spirometry worsens.
There was clear correlation between CT markers of both large airways disease and hyperinflation (a presumed surrogate for small airways disease) with LCI_{2.5}. The only CT component that did not demonstrate statistically significant correlation with LCI_{2.5} was the parenchymal score. This is to be expected as areas of collapsed or consolidated lung will not contribute to ventilation and as such are ‘invisible’ to LCI.
The only CT marker with significant correlation to disease stability, as inferred by the number of antibiotic courses in the preceding 6 months, was the hyperinflation component score with more exacerbations in those with higher hyperinflation scores (Pearson’s 0.642, p=0.001).
Figure 3 - a) Patient 3 (a 14 year old boy with cystic fibrosis) had normal lungs and airways on CT (CFCT summary score 0) and the lowest LCI of the cohort (LCI_{2.5} = 8.6). He had 2 courses of antibiotics in the 6 months preceding imaging. b) Compare this to patient 16 (a 16 year old boy with cystic fibrosis) who had the highest CFCT score (22.6% of the maximum possible score), the highest LCI (LCI_{2.5} = 20.1) and 4 courses of antibiotics in the 6 months preceding imaging.
3.4 Discussion:

Statement of principal findings

Twenty-two patients were prospectively recruited with a median age of 14 years (range 6-35). All had spirometry measures (median of 10 days between imaging and spirometry and a maximum period of 32 days), with a wide range of disease severities based on percent predicted FEV$_1$ (36% to 112%). Whilst six patients declined LCI measurement, 15 completed three successful LCI measurements within just 2 hours of their MRI examination. Whilst there was a wide range of LCI values across the cohort, it should be noted that only one patient's LCI fell within the normal range (LCI values ranged from 7.64 – 21.09 with a median of 11.53). This will somewhat limit the generalizability of our CT and subsequent MRI findings and, as with all CF imaging studies, our later results will have to be interpreted within the age and disease severity ranges of our cohort (i.e. the findings may not reasonably be extrapolated to younger cohorts with more subtle disease or to older cohorts with more severe disease).

Exacerbations, defined as episodes requiring treatment with either intravenous or oral antibiotics ranged from 0 to 5 for any antibiotic courses and 0-3 for IV antibiotics with no statistically significant association between number of exacerbations and participant age ($r=-0.076$, $p=0.736$).

In line with expectations at an institution which does not perform routine biennial CT surveillance of people with CF or PCD, the majority of scans were performed for declines in lung function with no clinically apparent
cause (generally searching for imaging evidence of clinically occult infection), recent infective exacerbation (performed at the end of admission for IV antibiotics as a form of ‘re-staging’ of disease severity, or as a single time-point surveillance scan at the time of transition from paediatric to adult care.

CFCT scores across the cohort demonstrated a relatively wide range of disease severities, but all scores were toward the lower end of severity compared to published studies. For example, Ciet et al imaged a similar number of people with CF by both CT and MRI with the CTs scored with the same CFCT scoring system. They recruited 38 patients, but with a much wider age range (6-51, median 21). Disease severity was only assessed by imaging, and only the 75th centiles of the bronchiectasis and hyperinflation scores are published, but the 75th centiles in Ciet’s study are in the region of our maximum scores (bronchiectasis score 75th centile 28.9% compared to our maximum score of 28.8%, median 6.4%; hyperinflation score 60%, compared to our maximum score of 51.9%, median 14.8%). Our bronchiectasis scores ranged from 0 – 28.8% of maximum possible, mucus plugging from 0- 63.9%, bronchial wall thickening from 0 – 31.5%, parenchymal scores from 0 – 14.8% and hyperinflation scores from 0 – 51.9%. This is important – as discussed in the introduction, cohorts with less severe disease have typically been found to show less good interobserver agreement in structural lung disease scores[76].
Interobserver agreement in CFCT scores was very good to excellent. ICC values for bronchiectasis varied from 0.951 – 0.974 at a lobar level and was 0.989 at a whole lung level with a slight tendency toward divergence between the two observers from a score of 10 upwards. At this level the limits of agreement were still in the order of 3 points – a 4% difference in percentage score.

ICC values for mucus plugging varied from 0.894 – 0.973 at a lobar level and was 0.976 at a whole lung level. The Bland Altman plot demonstrates a single outlier at the severe end of the spectrum, but limits of agreement of 2 to 3 points (3.7 – 5.5% of total possible score).

Bronchial wall thickening scores follow a similar trend with lobar ICC values from 0.872 – 0.988 and a whole lung level ICC of 0.900 with similarly close limits of agreement of around 2 points (a 3.7% difference in percentage possible score).

As should be expected, the best agreement was in parenchymal scores (consisting of complete lobar collapse or replacement by cicatrizing bronchiectasis). Lobar ICCs varied from 0.945 – 1.00 with a whole lung level ICC of 0.990 and limits of agreement of less than 1 point (1.9% of a maximum possible score).

Again, as expected, the greatest variability in scores between the two observers was within the hyperinflation scores. Lobar score ICCs varied from 0.625 to 0.919 with the lowest agreement within the smallest lobes (right middle lobe 0.625, lingula 0.773). At a whole lung level ICC was 0.888. The Bland Altman plot demonstrates 100% agreement in those scoring 0 for hyperinflation, but divergence in scores (in both directions) as the
degree of perceived hyperinflation increases. This is a particularly important finding as the hyperinflation score formed the greatest part of the median total scores (i.e. was the most prevalent/severe finding in our ‘average’ participant). Although not specifically published in any imaging trials I am aware of, it is clear from personal practice and from studies with a less broad participant age range, that younger patients tend to have more pronounced hyperinflation compared to the extent/severity of their large airways disease. This association did not reach significance within our small cohort, but will be explored further in future studies at the Royal Brompton. This observation highlights the importance of recognising and potentially quantifying hyperinflation as part of a CF imaging examination.

The importance of the hyperinflation score is borne out by the correlation of CFCT scores in our cohort with their other clinical measures of disease severity. The hyperinflation score was the only CFCT score to show significant correlation with the number of exacerbations within 6 months of the imaging tests (r=0.642, p=0.001). Other significant correlations were with $LCl_{2.5}$ (r=0.205 – 0.812, p=<0.001 - 0.482) and, to a lesser degree, spirometry (r=-0.263 to -0.510, p=0.015 - 0.238). It is possible that spirometry fared less well compared to CT as LCI was performed within a much shorter timeframe of imaging (mostly on the same day) whereas spirometry was collected opportunistically and retrospectively with up to 32 days between spirometry and imaging.
As expected, there was positive or near-positive correlation between CFCT score and participant age, although at the centre of age range there was still quite a large variability in CT score.

**Strengths and weaknesses**

Although the number of participants recruited is small, the age of our participants is very much centred on the early teenage years (median 14 and only 4 patients over 20). Whilst the extremes of our cohort will allow us to prove the utility of imaging at a young age and provide some more marked structural lung disease (in the younger and older patients respectively), most of the participants were recruited around the time of transition from paediatric to adult care. This is clearly a time of significant change (moving school, passing through puberty, gaining independence and beginning to push boundaries as a result) with all the foreseeable issues with compliance with a medical regimen that would challenge even the most strictly motivated of adults. This time in the life of a person with CF has been associated with a significant decline in lung function, demonstrated across multiple registry datasets [7,207,208]. Whilst this decline is likely multifactorial, decreased treatment adherence is likely a significant factor [209,210]. As treatments advance, if there is an age group to target for a regular surveillance test rationalising multiple system reviews into a single study, then this is the age group to choose.

The time between multiple breath wash-out testing (for LCI) and imaging is a particular strength, with the majority imaged on the same day as LCI measurement. It is unfortunate that only one participant had an LCI within
the normal range, as further analyses based on binary “normal” or “abnormal” classifications would be possible with more normal LCI participants, but given the necessity for a “clinically indicated CT scan” in our trial design, this is not a great surprise.

The longer time period between imaging and spirometry (as opposed to LCI) is perhaps a more notable weakness. It should also be noted that as the spirometry was collected retrospectively and the number of measurements collected varied widely (between 1 and 12 measurements each), no spirometric definition of stability could be used to select the most ‘appropriate’ spirometry values to use. As a result single time point measures of “most contemporaneous”, “highest” or “lowest” spirometry values had to be used with the possibility of bias being introduced (those with more stable disease will likely have fewer measurements and therefore fewer results to analyse).

A further weakness is the availability of information regarding antibiotic usage, used here as a measure of disease stability. Although the complete electronic patient record was searched for 6 months prior to imaging, it is feasible that antibiotics could have been prescribed by a GP or local hospital. Whilst this would likely be included in letters reviewed on our EPR, some courses may have been omitted.

A further weakness is the lack of spirometer guidance of the CT acquisitions. This will be further discussed later in the thesis, but, as discussed in the introduction, studies have shown significant differences in computer-based measures of bronchial geometry between inspiratory and
expiratory phase CT images [72]. The use of PRAGMA scoring in CF research studies requires the acquisition of 2 spirometer guided image sets, one in inspiration and a second in expiration. As discussed in the introduction, regular surveillance CT for people with CF is not our clinical practice in the UK as the exposure to ionising radiation is deemed to be unnecessary. Similarly, expiratory CT images are not generally acquired in people with CF at our institution as they are deemed an unjustified extra radiation exposure. The addition of expiratory images may well have increased interobserver agreement in CFCT hyperinflation scores, but this likely does not justify the extra exposure for a purely research element of an otherwise clinically indicated scan.

**Strengths and weaknesses compared to other studies (and discrepant results)**

As described above, Ciet et al imaged a similar number of people with CF by both CT and MRI with the CTs scored with the same CFCT scoring system. They recruited 38 patients, but with a much wider age range (6-51, median 21). In this respect, our cohort has considerable strengths, with the median around the age of expected lung function decline and a much tighter age range. Ciet et al only assessed disease severity by imaging, with no correlation to LCI, spirometry or exacerbations and their subsequent MR imaging was only structural. They did, however, manage to perform the CT and MRI on the same day in all patients – a considerable feat [211].
Robinson et al recruited 36 children of a similar age to our cohort (median 12, IQR 3.7) and examined the relationships of CFCT scores and spirometry over 4 scans in a 2 year period (baseline, 3 months, 1 year and 2 years) demonstrating no change at 3 months, but significant increases in mucus plugging and quantitative hyperinflation scores at 1 year with significant changes in bronchiectasis and total scores at 2 years. They additionally found that baseline “total” and “parenchymal” scores predicted progression in bronchiectasis at two years as did change in hyperinflation score over a one year time period. The addition of longitudinal follow up is clearly an advantage over our study, but the omission of LCI as a lung function measure is a considerable weakness and there is no subsequent comparison with MRI outputs.

Like ours, their study involved a training round followed by CFCT scoring by two observers. An adjudicator was used in cases of a discrepancy of more than 10 points or 5% of maximum score, with scores adjudicated by Alan Brody himself. Notably, this occurred in over 1/3rd of CTs scored. Whilst we did not have Alan Brody to adjudicate, our interobserver agreement was better across all domains, with significantly better agreement for parenchymal scores[66]. In fact, the only component score to breach a 5% limit of agreement, in our study, was mucus plugging (3.7-5.5% discrepancy).
<table>
<thead>
<tr>
<th>CFCT feature</th>
<th>ICC (This study)</th>
<th>ICC (Robinson et al.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiectasis</td>
<td>0.989</td>
<td>0.89 – 0.96 (across 4 CTs)</td>
</tr>
<tr>
<td>Bronchial wall</td>
<td>0.973</td>
<td>0.72 – 0.85</td>
</tr>
<tr>
<td>Mucus plugging</td>
<td>0.976</td>
<td>0.90 – 0.95</td>
</tr>
<tr>
<td>Parenchymal score</td>
<td>0.992</td>
<td>0.53 – 0.88</td>
</tr>
<tr>
<td>Hyperinflation</td>
<td>0.888</td>
<td>0.80 – 0.88</td>
</tr>
</tbody>
</table>

Ellemunter et al recruited 41 patients over a similar age range (6 – 26, median 14), with very similar ranges of LCI_{2.5} (6.1 – 10.6), demonstrating concordance of CT scores and LCI_{2.5}, however, this was only examined in a binary fashion comparing normal to abnormal. A linear association was reported, but no correlation coefficients published. Furthermore, they used a modified version of the Bhalla CT score (a non-CF specific airways disease scoring system), which does not include a domain for hyperinflation. No training round was reported prior to scoring and no interobserver variability data published [40].

Tepper et al examined the relationship between CFCT scores and Cystic Fibrosis Questionnaire Respiratory Symptom Scores (CFQ-R RSS) in 40 children and 32 adolescents demonstrating that bronchiectasis and hyperinflation scores correlated with symptoms scores (r=-0.38 and -0.35, p=<0.001 and 0.003 respectively) and that exacerbations were also
associated with bronchiectasis and hyperinflation (RR 1.1 and 1.02, 95% CI 1.02-1.19 and 1.00-1.05, p=0.002 and 0.034 respectively). The CTs were, however, scored by a single observer, with a second observer scoring only 35% of the studies. By comparison, in my study, all CTs were scored by two observers. There is also no mention of a training round prior to scoring. Perhaps as a result, there were significant differences in ICC values obtained for interobserver variability. Only whole lung level ICCs for bronchiectasis and hyperinflation are reported and these are summarised below[63].

<table>
<thead>
<tr>
<th>CFCT feature</th>
<th>ICC (This study)</th>
<th>ICC (Tepper et al.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiectasis</td>
<td>0.989</td>
<td>0.91</td>
</tr>
<tr>
<td>Hyperinflation</td>
<td>0.888</td>
<td>0.50</td>
</tr>
</tbody>
</table>

The addition of the CFQ-R questionnaire to our study would have been interesting and its inclusion will be considered as part of the planned follow up trial. However, LCI did not feature in Tepper’s study. Tepper et al managed to recruit far more patients than I did (72, compared to only 22), however, as discussed, CT practice varies significantly from country to country and this level of CT activity is just not present in the UK’s CF practice (and I believe this is entirely appropriate)[63]. Our recruitment is, however, quite similar in size to other published series of people with CF undergoing MRI (discussed in the next chapter).

A recent study by Sandvik et al, added a longitudinal assessment with PRAGMA scoring applied to the imaging of 57 children aged 6 – 18 at
baseline and 2 years subsequent. No interobserver variability in PRAGMA scoring was reported. Again, the addition of extra imaging time points is of considerable advantage, and allows an imaging-defined period of stability. Interestingly though, they found 50% of their cohort demonstrated a decrease in PRAGMA bronchiectasis scores (particularly interesting as bronchiectasis is considered to be an irreversible process - see the Fleischner society glossary of terms – it is for this reason that many prefer use of the term “bronchial dilatation” over “bronchiectasis” in paediatric practice) [212,213]. This highlights the need for longitudinal repeatability studies prior to the use of imaging as a primary trial endpoint and our single time point study is limited in this respect. Clearly, longitudinal studies of MRI findings are of particular interest as the ability to frequently repeat MR imaging without the cumulative radiation dose associated with follow up CT is arguably the major ‘selling point’ of structural lung MRI.

**Meaning of study**

We have successfully recruited a cohort of people with a wide range of disease severities, grouped around the disease severity expected from previously published data in cohorts of a similar age. The median age is in a particularly relevant period in the life of someone with chronic suppurative lung disease and will make the correlations with MRI outputs particularly relevant. My study has particular strengths, especially in the inclusion of LCI on the same day as imaging, and whilst the degree of structural disease on CFCT scoring is well toward the less severe end of the spectrum, our interobserver agreement in CFCT component scores is very good to
excellent throughout, generally higher than those in published datasets and, likely the result of the training rounds performed prior to study scoring. Meanwhile, weaknesses were generally unavoidable, including low recruited numbers secondary to infrequent use of CT, longer time difference between spirometry and lack of use of a validated symptom questionnaire such CFQ-R, the addition of which into an already full day of tests would likely have not been logistically possibly. This background data will be put to good use in comparison with the MRI outputs discussed in the subsequent chapter.

Unanswered questions and future research

It remains to be seen, as is the focus of the subsequent chapters, how MRI structural scores will compare to CFCT scores and particularly how MRI measures of ventilation may prove to be a significant advance in comparison to the relatively less reproducible CFCT hyperinflation score. It would also be interesting to know whether a form of quantitative CT technique (such as low attenuation mapping) could improve on semiquantitative visual assessment of hyperinflation. This is addressed in chapter 5.

The data supporting, but not proving, my observation of an inversion in small airways:large airways disease extent ratio by late teenage years, is worth following up and would benefit from a far larger dataset. The vertical model design of The Royal Brompton lends itself perfectly to a transition study and this will be considered in the near future. In the meantime, recent
recruitment to a start of triple therapy trial (RECOVER: NCT04602468) has provided us with spirometry controlled CTs for a number of teenagers and adults and is due to provide us with a matched cohort of younger children who will be followed up over a 3-year period. This dataset may provide further useful data regarding longer-term repeatability in CFCT scores, particularly in the context of highly effective small module therapies as well as providing further correlation with LCI and CFQ-R at each time point.
Chapter 4 - Rapid MRI Assessment of Structural Lung Disease

4.1 Introduction –

As discussed in the introduction, there have been many prior studies into the sensitivity and specificity of different MRI sequences to features of structural lung disease using CT as the gold standard. Particular success has been reported with ultrashort and zero echo time sequences, but these are not currently commercially available and are not therefore widely implementable. The most successful, widely available conventional sequences reported to date are the relatively motion insensitive radial acquisition techniques. Ciet et al reported use of a PROPELLER sequence with respiratory gating via a navigator technique, triggering acquisition at end expiration. This required 20-45 minutes for acquisition of a single proton density weighted axial dataset with a reported specificity for bronchiectasis of 100% compared to CT, but a sensitivity of only 33%, in a cohort with more marked structural lung disease than ours. The authors concluded that the technique was not adequate for diagnosis, but was appropriate for follow up[211].

Respiratory navigator gating has since improved with a more robust phase scout for respiratory triggering (this detects tiny fluctuations in the B0 field induced by respiratory motion), but still results in relatively lengthy acquisition times.
The majority of young patients with cystic fibrosis are not significantly short of breath and are, therefore, likely able to perform short breath holds. It is possible that with the better radial acquisition sequences now available combined with short repeated breath holds, structural lung imaging could be achieved with adequate image quality, in a considerably shorter time period than previously possible. A shorter structural lung disease protocol would allow sufficient extra time on the scanner for the addition of the quantitative ventilation imaging techniques discussed in later chapters - all within a single MRI examination.

The objective of this chapter is to compare scoring of a fast, widely available MR sequence for structural imaging to scores from CT, and to compare MRI-CT correlation with published data from previous comparison studies using slower MR techniques. The aim is to assess whether these fast acquisitions are of good enough quality to include both structural and functional lung MRI techniques in a single examination.

Eichinger et al developed a semiquantitative visual scoring system specifically for MR imaging in CF imaging. There are significant differences between CFCT and Eichinger scoring systems, with system design influenced by the investigators own experience of lung MRI. The lower spatial and temporal resolution of MRI compared to CT led Eichinger et al to combine bronchiectasis and bronchial wall thickening into a single measure ‘bronchiectasis/bronchial wall thickening’ based on their experience that differentiating dilatation from thickening is not generally possible by MRI.
and increased prominence of a visualised airway is likely to be secondary to a combination of thickening and dilatation. This aligns with my experience from previous use of MRI in people with CF and, although this is not backed up by published evidence, this is one of the reasons this scoring system was chosen for this study rather than merely applying a CT scoring system to the MR images. The other key difference is that CFCT scores several features (including bronchiectasis and bronchial wall thickening) in both severity and extent, whereas Eichinger scoring is purely extent based. The reasoning here is identical. Severity scoring of bronchial wall thickening, for example, involves comparison of bronchial wall diameter to adjacent pulmonary artery diameter. When individual bronchial walls cannot be completely resolved, addition of a severity component to MR scoring would be inappropriate.

**4.2 Methods –**

This has described in detail in the methods chapter, but in brief, 6 mm thick non-fat saturated T2 BLADE images were acquired through the whole thorax in axial and coronal planes, using breath-holds of 14 seconds duration with a manually timed break of approximately 10 seconds, for between-breath recovery, and all images acquired in 3 concatenations (i.e. 1 minute and 2 seconds per dataset, 2 minutes 4 seconds for the matched axial and coronal sections). Images were scored using the Eichinger scoring system and scores compared to outputs from the CT scoring described in the previous chapter.
4.3 Results –

22 patients were prospectively recruited following clinical requests for CT. Of note, no patients approached declined MR scanning. The median interval between CT and MRI was 0 days (range 0 – 5 days). 12 patients had both studies performed on the same day within 3 hours of each other.

The full MRI protocol consisted of two mapping techniques, dynamic oxygen enhanced MRI, matrix pencil decomposition MRI (a more advanced equivalent of Fourier decomposition MRI) structural lung imaging and imaging of the liver and paranasal sinuses and took 45-60 minutes. All patients completed the full examination.

As described above each structural acquisition required only 1 minute, 2 seconds to complete.

4.3.1 MRI Structural Scores and Inter-Observer Variability

4.3.1.1 Bronchiectasis/Bronchial Wall Thickening

Lobar modified Eichinger scores for combined ‘bronchiectasis/bronchial wall thickening’ varied from 0 – 2 (median 0) out of a maximum possible 2. With whole lung bronchiectasis/bronchial wall thickening scores from 0 - 9 (median 3).

<table>
<thead>
<tr>
<th>ModEich Bx/BWT score</th>
<th>RUL</th>
<th>RML</th>
<th>RLL</th>
<th>LUL</th>
<th>Lingula</th>
<th>LLL</th>
<th>Whole lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.5</td>
<td>3</td>
</tr>
<tr>
<td>Min</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Max</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>9</td>
</tr>
</tbody>
</table>
Weighted Kappa values for interobserver variability in lobar Eichinger bronchiectasis/wall thickening scores and ICC for whole lung scores are presented in the table below.

<table>
<thead>
<tr>
<th>Lobe</th>
<th>Linear/quadratic weighted Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUL</td>
<td>0.612/0.694</td>
</tr>
<tr>
<td>RML</td>
<td>0.623/0.678</td>
</tr>
<tr>
<td>RLL</td>
<td>0.553/0.553</td>
</tr>
<tr>
<td>LUL</td>
<td>0.607/0.714</td>
</tr>
<tr>
<td>Lingula</td>
<td>0.583/0.615</td>
</tr>
<tr>
<td>LLL</td>
<td>0.727/0.727</td>
</tr>
<tr>
<td>Whole lung ICC</td>
<td>0.965</td>
</tr>
</tbody>
</table>

4.3.1.2 Mucus Plugging

Lobar modified Eichinger mucus plugging scores varied from 0 – 2 (median 0.25) out of a maximum possible 2. Whole lung mucus plugging scores varied from 0 – 9 (median 2.5).

<table>
<thead>
<tr>
<th>ModEich MP score</th>
<th>RUL</th>
<th>RML</th>
<th>RLL</th>
<th>LUL</th>
<th>Lingula</th>
<th>LLL</th>
<th>Whole lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>1</td>
<td>0</td>
<td>0.5</td>
<td>0</td>
<td>0</td>
<td>0.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Min</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Max</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>9</td>
</tr>
</tbody>
</table>

Kappa values for interobserver variability in the modified Eichinger lobar mucus plugging scores and ICC for whole lung mucus plugging scores are presented below.

<table>
<thead>
<tr>
<th>Lobe</th>
<th>Linear/quadratic weighted Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUL</td>
<td>0.845/0.865</td>
</tr>
<tr>
<td>RML</td>
<td>0.574/0.615</td>
</tr>
<tr>
<td>RLL</td>
<td>0.818/0.818</td>
</tr>
<tr>
<td>LUL</td>
<td>0.636/0.706</td>
</tr>
<tr>
<td>Lingula</td>
<td>0.505/0.505</td>
</tr>
<tr>
<td>LLL</td>
<td>0.545/0.545</td>
</tr>
<tr>
<td>Whole lung ICC</td>
<td>0.938</td>
</tr>
</tbody>
</table>
4.3.1.3 Abscesses/ Sacculations

No patients had a pulmonary abscess and all areas of saccular bronchiectasis were scored as bronchiectasis and were not therefore re-scored as sacculations.

4.3.1.4 Consolidation

Lobar modified Eichinger consolidation scores varied from 0 – 2 (median 0) out of a (max possible 2) with whole lung consolidation scores from 0 – 5 (median 1).

<table>
<thead>
<tr>
<th>ModEich consolidation score</th>
<th>RUL</th>
<th>RML</th>
<th>RLL</th>
<th>LUL</th>
<th>Lingula</th>
<th>LLL</th>
<th>Whole lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Min</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Max</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

Kappa values for interobserver variability in the modified Eichinger lobar consolidation scores and ICC for whole lung consolidation scores are presented below.

<table>
<thead>
<tr>
<th>Lobe</th>
<th>Linear/ quadratic weighted Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUL</td>
<td>0.699/0.699</td>
</tr>
<tr>
<td>RML</td>
<td>0.820/0.871</td>
</tr>
<tr>
<td>RLL</td>
<td>0.744/0.744</td>
</tr>
<tr>
<td>LUL</td>
<td>0.450/0.450</td>
</tr>
<tr>
<td>Lingula</td>
<td>0.708/0.776</td>
</tr>
<tr>
<td>LLL</td>
<td>0.891/0.891</td>
</tr>
<tr>
<td>Whole lung ICC</td>
<td>0.877</td>
</tr>
</tbody>
</table>
### 4.3.1.5 Summary Tables

Summary tables of whole lung component scores and of interobserver agreement at a lobar (Kappa) and whole lung (ICC) level are presented below.

#### Component scores

<table>
<thead>
<tr>
<th>Component</th>
<th>Max possible whole lung score</th>
<th>Median whole lung score (%)</th>
<th>Min whole lung score (%)</th>
<th>Max whole lung score (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiectasis/Wall thickening</td>
<td>12 (2x6)</td>
<td>3 (25%)</td>
<td>0</td>
<td>9 (75%)</td>
</tr>
<tr>
<td>Mucus plugging</td>
<td>12 (2x6)</td>
<td>2.5 (20.8%)</td>
<td>0</td>
<td>9 (75%)</td>
</tr>
<tr>
<td>Collapse/consolidation</td>
<td>12 (2x6)</td>
<td>1 (8.3%)</td>
<td>0</td>
<td>5 (41.7%)</td>
</tr>
</tbody>
</table>

#### Inter-observer agreement

<table>
<thead>
<tr>
<th>Component</th>
<th>Median lobar linear Kappa (range)</th>
<th>Median lobar quadratic Kappa (range)</th>
<th>Median whole lung ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiectasis/Wall thickening</td>
<td>0.610 (0.553-0.727)</td>
<td>0.686 (0.553-0.727)</td>
<td>0.965</td>
</tr>
<tr>
<td>Mucus plugging</td>
<td>0.605 (0.505-0.843)</td>
<td>0.661 (0.505-0.865)</td>
<td>0.938</td>
</tr>
<tr>
<td>Collapse/consolidation</td>
<td>0.726 (0.450-0.891)</td>
<td>0.760 (0.450-0.891)</td>
<td>0.877</td>
</tr>
</tbody>
</table>

(Kappa 0.5 moderate, 0.7 good, 0.8 excellent)
4.3.2 Comparison of Inter-observer Agreement at a Whole Lung Level Between MRI and CT

ICC for whole lung CFCT component scores was presented in the previous chapter and are summarised in the table below. Remembering that this is a comparison of different scoring systems applied to their specific modality, at a component level interobserver variability seems comparable between the two techniques.

<table>
<thead>
<tr>
<th>Component</th>
<th>MRI Median whole lung ICC</th>
<th>CT Median whole lung ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiectasis/Wall thickening</td>
<td>0.965</td>
<td>0.989(Bx)/0.979(BWT)</td>
</tr>
<tr>
<td>Mucus plugging</td>
<td>0.938</td>
<td>0.976</td>
</tr>
<tr>
<td>Consolidation/Parenchymal findings</td>
<td>0.877</td>
<td>0.877(consolidation only)/0.992 (complete parenchymal score)</td>
</tr>
</tbody>
</table>

4.3.3 Comparison of Disease Severity by MRI vs CT –

To examine concordance in assessment of overall disease severity, summary scores of all features could be compared, bearing in mind that there are problems with this approach. Summary scores are un-weighted composite indices of a set of component scores and as such may mask discrepancies in individual component scores[62].
A Kolmogorov-Smirnov test confirmed that none of the summary or component scores are normally distributed within our cohort so Spearman's rank was used as the correlation method throughout.

4.3.3.1 Whole Lung Summary Disease Severity Scores

Total disease summary scores correlated very well (Spearman’s rho 0.857, p <0.001). The scatter and Bland-Altman plots below both demonstrate a tendency for the Eichinger MRI scoring to exaggerate disease severity compared to CT. The degree of exaggeration increases as the disease severity increases, as would be expected given the reduced granularity in attainable scores compared to the CFCT system.
4.3.3.2 Bronchiectasis/Bronchial Wall Thickening

Comparison of bronchiectasis and bronchial wall thickening component scores is more complicated as, quite reasonably, the Eichinger MRI score groups bronchiectasis and bronchial wall thickening into a single composite score, the argument for combining them being that MRI cannot differentiate the two features. Perhaps more importantly, as discussed in an editorial by A Calder et al. there is also significant inter-dependence of the two features – i.e. rarely is bronchiectasis seen in chronic suppurative lung disease without a degree of bronchial wall thickening[62].

Taking the scores from the Eichinger MRI system and CFCT CT system and comparing the two expressed as percentages of maximum scores, MRI score correlation was strong with CT measures of both ‘bronchiectasis’
(Spearman's Rho 0.743, p=<0.001) and ‘bronchial wall thickening’ (Spearman's Rho 0.766, p=<0.001). However, it should be remembered that lobar bronchiectasis extent scores in CFCT are out of a maximum score of 6 (central and peripheral lung each scored from 0 - 3 in thirds affected) with a multiplier introduced based on the perceived severity of bronchiectasis (from 0 – 3 based on airway diameter compared to that of the adjacent pulmonary artery with a multiplier applied according to the table below).

<table>
<thead>
<tr>
<th>Average perceived severity</th>
<th>Multiplier applied</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1.5</td>
<td>1.25</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
</tr>
<tr>
<td>2.5</td>
<td>1.75</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

A similar system is in place for bronchial wall thickening score by CFCT with severity multipliers of 0-1.5 added according to severity of wall thickening (judged in thirds of the diameter of the adjacent pulmonary artery). As the Eichinger MRI score combines bronchiectasis and bronchial wall thickening into a single measure and does not take feature severity into account (merely extent of disease within each lobe) careful manipulation of the CT data may offer insights into the nature of the features perceived as ‘bronchiectasis’ on MRI.

To better compare with Eichinger MRI scores (composite of bronchiectasis/wall thickening extent expressed in 3 groups, 0 = no disease, 1 = up to 50% involvement, 2 = over 50% involvement), the CFCT ‘bronchiectasis’ and ‘wall thickening’ severity multipliers were removed and the feature extent scores re-scaled such that a CFCT extent score of 0
remained 0, 1-3 was reclassified as a score of 1 (i.e. up to 50% involvement) and 4-6 was reclassified as a score of 2 (i.e. >50%) such that the CFCT extent scores are presented on the same scale as the modified Eichinger MRI scores. Correlation via Spearman’s rank is presented in the table below.

Two further variables were created taking the highest score (bronchiectasis OR wall thickening) and the mean of the two scores (bronchiectasis AND wall thickening). This was done at a whole lung (highest summary score) and individual lobar (sum of the highest lobar component) level.

<table>
<thead>
<tr>
<th>Comparison with MRI Bx/BWT score</th>
<th>Spearman’s Rho</th>
<th>Significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFCT Bx extent</td>
<td>0.735</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CFCT BWT extent</td>
<td>0.748</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CT Bx extent recoded to Eichinger scale</td>
<td>0.677</td>
<td>0.001</td>
</tr>
<tr>
<td>CT BWT extent recoded to Eichinger scale</td>
<td>0.738</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximum CT Eichinger feature extent (Bx or BWT) at whole lung level</td>
<td>0.811</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean CT Eichinger extent score (Bx and BWT) at whole lung level</td>
<td>0.819</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximum CT Eichinger feature extent (Bx or BWT) at lobar level</td>
<td>0.828</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean CT Eichinger extent score (Bx and BWT) at lobar level</td>
<td>0.798</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
All versions of the CT bronchiectasis (Bx) and bronchial wall thickening (BWT) extent scores demonstrate strong to very strong, statistically significant correlation with MRI BxBWT scores. Of note, the bronchial wall thickening component scores seem to correlate very slightly better than the bronchiectasis component scores, but the degree of correlation is further improved by inclusion of both feature scores expressed as a maximum of the two or a mean of both. This suggests that bronchial wall thickening may play more of a role in the detection of large airways disease by MRI than bronchiectasis, but that both are important.

**Figure 4** – Very mild, thin-walled bronchiectasis demonstrated in the left upper lobe in a 9 year old with CF is very hard to discern on the structural MR images (b).
Figure 5 – Thicker walled bronchiectasis in the left lower lobe of the same 9 year old with CF is far easier to appreciate on MRI.

Bronchiectasis extent, recoded to an Eichinger scale, correlated least well.

This is to be expected, as thin-walled bronchiectasis would be far harder to resolve by MRI than by CT no matter how extensive it may be.
The graph above compares the different versions of the CT extent scores to the MRI composite Bx/BWT score. The black line represents $y=x$. The line of best fit to the ‘whole lung mean CT bronchiectasis/wall thickening scores’ (in light pink), runs almost perfectly in parallel ($y = 0.99x + 1.65$) with $y=x$ and is demonstrated separately below.
Simple Scatter of MRI composite Bx/BWT score by mean CT Bx and BWT component extent scores recoded on an Eichinger scale (%)

Bland-Altman plot of MRI Bx/BWT composite scores and mean CT Bx and BWT component extent scores re-coded on an Eichinger scale

R² Linear = 0.580
Severity of bronchiectasis and bronchial wall thickening significantly should also impact the potential for adequate returned signal for visualisation on MRI.

As demonstrated in the table below, the correlation of CT severity scores also demonstrated a marginally better correlation of bronchial wall thickening severity with MRI Bx/BWT scores (as opposed to CT bronchiectasis severity scores). Again, the best level of correlation was with a combined measure comprising the highest of the two scores (Bx or BWT), in keeping with the previously mentioned interdependence of the two features.

<table>
<thead>
<tr>
<th>Correlation with MRI Bx/BWT score (%)</th>
<th>Spearman's Rho</th>
<th>Significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT Bx severity</td>
<td>0.740</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CT BWT severity</td>
<td>0.756</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximum whole lung summary CT Bx or BWT severity score</td>
<td>0.840</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean whole lung CT Bx and BWT severity score</td>
<td>0.823</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sum of maximum lobar Bx or BWT severity scores</td>
<td>0.829</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean of lobar Bx and BWT severity scores</td>
<td>0.798</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Of note, however, and as mentioned above, when visualised as a scatter plot, although correlation of MRI composite Bx/BWT scores with CT severity is very good, the line of best fit of extent scores runs almost perfectly through
y = x. Although severity plays a role in visualisation of large airways disease on MRI, it is solely the disease extent that is being scored as part of the Eichinger score.

4.3.3.3 Mucus Plugging

Comparison of the mucus plugging scores is considerably simpler as both scoring systems merely consider extent of mucus plugging (no measure of severity is included). The Eichinger MRI mucus plugging scores were expressed as percentage (maximum 12) and compared to the CFCT mucus plugging scores also expressed as a percentage (maximum score 36). The CFCT scores were also re-scaled to an Eichinger scale via the same method described in the BxBWT section.
There was very good correlation between the MRI and CT mucus plugging scores with a Spearman’s rho of 0.812 (p<0.001). As was demonstrated with the total disease summary scores, there was a tendency for MRI to exaggerate mucus plugging extent. The Bland-Altman plot below compares the CFCT mucus plugging scores (not converted to an Eichinger scale) to the MRI mucus plugging scores.

<table>
<thead>
<tr>
<th>Comparison with MR mucus plugging score</th>
<th>Spearman’s Rho</th>
<th>Significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFCT mucus plugging score (%)</td>
<td>0.812</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CFCT mucus plugging score re-scaled to an Eichinger scale (%)</td>
<td>0.796</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
**Figure 6** – a) Extensive tree-in-bud (acinar mucus plugging) in a 17 year old girl with CF who had the highest mucus plugging score of our cohort (CFCT mucus plugging score 63.9% maximum). b) Although the rosette morphology of tree-in-bud is harder to appreciate on MRI, nodularity is clearly demonstrated (as is the right upper lobe thick walled bronchiectasis). The Eichinger MRI score was 75% maximum).
4.3.3.4 Abscesses / Sacculations

As stated previously, none of the patients in our cohort had an abscess demonstrated on CT or MRI and saccular bronchiectasis was included in the bronchiectasis component scores on MRI scoring (quite reasonably, there is no separate CFCT component score for sacculations).

4.3.3.5 Collapse / Consolidations

The parenchymal component score from CFCT consists of summed extent-based scores (i.e. no severity assessment) of ‘opacification/atelectasis’, ‘ground glass’ and ‘cysts/bullae’. Collapse, consolidation and ground glass opacification would all be scored as part of the ‘collapse/consolidation’ component of the Eichinger score and as such, removing the cysts/bullae component of the CFCT score will allow comparison of the two modalities.

Figure 7 – Axial CT a) and MRI b) images from the same 17 year old CF patient with extensive tree-in-bud pattern acinar mucus plugging. Again, whilst the spatial resolution of the MRI is clearly inferior to that of CT, the nodular mucus plugging is clearly evident.
<table>
<thead>
<tr>
<th>Comparison with MRI collapse/consolidation score (%)</th>
<th>Spearman’s Rho</th>
<th>Significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFCT combined opacity, atelectasis and ground glass scores (%)</td>
<td>0.564</td>
<td>0.006</td>
</tr>
<tr>
<td>CFCT opacity scores (%)</td>
<td>0.721</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CFCT combined opacity and ground glass scores (%)</td>
<td>0.729</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

As demonstrated in the scatter plot above, taking the CT opacity component alone seems to correlate best with MRI collapse/consolidation scores with the closest fit to y=x and a very slight tendency of MRI to overestimate mild disease and underestimate more severe disease. The Bland-Altman plot below compares the CFCT opacity component score to MRI. The upper and
lower control limits are close (10% would represent a difference in whole lung CT opacity score of only 2 points).

**Figure 8** – a) Coronal CT reconstruction of a 36 year old woman with CF with complete replacement of the left upper lobe by bronchiectasis. b) The cicatrizing bronchiectasis is seen just as well on MRI as on CT.
Figure 9 – a) the same 36 year old also had a round focus of consolidation with peripheral ground glass in the left lower lobe, in keeping with known pulmonary aspergillosis. b) The ground glass halo is less easy to appreciate, but the consolidation is well demonstrated with an ill defined border (the MRI equivalent of the ground glass halo on CT).

4.3.3.6 Summary Table

A summary of the above comparisons is below.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Spearman’s</th>
<th>Significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole lung summary score</td>
<td>0.857</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bronchiectasis/bronchial wall thickening extent (maximum CT Bx or BWT extent score)</td>
<td>0.828</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mucus plugging</td>
<td>0.812</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Collapse/consolidation</td>
<td>0.729</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
4.3.4 Sensitivity, Specificity and Positive and Negative Predictive Values

Taking CT as the ground truth, sensitivity, specificity and positive and negative predictive values were calculated for each feature at a lobar and whole lung level. The whole lung level was included as this is the most likely metric to be reported in studies and also as it allows for misclassification of disease location (the interlobar fissures are not so easily resolved by MRI as by CT).

4.3.4.1 Bronchiectasis and Bronchial Wall Thickening -

**Bronchiectasis**

<table>
<thead>
<tr>
<th>Lobe</th>
<th>Prevalence</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUL</td>
<td>15/22 (68.2%)</td>
<td>13/15 (86.7%)</td>
<td>5/7 (71.4%)</td>
<td>13/15 (86.7%)</td>
<td>5/7 (71.4%)</td>
</tr>
<tr>
<td>RML</td>
<td>10/22 (45.5%)</td>
<td>5/10 (50%)</td>
<td>10/12 (83.3%)</td>
<td>5/7 (71.4%)</td>
<td>10/15</td>
</tr>
<tr>
<td>RLL</td>
<td>10/22 (45.5%)</td>
<td>7/10 (70%)</td>
<td>9/12 (75%)</td>
<td>7/10 (70%)</td>
<td>9/12 (75%)</td>
</tr>
<tr>
<td>LUL</td>
<td>10/22 (45.5%)</td>
<td>8/10 (80%)</td>
<td>11/12 (91.7%)</td>
<td>8/9 (89.9%)</td>
<td>11/13 (84.6%)</td>
</tr>
<tr>
<td>Lingula</td>
<td>5/22 (22.7%)</td>
<td>4/5 (80%)</td>
<td>12/17 (70.6%)</td>
<td>4/9 (44.4%)</td>
<td>12/13 (92.3%)</td>
</tr>
<tr>
<td>LLL</td>
<td>13/22 (59.1%)</td>
<td>11/13 (84.6%)</td>
<td>9/9 (100%)</td>
<td>11/11 (100%)</td>
<td>9/11 (81.8%)</td>
</tr>
<tr>
<td>Whole lung</td>
<td>18/22 (81.8%)</td>
<td>17/18 (94.4%)</td>
<td>2/4 (50%)</td>
<td>17/19 (89.5%)</td>
<td>2/3 (66.7%)</td>
</tr>
</tbody>
</table>
**Bronchial Wall Thickening**

<table>
<thead>
<tr>
<th>Lobe</th>
<th>Prevalence</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUL</td>
<td>16/22 (72.7%)</td>
<td>14/16 (87.5%)</td>
<td>5/6 (83.3%)</td>
<td>14/15 (93.3%)</td>
<td>5/7 (71.4%)</td>
</tr>
<tr>
<td>RML</td>
<td>9/22 (40.9%)</td>
<td>5/9 (55.6%)</td>
<td>11/13 (84.6%)</td>
<td>5/7 (71.4%)</td>
<td>11/15 (73.3%)</td>
</tr>
<tr>
<td>RLL</td>
<td>12/22 (54.45%)</td>
<td>8/12 (66.7%)</td>
<td>8/10 (80%)</td>
<td>8/10 (80%)</td>
<td>8/12 (66.7%)</td>
</tr>
<tr>
<td>LUL</td>
<td>10/11 (45.5%)</td>
<td>8/10 (80%)</td>
<td>11/12 (91.7%)</td>
<td>8/9 (88.9%)</td>
<td>11/13 (91.7%)</td>
</tr>
<tr>
<td>Lingula</td>
<td>7/22 (31.8%)</td>
<td>6/7 (85.7%)</td>
<td>12/15 (80%)</td>
<td>6/9 (66.7%)</td>
<td>12/13 (92.3%)</td>
</tr>
<tr>
<td>LLL</td>
<td>13/22 (59.1%)</td>
<td>9/13 (69.2%)</td>
<td>7/9 (77.8%)</td>
<td>9/11 (81.8%)</td>
<td>7/11 (63.6%)</td>
</tr>
<tr>
<td>Whole lung</td>
<td>16/22 (72.7%)</td>
<td>16/16 (100%)</td>
<td>3/6 (50%)</td>
<td>16/19 (84.2%)</td>
<td>3/3 (100%)</td>
</tr>
</tbody>
</table>

**Bronchiectasis OR Bronchial Wall Thickening**

<table>
<thead>
<tr>
<th>Lobe</th>
<th>Prevalence</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole lung</td>
<td>19/22 (86.4%)</td>
<td>18/19 (94.7%)</td>
<td>2/3 (66.7%)</td>
<td>18/19 (94.7%)</td>
<td>2/3 (66.7%)</td>
</tr>
</tbody>
</table>

Generally the poorest figures are those of the middle lobe and lingula, as would be expected given these are the smallest lobes, adjacent to the heart (therefore experiencing the most cardiac pulsation related motion artefact) and the most likely to have disease misregistered as being within a different lobe.

Again, as expected, the MRI appears to be more specific than sensitive at a lobar level. The apparent reversal of this trend at a whole lung level is likely the result of the high feature prevalence at a whole lung level (i.e. the denominator of the specificity is particularly low).
### 4.3.4.2 Mucus Plugging

<table>
<thead>
<tr>
<th>Lobe</th>
<th>Prevalence</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUL</td>
<td>15/22 (68.2%)</td>
<td>13/15 (86.7%)</td>
<td>6/7 (85.7%)</td>
<td>13/14 (92.9%)</td>
<td>6/8 (75%)</td>
</tr>
<tr>
<td>RML</td>
<td>11/22 (50%)</td>
<td>7/11 (63.6%)</td>
<td>8/11 (72.7%)</td>
<td>7/10 (70%)</td>
<td>8/12 (66.7%)</td>
</tr>
<tr>
<td>RLL</td>
<td>15/22 (68.2%)</td>
<td>11/15 (73.3%)</td>
<td>7/7 (100%)</td>
<td>11/11 (100%)</td>
<td>7/11 (63.6%)</td>
</tr>
<tr>
<td>LUL</td>
<td>12/22 (54.5%)</td>
<td>8/12 (66.7%)</td>
<td>8/10 (80%)</td>
<td>8/10 (80%)</td>
<td>8/12 (66.7%)</td>
</tr>
<tr>
<td>Lingula</td>
<td>9/22 (40.9%)</td>
<td>5/9 (55.6%)</td>
<td>12/13 (92.3%)</td>
<td>5/6 (83.3%)</td>
<td>12/16 (75%)</td>
</tr>
<tr>
<td>LLL</td>
<td>15/22 (68.2%)</td>
<td>10/15 (66.7%)</td>
<td>6/7 (85.7%)</td>
<td>10/11 (90.9%)</td>
<td>6/11 (54.5%)</td>
</tr>
<tr>
<td>Whole lung</td>
<td>19/22 (86.4%)</td>
<td>17/19 (89.5%)</td>
<td>2/3 (66.7%)</td>
<td>17/18 (94.4%)</td>
<td>2/4 (50%)</td>
</tr>
</tbody>
</table>

Again, generally the specificity of MRI for mucus plugging was higher than its sensitivity with lower sensitivity within the middle and lingula lobes but high positive predictive values throughout. As for bronchiectasis, the low number of cases with no mucus plugging within any lobe adversely affects the figure for specificity at a whole lung level.
4.3.4.3 Collapse/ Consolidation (Taking CT collapse/consolidation and ground glass from the parenchymal component score)

<table>
<thead>
<tr>
<th>Lobe</th>
<th>Prevalence</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUL</td>
<td>4/22 (18.2%)</td>
<td>3/4 (75%)</td>
<td>16/18 (88.9%)</td>
<td>3/5 (60%)</td>
<td>16/17 (94.1%)</td>
</tr>
<tr>
<td>RML</td>
<td>8/22 (36.4%)</td>
<td>5/8 (62.5%)</td>
<td>14/14 (100%)</td>
<td>5/5 (100%)</td>
<td>14/17 (82.4%)</td>
</tr>
<tr>
<td>RLL</td>
<td>4/22 (18.2%)</td>
<td>2/4 (50%)</td>
<td>16/18 (88.9%)</td>
<td>2/4 (50%)</td>
<td>16/18 (88.9%)</td>
</tr>
<tr>
<td>LUL</td>
<td>3/22 (13.6%)</td>
<td>2/3 (66.7%)</td>
<td>19/19 (100%)</td>
<td>2/2 (100%)</td>
<td>19/20 (95%)</td>
</tr>
<tr>
<td>Lingula</td>
<td>8/22 (36.4%)</td>
<td>5/8 (62.5%)</td>
<td>13/14 (92.9%)</td>
<td>5/6 (83.3%)</td>
<td>13/16 (81.3%)</td>
</tr>
<tr>
<td>LLL</td>
<td>9/22 (40.9%)</td>
<td>6/9 (66.7%)</td>
<td>12/13 (92.3%)</td>
<td>6/7 (85.7%)</td>
<td>12/15 (80%)</td>
</tr>
<tr>
<td>Whole lung</td>
<td>15/22 (68.2%)</td>
<td>12/15 (80%)</td>
<td>4/7 (57.1%)</td>
<td>12/15 (80%)</td>
<td>4/7 (57.1%)</td>
</tr>
</tbody>
</table>

It is also worth calculating sensitivity etc for collapse/consolidation excluding ground glass opacification (likely the hardest feature to resolve via MRI).

Collapse/ consolidation (Collapse consolidation alone i.e. excluding ground glass)
The results for collapse/consolidation with or without the inclusion of ground glass opacification are harder to interpret than the other features as the prevalence per lobe was low.

### 4.3.4.4 Summary

The table below summarises the sensitivity, specificity and positive and negative predictive values at a whole lung level.

<table>
<thead>
<tr>
<th>MRI feature</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiectasis or bronchial wall thickening</td>
<td>94.7%</td>
<td>66.7%</td>
<td>94.7%</td>
<td>66.7%</td>
</tr>
<tr>
<td>Mucus plugging</td>
<td>89.5%</td>
<td>66.7%</td>
<td>94.4%</td>
<td>50%</td>
</tr>
<tr>
<td>Collapse consolidation</td>
<td>80%</td>
<td>57.1%</td>
<td>80%</td>
<td>57.1%</td>
</tr>
</tbody>
</table>
## 4.3.5 Comparison with Clinical Measures

The table below displays Spearman's Rho (p) for correlation between the MRI and CT component scores, age and clinical markers of disease severity.

<table>
<thead>
<tr>
<th>Feature score</th>
<th>Imaging modality</th>
<th>Age</th>
<th>IV and PO antibiotic courses</th>
<th>Lowest FEV$_1$ (%)</th>
<th>Lowest FEV$_1$/FVC</th>
<th>LCI$_{2.5}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total disease summary score</strong></td>
<td>MRI</td>
<td>0.548** (0.008)</td>
<td>0.369</td>
<td>-0.442* (0.039)</td>
<td>-0.502* (0.017)</td>
<td>0.629* (0.016)</td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>0.544* (0.009)</td>
<td>0.380</td>
<td>-0.456* (0.033)</td>
<td>-0.497* (0.019)</td>
<td>0.737 (0.003)</td>
</tr>
<tr>
<td><strong>Bronchiectasis/Wall thickening</strong></td>
<td>MRI</td>
<td>0.579* (0.005)</td>
<td>0.276</td>
<td>-0.350</td>
<td>-0.418</td>
<td>0.606* (0.022)</td>
</tr>
<tr>
<td></td>
<td>CT Bx</td>
<td>0.690** (&lt;0.001)</td>
<td>-0.053</td>
<td>-0.215</td>
<td>-0.356</td>
<td>0.749 (0.002)</td>
</tr>
<tr>
<td></td>
<td>CT BWT</td>
<td>0.454* (0.034)</td>
<td>0.379</td>
<td>-0.340</td>
<td>-0.286</td>
<td>0.509</td>
</tr>
<tr>
<td><strong>Mucus plugging</strong></td>
<td>MRI</td>
<td>0.611** (0.003)</td>
<td>0.225</td>
<td>-0.419</td>
<td>-0.543** (0.009)</td>
<td>0.624* (0.017)</td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>0.465* (0.029)</td>
<td>0.275</td>
<td>-0.353</td>
<td>-0.426* (0.048)</td>
<td>0.708** (0.005)</td>
</tr>
<tr>
<td><strong>Collapse/consolidation</strong></td>
<td>MRI</td>
<td>-0.085 (0.708)</td>
<td>0.280</td>
<td>-0.114</td>
<td>-0.058</td>
<td>0.142 (0.628)</td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>-0.015 (0.947)</td>
<td>0.343</td>
<td>-0.285</td>
<td>-0.475* (0.026)</td>
<td>0.366 (0.199)</td>
</tr>
</tbody>
</table>

Spearman's correlation coefficient (p value)
* p<0.05  
**p<0.01

Correlation with clinical markers of disease severity was similar between CT and MRI based component scores with the exception of collapse/consolidation where there was a statistically significant correlation between CT parenchymal score and the lowest FEV$_1$/FVC in the 6 months preceding imaging. The relationships of each modalities component scores and clinical markers are explored below.
Of note, none of the structural MRI indices demonstrated significant correlation with the number of antibiotic courses in the preceding 6 months (a marker of disease stability), whilst the CT hyperinflation score demonstrated significant correlation (Spearman's Rho 0.673, p=0.001).
Note that an increase in CT summary score is associated with a greater decrease in FEV$_1$ than with the same increase in MRI summary score. The same is true of FEV$_1$/FVC ratio.

Similarly, per unit increase in CT disease summary score the increase in LCI$_{2.5}$ (i.e. worse disease severity) is greater compared to MRI. This effect is even more significant when examining the bronchiectasis component scores (see below).
There is minimal difference, however, in the overall association of mucus plugging scores with the lowest FEV₁/FVC ratio in the 6 months preceding imaging and only a small difference in LCI₂.₅ between the two modalities.
Grouped scatter of 6 month lowest FEV1/FVC by mucus plugging score (%)

Mucus plugging score (%)

Grouped scatter of LCI-2.5 by mucus plugging score (%)

Mucus plugging score (%)

Imaging measure
CT mucus plugging score (%)
MRI mucus plugging score (%)

LCI-2.5
4.3.6 Patient experience

*Structural lung imaging* -

All patients scored the breath hold required for CT as “easy” or “easy enough” (77% “easy”). For the MRI protocol (which, in addition to the repeated 14s breath holds for structural imaging, also included twelve 9 second breath holds for ufbSSP mapping and a 14 second breath hold for VIBE imaging of the liver) 81% scored the breath holding as “easy” or “easy enough”. No-one considered the breath holding “far too difficult” and only one participant (an 18 year old girl with CF) considered it “quite difficult”.
More general questions –

The majority of patients had previously undergone CT imaging, with only six patients attending for their 1st CT. In contrast, only 4 patients had previously undergone an MRI scan. In advance of any imaging, one patient reported anxiety of the possibility of feeling claustrophobic for both CT and MRI (a 9 year old boy who had not undergone either CT or MRI previously) and an 18 year old girl reported anxiety regarding imaging in general, as she too had not undergone either CT or MRI previously.

Responses regarding the length of the scan demonstrated around 2/3 of patients felt the MRI protocol was too long (14 responses of too long vs 8 of ‘about right’).
A similar split was demonstrated regarding scanner noise, with around 2/3 reporting too much noise from MRI (14 vs 8 for ‘not too noisy’).

Regarding remaining still for the scans, only one reported difficulty staying still for CT (a 9 year old boy), where as MRI was reported as difficult or too difficult by 9 patients (7 “difficult” and 2 “too difficult”). The two patients who reported staying still was “far too difficult” were aged 7 and 10 years (both boys), the “quite difficult” group included a wide range of ages from 9 to the oldest patient (35 years). Despite this, image quality of the quantitative ventilation and perfusion MRI techniques, discussed in the following chapter, was sufficient for analysis in all participants.
Only one patient reported claustrophobia on MRI (none on CT) with 7 reporting MRI made them feel “a bit claustrophobic” compared with just one by CT (this patient, a 17 year old girl reported both CT and MRI made her feel “a bit claustrophobic”) and all patients completed the full protocol without a break off the scanner bed.
When asked which of the two modalities they would rather have for follow up imaging around 2/3 opted for CT. The most commonly mentioned reason was length of time taken. Other interesting responses included “worried about radiation risk from repeat scans, but CT easier and quicker so better for one off or occasional scans”, “MRI more comfortable (didn’t have to raise arms and could listen to music)”, MRI was “noisy, but may give more information” and “MRI was not too bad, didn’t feel like an hour”.

![Claustrophobia Chart](chart.png)
4.4 Discussion and Conclusions

Principal findings

All 22 patients approached agreed to the research MRI and all completed the full protocol, including structural and functional lung, liver and sinus imaging, with no breaks for claustrophobia or other reasons. This suggests that a multisystem MRI examination specifically for chronic suppurative lung disease is indeed feasible, at least from a patient perspective.

The majority had previously undergone imaging via CT, but only 4 had been in an MRI scanner before and none had undergone prior lung MRI. Despite this, only two participants reported feeling nervous prior to imaging (nervous about both CT and MRI) and only one (a 17 year old) reported
feeling claustrophobic after imaging (with the same feeling at the time of MRI and CT and without needing to abort either scan, take a break etc).

Two thirds reported the MRI felt too long, highlighting the need to rationalise sequences. This will be addressed in the following chapters, based on the perceived usefulness of the various quantitative ventilation methods included. Staying still enough for the scan was reported as being difficult by 9 of the 22 participants, over a very wide age range (not just the 6 year olds), but despite this, all analyses were possible in all patients. It worth mentioning that no lung imaging sequences required repeating due to patient movement.

When asked which of the two imaging tests participants would choose for future follow up, 1/3 opted for MRI despite the long examination times, stating reasons including “worries of radiation risk” from CT, MRI being “more comfortable, without needing to lift my arms up” and perceiving that MRI was “giving more information”.

Particularly relevant to the structural imaging discussed in this chapter, the breath holds (both for structural imaging and some of the mapping techniques described in the next chapter) were considered to be “easy” or at least “easy enough” by 88% of our cohort with only a single patient (an 18 year old) reporting them as “quite difficult”. This patient had the equal lowest FEV1 of the cohort at 33.6 percent predicted.
At a whole lung level, interobserver agreement in MRI scores was comparable to those of CT, suggesting that image quality was good. It is quite possible that the lower level of agreement in lobar scores, compared to CT, can be explained by MRIs inadequate demonstration of the very thin interlobar fissures. As a result, pathology may be misclassified as being in a different lobe. It is notable that many of the lower kappa values for lobar scores were in the middle lobe and lingula. The MR images were viewed in both axial and coronal plane and misclassification of middle or lingula lobe disease as lower lobe disease is very easy, particularly on coronal images.

MRI scores correlated very well with equivalent CT scores ($r=0.729 - 0.857$, $p<0.001$). The Bland-Altman plots for total disease summary score and mucus plugging score both demonstrate a trend toward greater exaggeration of disease extent scored by MRI compared to CT, as disease worsens. The clinical significance of this exaggeration is difficult to assess, but is not likely to be large, as demonstration of stable marked disease on follow up imaging is less likely to trigger a new intervention than the presence of new or worsening disease in a person with a mild structural lung disease burden. Bland-Altman comparison of composite bronchiectasis-wall thickening and parenchymal scores demonstrate more of an even scatter of error with limits of agreement of around 10%. This corresponds to 3.6-point difference in perceived extent of disease. In a cohort such as ours, with mild structural lung disease this difference is likely accounted for by the previously mentioned problems of applying lobar scores to a modality unable to adequately delineate interlobar
fissures. For example, a patient with minimal right lower and middle lobe disease could score 2 on CT (minimal disease in each lobe would both score 1), but on MRI this could be coded as both foci being in the lower lobe alone, but the sum not reaching the >50% extent required to score “2” for a single lobe. This would result in an MRI score of only 1 whilst the same disease extent could score 2 on CT.

Using two different scoring systems allows further investigation of the origin of MR signal in large airways disease. As explained above, the MR score is a composite of both bronchial dilatation (bronchiectasis) and bronchial wall thickening. Both components are scored separately in CT and whilst Eichinger scoring only assesses extent, CFCT also adds an assessment of severity to both (which dictates a multiplier of 0 – 1.75, which is then multiplied by the extent score to form the “bronchiectasis score”). The constituent parts of the CT scores can, therefore, be used to ascertain the relative importance of bronchiectasis vs wall thickening and their relative severity to the subsequent MR appearance. At a simple extent level, wall-thickening correlates better with subsequent MR score than bronchiectasis \(r=0.738 \text{ vs } 0.677, p=0.001\) but the inclusion of both features, expressed as a mean or highest of the two values correlates better \(r=0.798 \text{ and } 0.828 \text{ respectively, } p<0.001\). Severity scores demonstrated similar correlation between bronchiectasis severity and MR score than wall-thickening severity \(0.756 \text{ vs } 0.740, p<0.001\) but again, better correlation was demonstrated when the features were combined (mean of both components \(r=0.798, p<0.001\) vs maximum of the two components \(r=0.829, p<0.001\)). These data
add weight to the common sense deduction that better demonstration of an airway on MRI should require it to be both bigger and thicker, and that thickness of the wall is likely more important, as even a hugely dilated airway will be very difficult to demonstrate by MRI if its wall is exquisitely thin. It also goes some way to justifying the decision by Eichinger et al to combine bronchiectasis and wall-thickening into a single measure.

Using CT as the gold standard, MRI sensitivity and specificity analysis demonstrated high specificity of both bronchiectasis and bronchial wall thickening (70.6-100% and 77.8-91.7% at a lobar level, respectively) and sensitivities from 50-86.7% and 55.6-87.5% respectively. Similar trends were demonstrated in mucus plugging (sensitivities 55.6-86.7%, specificities 72.7-100%) and parenchymal disease (50-75% and 88.9-100% respectively). The high specificity supports the use of MRI in the setting of disease surveillance, but not in the setting of primary diagnosis where sensitivity to more mild structural disease is likely to be important. As described in chapter 3, there was an almost 50:50 split in imaging indication between “surveillance” and “unexplained decline in lung function”. The appearance of a new abnormality on a subsequent MR could be deemed important, but the relative lack of sensitivity compared to CT could be of concern if the scan was intended to identify subtle tree-in-bud nodularity in the setting of an infective exacerbation.

Given the high levels of agreement between CT and MRI scores, correlation with clinical measures being similar between modalities was as expected. It
is notable though that the only CT measure to correlate significantly with the number of infective exacerbations was the hyperinflation score (0.642, p=0.001). There is no equivalent of this score in the Eichinger scoring system and no structural MRI output correlated significantly with exacerbation number.

**Strengths and weaknesses**

There are many studies comparing MRI with CT in cystic fibrosis (discussed below), but the key strength to this study is the use of a widely available conventional MRI sequence, a version of which will be found on the vast majority of MRI scanners across the UK and further afield. The fact that a high level of correlation with CT scores and high interobserver agreement was demonstrated, despite participants reporting some difficulties remaining still and the absence of any repeat imaging, further highlights the advantage of using this particular sequence. Another strength is the specific aim of testing a protocol that is so fast that it can be included in a more comprehensive MRI protocol, including advanced ventilation imaging, which requires far more time on the scanner. This is always of particular concern when imaging children and teenagers. It is, of course, also possible to perform the structural imaging alone, requiring a length of imaging appointment similar to that of a CT scan.

Another strength is the use of separate CT and MR scoring systems, rather the application of a CT scoring system to both CT and MRI, which ignores the significant differences in technique. The data in support of a combined
measure of bronchiectasis and wall thickening, the understanding that MRI is better able to demonstrate thick-walled airways than dilated but thin walled airways, and the relatively lower sensitivities to disease compared to CT add further evidence to the argument that MRI could represent a very appropriate imaging modality for regular surveillance imaging, but that CT likely remains the modality of choice where a primary/de novo diagnostic question needs to be answered.

The patient feedback questionnaire is not validated, but nevertheless provided valuable information that will influence future protocol design, particularly in dictating the maximum examination time. Whilst all managed the complete protocol, the majority reported the examination was too long.

**Strengths and weaknesses in relation to other studies and discrepant results**

A potentially significant weakness is the lack of any T1-weighted imaging from the structural part of the MRI protocol. Dournes et al have previously shown that the finding of mucus visible as high signal on T1 weighted imaging, but low-absent signal on T2 weighted imaging is 94% sensitive and 100% specific for allergic bronchopulmonary aspergillosis (ABPA), and is akin to the high attenuation mucus described in CT of people with ABPA[214]. None of our cohort had CT evidence of ABPA, so we cannot assess the probability of missing absent T2 signal mucus plugs on imaging via T2 BLADE.
The same group have previously described a 3D MRI acquisition with extremely high spatial resolution (0.86mm$^3$) called PETRA[215]. Reproducibility of scoring (Bhalla scoring system) was better by PETRA than by T2 BLADE (ICC-0.97 vs 0.88) with far better agreement between CT and MRI by PETRA than by T2 BLADE. It is, however, worth noting that the Bhalla score was not specifically designed for CF imaging and involves measures such as “bronchial generation involved” and “emphysema extent” both of which are likely irrelevant in the setting of CF surveillance and have predictably low ICC values when scored via T2 BLADE (0.37 and 0.18 respectively)[113]. Secondly, Bhalla scores are by pulmonary segment and each segment of each patient was scored individually and in a random order (i.e. the observers scored 540 bronchopulmonary segments, rather than the lungs of 30 people with CF). Again, this methodology is questionable in the setting of defining “adequate” image quality for CF surveillance by MRI and is highly biased toward a sequence able to demonstrate fissures and smaller normal airways. The same disease may be evident on both images but scored as being in completely different segments by different reviewers. This would result in identical pathology demonstrated on each sequence being considered completely discrepant. Thankfully, few CF physicians request detailed imaging reports of a single bronchopulmonary segment, and more generalised assessment of disease extent within the entirety of a person’s lungs is likely to be considerably more important than its exact segmental location.
Whilst the resolution of PETRA is impressive, each acquisition requires around 12 minutes of respiratory-triggered imaging and the sequence is not widely available. (The sequence itself is commonly used in neuroimaging, but in order to apply it to lung imaging, respiratory triggering had to be added to the sequence with significant input from Siemens Engineers and the respiratory-gated version is still not included on clinical scanners).

By contrast, Ciet et al published a study of CT vs. structural MRI, very similar to that reported here. They recruited 38 patients (6-51 years old) who underwent CT and structural lung MRI on the same day and scored the images using CFCT and CFMR (essentially the same scoring system, but applied to MRI). They used a proton density weighted PROPELLER sequence (an older BLADE-like acquisition) with 5 mm thick sections and achieved similar correlation with CT scores (see table below).
A significant difference in the protocol used by Ciet et al was the use of respiratory triggering instead of breath holds. As a result, the acquisition time was 7 – 10 minutes. Furthermore, the total protocol time reported was 20 – 45 minutes, implying that acquisitions had to be repeated more than once in many instances. The fact that our interobserver agreement appears higher (ICC 0.88-0.97 vs 0.60-0.85) suggests that image quality did not suffer significantly from our decision to replace respiratory triggering with breath holds[110].

The only CT measure to demonstrate significant correlation with exacerbation frequency in our cohort was the hyperinflation score (r=0.642, p=0.001). Whereas our breath hold images were acquired in end inspiration, attempts to demonstrate hyperinflation via MRI have involved

<table>
<thead>
<tr>
<th>Feature</th>
<th>Comparison of CT vs MRI</th>
<th>Interobserver agreement (MRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ciet et al (ICC)</td>
<td>Our data (Spearman’s R)</td>
</tr>
<tr>
<td>Bronchiectasis/bronchial wall thickening</td>
<td>0.78</td>
<td>0.83</td>
</tr>
<tr>
<td>Mucus plugging</td>
<td>0.76</td>
<td>0.81</td>
</tr>
<tr>
<td>Collapse/consolidation</td>
<td>0.84</td>
<td>0.73</td>
</tr>
</tbody>
</table>
end-expiratory imaging. Ciet et al used end expiratory respiratory triggering, but only achieved a Spearman’s correlation coefficient of 0.46 for MRI vs CT hyperinflation score (compared to 0.87 for CT interobserver agreement)[114].

Pennati et al had a more advanced method of demonstrating trapped gas. They acquired end inspiratory and end expiratory images and registered the images via deformable image registration to enable calculation of regional change in proton density (PD) between inspiration and expiration, thus showing air trapping. The quartile coefficient of variation in PD correlated significantly with LCI_{2.5} (r^2=0.51, p<0.001) and the % low-ventilation volume (the % of pixels demonstrating a change of less than 5A.U. or matched low PD signal on both inspiratory and expiratory imaging) correlated even better with LCI_{2.5} (r^2=0.66, p<0.001) [216]. This study demonstrates the considerable advantage of acquisition and analysis of multiphase images (be that static images at end inspiration and end expiration, or dynamic imaging). This is further explored in later chapters.

**Meaning of the study**

I have shown that this time efficient, widely available MRI sequence is well tolerated by children and young adults with CF and PCD and is likely to provide adequate gross morphologic detail for regular surveillance of large airways disease severity.
Unanswered questions and future research

Whilst scores from single time point MR imaging studies appear to be reproducible from one observer to another and correlate well with clinical measures of disease severity, several important questions remain to be answered prior to MRI’s use as a surveillance tool. Firstly variability in scores over time will be extremely important in determining “clinically significant” change in disease severity or extent. It remains to be seen whether MRI can pick up subtle changes in structural disease over time. Furthermore, one of the key advantages of MRI is the ability to repeat imaging at more frequent intervals than would be reasonable by CT. If frequent MRI was to be included in a research protocol, for example examining the efficacy of a new treatment, it would be extremely important to understand the variability in disease appearance over time in a stable CF population before assuming any change seen represented either treatment response or failure. This would require a future long term follow up study examining CF patients over a long period of disease stability as well as over periods of clinically defined exacerbation to differentiate clinically insignificant variability in appearance and scores from significant disease alteration. The age of recruited individuals will be of utmost importance as “normal” variability is like to differ significantly with disease severity. It is also likely that the increasing use of highly effective modulator therapies will result in significant changes to what is considered normal for CF, with the development and progression of significant structural disease limited and delayed.
As gross structural disease becomes less significant and is delayed to a later age, changes in small airways disease may become more relevant in the management of children and young people with chronic suppurative lung diseases, and it may be that quantitative MR measures of ventilation and pulmonary perfusion become more relevant than CT measures of gross structural disease.
Chapter 5 – Comparison of Quantitative CT to Quantitative MRI

5.1 Introduction

Whilst the component scores from grossly apparent structural disease elements such as bronchial wall thickness by CT and MRI correlate well, the subtle mosaic attenuation on CT, indicative of small airways disease and requiring a different treatment approach, is not well demonstrated on structural MRI. The previous chapters have shown the predominance of small airways disease over large airways disease in younger CF and PCD patients compared to older patients and has discussed the statistically significant correlation between CT hyperinflation scores and disease stability (as determined via antibiotic prescription frequency). The new advanced forms of ventilation MRI offer a potential remedy to the lack of small airways information via structural MRI whilst simultaneously removing the interobserver variability of this visually assessed CT component score (the highest variability of all structural component scores, both in my data and in the published literature discussed in previous chapters).

Before comparing the results of ventilation MRI measures to clinical measures of disease severity and stability, it is worth comparing potential static quantitative MRI measures of disease severity to the equivalent CT signs of small airways disease. In addition to simple visual scoring of
hyperinflation on CT, low attenuation mapping can be used to quantify individual voxels below a threshold, removing the higher interobserver variability of the hyperinflation score relative to the other visual measures of disease severity. CT low attenuation mapping is well established in the quantification/disease severity assessment of emphysema in adult smokers with voxels below a threshold of -950 HU counted as representing emphysematous lung. These voxels can then be expressed as a percentage of lung volume. It should be remembered, however, that voxel HU measurements are dependant on a number of factors. Whilst some factors can be controlled for (particularly CT scanner settings – kV and mAs, image reconstruction kernel and use of iterative reconstruction), others are harder to standardise. The level of inspiration at image acquisition is particularly relevant in a population including young children who may not entirely comply with breathing instructions. Furthermore, the low attenuation regions of mosaic attenuation in small airways disease are variable and often far less markedly low attenuation than in emphysematous lung, so the -950HU threshold used in emphysema studies may not be the most appropriate threshold to employ as an automated measure of small airways disease extent in chronic suppurative airways diseases.

MRI mapping techniques measure T1 and T2 relaxation times, forming truly quantitative measures of signal resulting from specific tissues/materials. T1 signal within the lung largely originates from soft tissue and, as such, T1 mapping has previously been investigated as a potential method of
quantifying the emphysema and pulmonary fibrosis [125,217,218]. T2 signal originates from fluid and fat. Within the lung, areas of high T2 signal could be expected to represent high fluid content mucus plugs and oedematous inflamed airways [219].

The aim of this chapter is to establish an appropriate thresholding method for automated quantification of mosaic attenuation on CT to replace the visual ‘hyperinflation’ component score of the CFCT scoring system and then to compare automated CT measurements and MRI mapping techniques with the clinical measures of disease severity discussed in previous chapters.

5.2 Methods

5.2.1 Computed Tomography (CT) -

As detailed in the methods chapter, non-contrast thoracic CTs were acquired during a single breath hold at end-inspiration. Expiratory acquisitions were not obtained as our institution does not deem them to be clinically necessary, and therefore consider them to add unnecessary extra ionising radiation dose.

Visual scoring has been explained in the previous chapters. These scores were compared to computational measures of low attenuation volume described in full in the methods chapter. In brief, thresholds of -950HU and -910HU were taken from clinical emphysema imaging practice and patient-specific levels were determined via the placing of a 1cm diameter circular region of interest (ROI) in an area of visually ‘normal’ appearing lung by a
single observer. The threshold level was set at the median HU value minus 2 standard deviations of voxel values within the ROI. Each of the 3 methods was used to express the volume of abnormally low attenuation lung as a percentage of total segmented lung volume. Further analysis was performed, only considering clusters of adjacent low attenuation voxels with a minimum 187 mm³ volume to reduce the effect of random image noise [220].

5.2.2 Quantitative MRI –

5.2.2.1 Static T1 (IR-HASTE and ufbSSFP based) and T2 mapping (ufSSFP)

Again, these are discussed in more detail in the methods chapter, but in brief, T1 mapping was performed via two methods – 1) IR-HASTE acquired via repeat acquisitions at differing inversion times over 5 minutes of free breathing of bottled medical air, with subsequent automated non-rigid registration of images as per the method of Parker et al [206] and 2) ufbSSFP mapping during a 7 second breath hold at full inspiration as per the method of Bieri et al [221]. Both techniques produce 10 mm thick coronal section T1 maps. The ufbSSFP technique also allows simultaneous calculation of T2 maps. Both techniques employ automatic segmentation of the lungs with calculation of whole lung values of T1 and T2 relaxation time.
5.3 Results

5.3.1 Semi-Quantitative Visual CT Scoring –

The results of the visual scoring have been discussed previously (see ‘population and CT disease severity scoring’ chapter), but briefly: lobar scores of hyperinflation varied from 0 – 3 (maximum possible score 4.5, median 1) with whole lung hyperinflation scores from 0 to 14 (maximum possible 24, median 4). Expressed as a percentage of maximum possible score, hyperinflation gave the highest median component score (14.8%) within the cohort (i.e. was the most prevalent feature). There was no statistically significant association between visual hyperinflation score and age (Pearson’s correlation coefficient 0.143, p=0.526).

5.3.2 Low Attenuation Mapping –

Low attenuation mapping was possible for all 22 CT scans. For each method of low attenuation mapping, the cluster based analysis (effectively noise reduction) correlated better with visual scores than the individual voxel method, with the bespoke threshold method providing the most significant correlation with visual scores (Pearson’s correlation coefficient 0.540, p=0.009).

<table>
<thead>
<tr>
<th>Low attenuation determination method</th>
<th>Correlation with visual CFCT hyperinflation score (whole lung level) (Pearson’s correlation coefficient)</th>
<th>Significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-950 HU threshold</td>
<td>0.138</td>
<td>0.540</td>
</tr>
<tr>
<td>-950 HU cluster based</td>
<td>0.188</td>
<td>0.402</td>
</tr>
<tr>
<td>-910 HU threshold</td>
<td>0.141</td>
<td>0.417</td>
</tr>
<tr>
<td>-910 HU cluster based</td>
<td>0.182</td>
<td>0.417</td>
</tr>
<tr>
<td>Bespoke HU threshold</td>
<td>0.525*</td>
<td>0.012</td>
</tr>
<tr>
<td>Bespoke HU cluster based</td>
<td>0.540*</td>
<td>0.009</td>
</tr>
</tbody>
</table>
The bespoke method also correlated best with LCI<sub>2.5</sub> (better than visual CFCT hyperinflation scores), but correlation with spirometry is harder to interpret.

**Figure 10** – An 8 year old boy with cystic fibrosis and marked mosaic attenuation. a) Blue voxels represent HU values under -950 HU. b) Increasing the threshold to -910 includes more voxels, but moving to a patient-specific threshold c) better matches visual assessment. d) Only including voxels under the patient-specific threshold which form clusters of abnormal adjacent voxels >187mm<sup>3</sup> removes some voxels of presumed ‘noise’ (green, yellow and blue voxels).

<table>
<thead>
<tr>
<th>Clinical measure</th>
<th>Correlation with -950HU threshold clusters (Pearson’s)</th>
<th>Significance (p)</th>
<th>Correlation with bespoke HU threshold clusters (Pearson’s)</th>
<th>Significance (p)</th>
<th>Correlation with CFCT hyperinflation score (%) (Pearson’s)</th>
<th>Significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contemporaneous FEV&lt;sub&gt;1&lt;/sub&gt; (%predicted)</td>
<td>-0.425*</td>
<td>0.049</td>
<td>-0.366</td>
<td>0.094</td>
<td>-0.423*</td>
<td>0.050</td>
</tr>
<tr>
<td>Contemporaneous FVC (%predicted)</td>
<td>-0.019</td>
<td>0.934</td>
<td>-0.155</td>
<td>0.501</td>
<td>-0.296</td>
<td>0.181</td>
</tr>
<tr>
<td>Contemporaneous FEV&lt;sub&gt;1&lt;/sub&gt;/FVC</td>
<td>-0.704*</td>
<td>&lt;0.001</td>
<td>-0.442*</td>
<td>0.040</td>
<td>-0.406</td>
<td>0.060</td>
</tr>
<tr>
<td>LCI&lt;sub&gt;2.5&lt;/sub&gt;</td>
<td>0.336</td>
<td>0.240</td>
<td>0.775*</td>
<td>0.001</td>
<td>0.599*</td>
<td>0.024</td>
</tr>
<tr>
<td>Courses of IV Abx</td>
<td>0.234</td>
<td>0.294</td>
<td>0.201</td>
<td>0.370</td>
<td>0.365</td>
<td>0.095</td>
</tr>
<tr>
<td>Courses of PO Abx</td>
<td>0.029</td>
<td>0.899</td>
<td>0.293</td>
<td>0.186</td>
<td>0.484*</td>
<td>0.022</td>
</tr>
<tr>
<td>Combined (courses of IV or PO Abx)</td>
<td>0.172</td>
<td>0.443</td>
<td>0.375</td>
<td>0.085</td>
<td>0.642*</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Somewhat disappointingly, no computed method demonstrated statistically significant correlation with the number of antibiotic courses (unlike the visual CT score). This likely reflects the combination of visual features used to identify mosaic attenuation. There is potentially a significant advantage to the ability of a human observer to adapt a perceived threshold of normality to exclude artefacts and image noise and to include more subtle regions of low attenuation adjacent to other structural changes (bronchial wall thickening etc) which otherwise would not be included in a computerised score of mosaic attenuation.

5.3.3 Static T1 Mapping Techniques

All 22 patients underwent T1 mapping via the IR-HASTE method. The first patient recruited was scanned prior to set up of the ufSSFP sequence so a total of 21 patients underwent mapping by both techniques.

Whilst a degree of error in measured T1 would be expected using different mapping methods, the median values for T1 were 909ms by IR-HASTE compared to 1477ms via ufSSFP and correlation between mean whole lung values of T1 was only moderate (Pearson’s correlation coefficient 0.430, p=0.046).
Scatter chart of IR-HASTE versus ufSSFP derived T1 values. Note the difference in x- and y-axis scales. The green line is y=x.

There is clearly a systematic error, with consistently higher T1 values derived via ufSSFP compared to those from IR-HASTE.
<table>
<thead>
<tr>
<th>Low attenuation determination method</th>
<th>Correlation with mean IR-HASTE T1</th>
<th>Significance (p)</th>
<th>Correlation with mean ufbSSFP T1</th>
<th>Significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-950 HU threshold</td>
<td>0.170</td>
<td>0.449</td>
<td>0.048</td>
<td>0.838</td>
</tr>
<tr>
<td>-950 HU cluster based</td>
<td>0.177</td>
<td>0.429</td>
<td>0.022</td>
<td>0.924</td>
</tr>
<tr>
<td>-910 HU threshold</td>
<td>0.202</td>
<td>0.367</td>
<td>0.178</td>
<td>0.441</td>
</tr>
<tr>
<td>-910 HU cluster based</td>
<td>0.179</td>
<td>0.425</td>
<td>0.165</td>
<td>0.475</td>
</tr>
<tr>
<td>Bespoke HU threshold</td>
<td>-0.137</td>
<td>0.544</td>
<td>-0.264</td>
<td>0.247</td>
</tr>
<tr>
<td>Bespoke HU cluster based</td>
<td>-0.134</td>
<td>0.552</td>
<td>-0.262</td>
<td>0.251</td>
</tr>
<tr>
<td>Visual score (CFCT hyperinflation score)</td>
<td>0.048</td>
<td>0.831</td>
<td>-0.250</td>
<td>0.274</td>
</tr>
</tbody>
</table>

As can be seen in the table above, there was no significant correlation between T1 values via either method with the degree of hyperinflation as scored by quantitative CT or by visual scoring of hyperinflation via CFCT.

**Figure 11** – The same 8 year old boy with CF. a) CT on a narrow window width demonstrates marked mosaic attenuation in keeping with small airways disease. T1 maps calculated via b) free breathing IR-HASTE and c) breath hold ufbSSFP demonstrate heterogeneity in T1 relaxation time, but summary values of T1 did not correlate significantly with CFCT scores or other clinical measures of disease severity.
<table>
<thead>
<tr>
<th></th>
<th>Correlation with mean T1 via IR-HASTE method</th>
<th>Correlation with mean T1 via ufbSSFP method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pearson’s / Spearman’s</td>
<td>Significance (p)</td>
</tr>
<tr>
<td>Age</td>
<td>0.446*</td>
<td>0.037</td>
</tr>
<tr>
<td><strong>CFCT scores</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total lung score</td>
<td>0.176</td>
<td>0.434</td>
</tr>
<tr>
<td>Total bronchiectasis</td>
<td>0.134</td>
<td>0.553</td>
</tr>
<tr>
<td>score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total mucus plugging</td>
<td>0.246</td>
<td>0.155</td>
</tr>
<tr>
<td>score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total peribronchial</td>
<td>0.044</td>
<td>0.845</td>
</tr>
<tr>
<td>thickening score</td>
<td></td>
<td></td>
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<tr>
<td>Total parenchymal</td>
<td>0.223</td>
<td>0.319</td>
</tr>
<tr>
<td>score</td>
<td></td>
<td></td>
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<tr>
<td>Total hyperinflation</td>
<td>0.048</td>
<td>0.831</td>
</tr>
<tr>
<td>score</td>
<td></td>
<td></td>
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<tr>
<td><strong>Lung function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCI2.5</td>
<td>-0.232</td>
<td>0.405</td>
</tr>
<tr>
<td>Contemporaneous FEV1(%)</td>
<td>0.059</td>
<td>0.793</td>
</tr>
<tr>
<td>Contemporaneous FVC(%)</td>
<td>0.189</td>
<td>0.400</td>
</tr>
<tr>
<td>Contemporaneous FEV1/FVC</td>
<td>-0.203</td>
<td>0.364</td>
</tr>
<tr>
<td><strong>Exacerbations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of IV Abx courses</td>
<td>0.290</td>
<td>0.190</td>
</tr>
<tr>
<td>in prior 6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined IV and PO Abx</td>
<td>0.071</td>
<td>0.752</td>
</tr>
<tr>
<td>courses in prior 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**T2 Mapping via ufbSSFP –**

Correlation between mean T2 values from the ufbSSFP images and established clinical measures are in the table below.

<table>
<thead>
<tr>
<th>Correlation with mean T2 via ufbSSFP method</th>
<th>Pearson’s / Spearman’s correlation coefficient</th>
<th>Significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.180</td>
<td>0.434</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CFCT scores</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total lung score</td>
<td><strong>-0.594</strong></td>
<td><strong>0.005</strong></td>
</tr>
<tr>
<td>Total bronchiectasis score</td>
<td><strong>-0.514</strong></td>
<td><strong>0.017</strong></td>
</tr>
<tr>
<td>Total mucus plugging score</td>
<td><strong>-0.576</strong></td>
<td><strong>0.006</strong></td>
</tr>
<tr>
<td>Total peribronchial thickening score</td>
<td><strong>-0.655</strong></td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Total parenchymal score</td>
<td>0.142</td>
<td>0.538</td>
</tr>
<tr>
<td>Total hyperinflation score</td>
<td>-0.298</td>
<td>0.189</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lung function tests</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LCI_{2.5}</td>
<td><strong>-0.540</strong></td>
<td><strong>0.046</strong></td>
</tr>
<tr>
<td>Contemporaneous FEV$_1$(%)</td>
<td>0.111</td>
<td>0.633</td>
</tr>
<tr>
<td>Contemporaneous FVC(%)</td>
<td>0.184</td>
<td>0.425</td>
</tr>
<tr>
<td>Contemporaneous FEV$_1$/FVC</td>
<td>-0.049</td>
<td>0.832</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exacerbations</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of IV Abx courses in prior 6 months</td>
<td>-0.108</td>
<td>0.640</td>
</tr>
<tr>
<td>Combined IV and PO Abx courses in prior 6 months</td>
<td>-0.185</td>
<td>0.423</td>
</tr>
</tbody>
</table>

There is moderate to strong correlation between patients' mean T2 values and their CT severity scores, with particularly strong correlation with the peribronchial thickening score. Perhaps surprisingly though, the
The correlation is negative, i.e., patients with faster T2 relaxation (lower signal intensity on T2-weighted sequences) have worse disease by CT.
There was also moderate correlation between mean T2 relaxation and LCI_{2.5}.
Figure 12 – a) Coronal CT on narrow with from the same 8 year old boy with CF. b) The corresponding T2 map from a breath hold.ufbSSFP demonstrates heterogeneity in T2 relaxation, with higher T2 values around the central pulmonary vessels (higher T2 values in green, lower in blue).

5.4 Discussion and Conclusions

Principal findings

As described previously, hyperinflation or small airways disease was the most prevalent finding on CFCT scoring of our cohort (median score 14.8% of maximal possible score) and demonstrated moderate correlation with both LCl_{2.5} and exacerbation frequency (r=0.599 and 0.642, p=0.024 and 0.001 respectively). It is also the most likely finding to be picked up in a
young cohort, and thanks to the uptake of highly effective modulator therapies, is likely to become the predominant CT feature until a much later age in future cohort studies. Although the hardest feature to detect by MRI, it is therefore arguably the most important.

As the MRI measures are automated and truly quantitative, it was felt that a more automated version of hyperinflation component scoring was required to adequately assess the appropriateness of replacing CT surveillance with MRI surveillance.

Use of Housfield unit (HU) thresholds taken from emphysema imaging did not demonstrate any significant correlation with visual hyperinflation scores or clinical measures of disease severity (r=0.138-0.188, p=0.402-0.540). This is perhaps unsurprising as these thresholds were chosen based on radiology-pathology correlation in adults with smoking related emphysema[201]. Although cysts and bullae are seen in severe CF lung disease, none were demonstrated within our cohort and the mosaic attenuation we were aiming to quantify is significantly more subtle than the decreased attenuation seen in emphysema. Significant correlation between automated CT quantification and visual scoring was, however, regained on using the bespoke threshold technique and further improved by applying the necessity of clusters of voxels below a threshold rather than counting individual voxels (r=0.525 p=0.012 and r=0.540, p=0.009 respectively). The use of cluster-based assessment reduces the influence of image noise. Random image noise may result in individual voxels registering as lower HU values, but is unlikely to result in large volumes of adjacent voxels all
registering inappropriately low HU values. Noise is of particular significance in low dose CT imaging with recent studies of diagnostic accuracy in adult emphysema imaging reporting lower sensitivities and specificities of low dose and ultralow dose CT protocols when compared to standard dose CT (sensitivities and specificities reported as 65-90% and 92-99% respectively) [222,223]. These studies examined only visual diagnosis of pathologic low attenuation and the effect of low dose CT protocols on computation assessment is likely to be significantly higher. Use of a cluster-based bespoke threshold measure resulted in a stronger correlation with LCI_{2.5} than CFCT visual scores (r=0.775, p=0.001 compared to 0.599, p=0.024 by CFCT), but in the loss of significant correlation with exacerbation frequency. It is quite likely that an observer will be influenced not just by the low attenuation (dark) appearance of the region of lung in question, but also by the presence of other local disease features such as bronchiectasis, wall thickening and mucus plugging, such that an observers internal threshold will be constantly updated to be specific to each region of lung rather than both lungs as a single structure. I therefore believe that determining a single threshold for ‘abnormal’ attenuation in suppurative airways disease is unlikely to be as successful as emphysema thresholds have been both in research and clinical practice.

There was a systematic discrepancy in T1 values calculated for lung parenchyma by the two methods of T1 mapping, with significantly longer T1 relaxation times suggested by ufSSFP compared to IR-HASTE.
Furthermore, correlation between the two methods was only moderate 
\(r=0.446, p=0.037\).

T2 mapping demonstrated stronger but negative correlation with CT 
structural lung scores, particularly bronchial wall thickening \(r=-0.655, 
\ p=0.001\) and with LCl2.5 \(-0.540, \ p=0.046\). As discussed in the introduction 
to this chapter, high T2 signal is generally associated with water and/or fat 
rich tissues and you might expect an actively inflamed bronchus to be 
oedematous and therefore have higher T2 signal (the result of a longer T2 
relaxation time). Likewise, mucus plugs could be expected to have a high 
water content and to also be T2 bright (outside of ABPA as discussed in the 
previous chapter). Whilst superficially this negative correlation may be 
unexpected, in hindsight, it is highly likely that most of the T2 signal from 
the lung originates from the pulmonary vasculature and that the T2 maps 
are therefore a surrogate of regional pulmonary perfusion. This would 
explain more severe structural disease being associated with a decrease in 
T2 signal (reduced regional pulmonary perfusion). This hypothesis is 
supported by a moderate correlation between T2 values and pulmonary 
perfusion as measured via matrix pencil decomposition imaging, discussed 
in the next chapter (for mean T2 vs. fraction of severely impaired perfusion 
\(r= -0.513, p=0.015\)).

**Strengths and weaknesses**

The addition of an automated measure of small airways disease was 
considered essential in providing a complete assessment of potential
Contributions to airways disease surveillance of CT and MRI. The testing of multiple different methods to determine a threshold for ‘normal’ lung attenuation is a considerable strength, particularly the formation of a bespoke patient-specific threshold as opposed to the far more simple use of a threshold from emphysema imaging; however, there are notable weaknesses to the design of this part of this study. The best correlation was with the bespoke method of threshold determination. This requires the manual placement of a region of interest within a visually normal appearing area of lung. Single observer data is presented in this chapter and subsequent assessment of repeatability and interobserver variability in threshold and subsequent read out is required for further validation. The CTs were obtained following a standard clinical protocol which does not use spirometric control and does not include expiratory imaging. This is discussed in the previous chapters, but expiratory phase CT imaging delineates air-trapping far more clearly than inspiratory imaging with a larger difference in HU values between normal and abnormal lung. Furthermore, the lack of spirometric control may influence the “true” respiratory phase of each patient’s CT imaging.

The same is true of the MRI mapping sequences. IR-HASTE T1 mapping was performed by imaging during free breathing. Multiple images are obtained at each of the inversion times required for mapping with subsequent non-rigid registration employed to combine these images and provide a single output of signal at each inversion time. Measured signal is therefore likely to be influenced by breathing pattern at the time of imaging. The
justification for this method is the use of the subsequent T1 maps for correction of the dynamic oxygen enhanced imaging performed immediately afterwards, presumed to be influenced by the same breathing pattern and conditions. By contrast, the ufbSSFP images are acquired during 7 second breath holds. Whilst this means no registration is required prior to the calculation of T1 and T2, it does mean that variation can be introduced by the lack of spirometric control/guidance of lung volume at the time of acquisition (a very similar situation to CT). It is therefore possible that the three methods described (CT, IR-HASTE and ufbSSFP) are measuring subtly different aspects of small airways disease.

**Strengths and weaknesses in relation to other studies and discrepant results**

The biggest single strength of this study over other published studies is the inclusion of structural CT scores, computational CT measures of small airways disease, multiple methods of T1 mapping and T2 mapping and the dynamic imaging methods discussed in the next chapter, all within the same cohort and within a short time period with most imaging and LCI performed on the same day.

Neemuchwala et al employed a modified Look-Locker inversion recovery (MOLLI) technique to T1 map the lungs of 5 children with CF (age 7 – 16 years, mean 11.2 years) finding that their T1 was significantly lower than healthy controls[224]. Although they did not publish T1 values, their graphs suggest that participants with stable CF had a whole lung T1 value of
around 300-1000ms. That compares to 769-971ms by IR-HASTE and 1341-1595ms by ufSSFP in my cohort. There are considerable differences in T1 values by all three methods, in similar cohorts, with considerable variation between individuals but no significant correlation with clinical measures in their study or mine. There are many methods of T1 mapping, but it seems clear that a single time point T1 map is of limited benefit in the assessment of CF disease severity. However, Neemuchwala et al also assessed 6 children’s progression in T1 values over an acute exacerbation, finding that T1 increased significantly following treatment for an exacerbation. Clearly, the examination of only 6 patients is a significant weakness compared to my study, but the addition of extra time points allows some interesting extra information to be gained.

Donnola et al used a similar MOLLI-based T1 mapping technique to assess the lungs of 8 adults with CF showing that T1 was significantly decreased in the upper lobes of people with CF compared to healthy controls with moderate correlation with %-predicted FEV$_1$ (r=0.68, p=0.008 in the left upper lobe, and r=0.46, p=0.1 in the right upper lobe) [123]. Rather than report whole lung measures of T1, they reported regional measures akin to upper lobes, anterior basal regions and posterior basal regions (rather than true lobes as fissures were not adequately demonstrated in all images). Whilst this would be very useful in follow up studies (for example tracking the response of focal disease to treatment), correlation of whole lung spirometric outcomes such as FEV$_1$ with part lung MRI measures seems illogical and will be heavily impacted by disease distribution in their cohort.
To date, there are no published results for T2 mapping in cystic fibrosis or primary ciliary dyskinesia. However, Buzan et al demonstrated an inverse relation between lung T2 and disease severity in a cohort of patients with interstitial lung disease. Significant differences were demonstrated between T2 values from regions of normal lung and regions of ground glass or reticulation in 12 patients with interstitial lung disease (UIP or NSIP). Normal lung had a median T2 of 41ms (range 38-49ms) compared to median T2 values of 67ms (60-72) in regions of ground glass opacification and 74ms (74-89ms) in areas of reticulation[219]. The median T2 in our cohort was 65ms with a large range of values from 44 to 102ms. As described above, it is highly likely that the majority of the T2 signal in our cohort (and indeed in that of Buzan et al) originates from the pulmonary vasculature and is a surrogate measure of pulmonary perfusion.

**Meaning of the study**

Computational quantification of small airways disease by CT may be possible, but a patient specific and even region specific threshold is needed to produce outputs which correlate with clinical measures of disease severity. As such, it is unlikely that a simple threshold-based technique will provide an adequate quantitative CT output for the investigation of small airways disease in children and young people with CF.

Taken together with the results from other studies discussed above, it is clear that differing methods of T1 mapping produce different ranges of
calculated lung T1, with large ranges of values that do not appear to correlate well with disease severity. However, if variables such as respiratory phase can be accounted for (for example by spirometric guidance), then following further research, it is feasible that repeated measures of T1 over time may provide a tool for disease monitoring and regional disease response to therapy. Of more interest though, T1 relaxation time is influenced by regional partial pressure of oxygen. This means that repeated T1 mapping before and after or repeatedly during a period of breathing 100% oxygen can be used to form maps of regional ventilation. This is the focus of the next chapter.

**Unanswered questions and future research**

Intra- and inter-observer variability in CT HU threshold determination for CF imaging still needs to be assessed, but a further related question is whether the application of a more advanced method of low attenuation mapping, based on artificial intelligence or machine learning, would be more successful given the findings that threshold likely needs to be altered not just on a patient to patient basis, but also from region to region within the same patient. It will also be important to examine the effect of differing scanner, settings (e.g. kV and mAs) and reconstruction methods (filtered back projection, differing forms of iterative and artificial intelligence image reconstruction etc) on subsequent quantitative outputs.

The effect of adding spirometric guidance to CT and MRI also needs to be examined. Two studies at The Royal Brompton will allow some of these
issues to be investigated further. One involves spirometer guided CT at 3
time points over 3 years, all of which include expiratory imaging as well as
inspiratory imaging. This study is already recruiting.

A long term follow up MRI study will allow the longitudinal monitoring of
lung T1 and T2 during stability and exacerbation to be assessed. However,
the more interesting output from these MRIs will be the measures of
regional ventilation made possible by repeated T1 mapping during wash in
and wash out of 100% oxygen. This is further discussed in the next chapter.
Chapter 6 – Dynamic MRI Assessment of Lung Function

6.1 Introduction:

As discussed in the previous chapter, quantitative imaging via CT is impacted by a number of variables, including the timing of image acquisition within the respiratory cycle. Static MRI based measures such as T1 and T2 mapping clearly suffer from the same limitations, but dynamic assessment of lung function is possible via several MRI techniques, reducing potential variability from differing breath holds and adding extra information akin to that obtained via pulmonary function testing with the added benefit of spatial localisation.

Spirometry has been the mainstay of pulmonary function testing in both research and clinical settings for many years, but is widely accepted as a blunt measure of lung and airway function. Problems with technique and significant variability in results are outweighed by its availability and essentially infinite repeatability. There has been significant progress in introducing more sensitive measures of lung function into cystic fibrosis research and clinical care, particularly the use of multiple breath washout tests. A full description can be found in the introduction and methods chapter, but in brief, in the case of this study the concentration of exhaled nitrogen is measured as it is replaced by 100% oxygen being inhaled through a closed circuit. The lung clearance index (LCI\textsubscript{2.5}) is the number of times total lung capacity must be turned over to reduce the concentration of
exhaled nitrogen to 2.5% of its original concentration. Low values represent rapid transit of gases throughout the airways with high values representing gas mixing and poor conductivity within diseased airways, as is seen in bronchiectasis and narrowed and mucus plugged bronchi. LCI has numerous advantages over spirometry including a narrow range of normal values with very little change related to age. It is more sensitive to mild disease than spirometry and demonstrates better correlation with CT structural lung disease scores [225]. However, as with other established respiratory function tests, no spatial data is acquired. A significant limitation of all current techniques is that non-aerated lung (i.e. a completely collapsed lobe, lung distal to a completely occlusive mucus plug or a lobe completely replaced with bronchiectasis) does not contribute to ventilation, does not alter washout of an inhaled gas and therefore remains invisible to the technique.

There are a number of methods of demonstrating respiratory function by MRI. Direct visualisation of ventilation is possible via inhalation of hyperpolarised or fluorinated gases. These are extremely powerful techniques, but as discussed in the Introduction chapter, both require specific hardware and extensive physics support, limiting their availability to a few select centres. If quantitative MRI is to become useful for multicentre clinical surveillance and research studies outside of these select centres, a more widely applicable technique is required. Recent advances using 100% oxygen as a contrast agent potentially makes quantitative ventilation MRI easily implementable on any clinical MRI scanner and have
already shown promise in the quantification of asthma severity[206].

Matrix pencil decomposition is another particularly promising technique capable of producing ventilation and pulmonary perfusion maps based on regional signal intensity related to changes in lung volume during respiration and in pulmonary blood volume during the cardiac cycle[156]. Whilst this technique requires non-proprietary sequences, it is feasible that this sequence could be added to any Siemens MRI scanner immediately and that similar sequences may become available for other scanners in the near future.

**Aims**

The aims of this chapter are (i) to investigate the ease of implementation of oxygen-enhanced and matrix pencil decomposition imaging on a clinical MRI system and in a cohort of children and young adults without the use of sedation or general anaesthesia and (ii) to explore correlations between resulting MR read outs and established clinical tests of disease severity.

**Hypothesis**

MRI measures of ventilation and pulmonary perfusion correlate with spirometry, LCl2.5 and disease stability, with the additional benefit of spatial information.
6.2 Methods:

6.2.1 Oxygen-enhanced MRI –

The techniques are explained in full in the methods chapter, but in brief, two forms of oxygen-enhanced ventilation MRI were investigated: a simple two time point method consisting of ufbSSFP mapping sequences performed during 7 second breath holds performed before and after a 5 minute period of breathing 100% oxygen via a non-rebreath mask; and a dynamic protocol consisting of 140 repeated IR-HASTE acquisitions over a 15 minute period of free breathing. The first 5 minutes breathing bottled medical air, the next 5 minutes 100% oxygen and the last 5 minutes back to bottled medical air. Images are then registered, signal corrected according to the previously described IR-HASTE T1 mapping protocol and used to calculate change in signal, change in modelled partial pressure of oxygen, oxygen wash-in time and oxygen wash-out time all at a voxel level. Outputs from this technique can be computed at a whole lung level (for example median wash-out time – this is the median of all individual voxels’ washout times) or expressed as distribution data, such as skew or kurtosis of wash-out time.

At this point, it is probably worth discussing what skew and kurtosis actually mean, as there are commonly held misconceptions of both. Skew is often considered to measure the degree to which the peak of a distribution is placed to the right or the left of the median and kurtosis is generally considered to be a measure of ‘peakedness’ of a distribution – neither definition is strictly true and this is particularly relevant in an imaging
situation such as this, where there is a limited set of possible outcomes (i.e. you cannot have negative figures for wash-in or wash-out time and the maximum possible time is determined by an arbitrary 5 minute wash-in or –out time period). The definitions of measures of data distribution are best explained in series, starting from standard deviation and working toward kurtosis.

Standard deviation is a measure of dispersion of data from its mean and is calculated via the formula below.

\[
\sigma = \sqrt{\frac{\sum(x_i - \mu)^2}{N}}
\]

\(x_i\) is the value of each data point and \(\mu\) the population mean. By squaring the difference between the two and taking the square root of their sum/the size of the population, the deviation of data from the mean is ‘standardised’ i.e. the direction of the deviation is removed from the output and interpreted in the context of the sample size \((N)\) – hence the term “standard deviation”.

Skewness takes this same principle one step further and is calculated by the formula below.
This time, the deviation of each data point from the mean is cubed. This has two effects on the output: 1) the direction of deviation from the mean is preserved (hence negative or positive skew) and 2) the distance of outliers from the mean more heavily influences the result (cubed rather than squared). Thus, skew is not merely a direction in which the peak of a distribution is moved away from the centre point (the median) but is a measure of the position and weight of the tail of the distribution (the relative outliers).

Kurtosis is calculated with the following formula.

\[
\hat{\mu}_3 = \frac{\sum_{i=1}^{N} (X_i - \bar{X})^3}{(N - 1) \sigma^3}
\]

Here each input is taken to the power of 4, again with two effects: 1) the direction of deviation of data points from the mean is lost and 2) the effect of relative outliers is even stronger than above. Therefore, kurtosis is not a measure of “peakedness” but an extreme measure of the weight of the tails of a distribution.
6.2.2 Matrix-Pencil Decomposition Imaging –

A 1 minute 15 second, free breathing ufSSFP sequence was utilised to obtain time-resolved images for matrix pencil decomposition imaging. Inspiration results in an increase in lung volume with a resultant decrease in proton density of the lung (the tissues providing signal are further apart and therefore provide less signal per unit volume – in this case per voxel). Conversely, exhalation is associated with a decrease of aerated lung volume, bringing more tissue into each voxel and resulting in an increase in signal. If motion is removed from the time series (an MRI video of the lungs moving over 1 minute 15 seconds of normal breathing) via non-rigid image registration (essentially distorting each individual frame of the video such that the lungs do not appear to move from one to the next) then the signal from each voxel will increase and decrease at respiratory frequency forming a sine wave of signal over time. The amplitude of this wave is proportional to the degree of local ventilation and, as such, if the amplitude is used as a pixel value, a map of ventilation mechanics can be produced to visualise regional differences in ventilation. Furthermore, a more subtle signal is present within the data representing changing pulmonary blood volume at pulse frequency with higher signal in systole than in diastole and, again the amplitude of this wave representing regional perfusion. These two combined signals can be split via Fourier decomposition or via a new technique developed by G Bauman et al, known as matrix pencil decomposition[156].

Registration of the images, segmentation of the lungs and analysis is automated and voxels demonstrating under 75% of median signal
amplitude classed as ventilation or perfusion defects. Voxels under this threshold were further divided into 3 equal classes: “moderately reduced”, “severely reduced” or “absent” ventilation/perfusion.

6.3 Results:

6.3.1 Oxygen-enhanced MRI –

6.3.1.1 Simple Two Time-point Protocol

Descriptive statistics of whole lung ufbSSFP-based measures of T1, T2 and signal intensity before and after 5 minutes of hyper-oxygenation are summarised below.

<table>
<thead>
<tr>
<th></th>
<th>Mean T1 (ms)</th>
<th>Mean T2 (ms)</th>
<th>Mean Signal intensity (AU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Air</td>
<td>1476.6 (1438.3 – 1525.1)</td>
<td>64.59 (57.2 – 80.2)</td>
<td>117.0 (98.1 – 142.6)</td>
</tr>
<tr>
<td>Post 5 minutes 100% oxygen</td>
<td>1424.9 (1352.3 – 1474.0)</td>
<td>56.3 (48.2 – 78.2)</td>
<td>110.8 (92.8 – 133.1)</td>
</tr>
<tr>
<td>Difference (pre to post O2) as %</td>
<td>3.7 (2.7 – 6.6)</td>
<td>5.7 (-17.4 – 25.6)</td>
<td>3.3 (-2.6 – 8.5)</td>
</tr>
</tbody>
</table>

Median (interquartile range)

By Wilcoxon Signed Rank testing, the change in T1 post-oxygenation was significant (Z -3.8, p<0.001). As should be expected, change in T2 and mean signal intensity (proton density) did not reach significance (Z -0.925, p=0.355 and Z -1.932, p=0.053 respectively).
**Figure 13** – A 14 year old boy with CF and structurally normal lungs on CT. Breath hold ufSSFP T1 maps a) pre and b) post administration of 100% oxygen via a non-rebreath mask. Following “hyper-oxygenation” there is a small, but statistically significant decrease in T1 relaxation time (i.e. T1 shortening).

There was, however, no statistically significant correlation between the extent of T1 change post oxygenation (i.e. degree of enhancement) and age or relevant clinical measures.

<table>
<thead>
<tr>
<th>Correlation with % change in T1 post O2</th>
<th>Age</th>
<th>LCI2.5</th>
<th>PO and IV antibiotic courses</th>
<th>Contemporaneous FEV1 (%predicted)</th>
<th>CFCT hyperinflation score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spearman's p</td>
<td>-0.083</td>
<td>-0.029</td>
<td>0.277</td>
<td>0.214</td>
<td>0.106</td>
</tr>
<tr>
<td>p</td>
<td>0.713</td>
<td>0.914</td>
<td>0.224</td>
<td>0.351</td>
<td>0.649</td>
</tr>
</tbody>
</table>
6.3.1.2 Dynamic Oxygen-enhanced Protocol

Descriptive statistics of the outputs of the dynamic oxygen-enhanced protocol are summarised below.

<table>
<thead>
<tr>
<th></th>
<th>Enhancement fraction</th>
<th>Median signal change (%)</th>
<th>Median Delta pO2max (mmHg)</th>
<th>Median oxygen wash-out time (min)</th>
<th>Median oxygen wash-in time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>0.66</td>
<td>10.39</td>
<td>333.89</td>
<td>0.72</td>
<td>2.85</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>0.42-0.77</td>
<td>7.56-14.04</td>
<td>242.79-396.78</td>
<td>0.49-1.15</td>
<td>1.74-5.27</td>
</tr>
</tbody>
</table>

Correlation with the same clinical measures as above demonstrates significant correlation between oxygen wash-in and LCI_{2.5}, but no other non-imaging measures of disease severity.

<table>
<thead>
<tr>
<th>OE-MRI output</th>
<th>Age</th>
<th>LCI_{2.5}</th>
<th>PO and IV antibiotic courses</th>
<th>Contemporaneous FEV$_1$ (%predicted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhancement fraction</td>
<td>0.053 (0.810)</td>
<td>0.285 (0.268)</td>
<td>-0.350 (0.111)</td>
<td>-0.084 (0.711)</td>
</tr>
<tr>
<td>Median signal change (%)</td>
<td>-0.031 (0.890)</td>
<td>0.228 (0.379)</td>
<td>-0.297 (0.180)</td>
<td>0.213 (0.342)</td>
</tr>
<tr>
<td>Median Delta pO2max (mmHg)</td>
<td>-0.325 (0.130)</td>
<td>-0.047 (0.573)</td>
<td>-0.105 (0.642)</td>
<td>-0.024 (0.915)</td>
</tr>
<tr>
<td>Median oxygen wash-in time (min)</td>
<td>0.284 (0.189)</td>
<td>0.600* (0.011)</td>
<td>0.314 (0.155)</td>
<td>-0.040 (0.859)</td>
</tr>
<tr>
<td>Median oxygen wash-out time (min)</td>
<td>-0.114 (0.606)</td>
<td>-0.159 (0.541)</td>
<td>-0.208 (0.353)</td>
<td>-0.383 (0.078)</td>
</tr>
</tbody>
</table>

Spearman’s co-efficient (p), * significant at p>0.05
There is, however, statistically significant correlation between the oxygen wash-in times and CT-based scores of structural disease extent and severity (see below).

<table>
<thead>
<tr>
<th>OE-MRI output</th>
<th>CFCT summary score</th>
<th>CFCT bronchiectasis score</th>
<th>CFCT mucus plugging score</th>
<th>CFCT parenchymal score</th>
<th>CFCT hyperinflation score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhancement fraction</td>
<td>-0.084 (0.711)</td>
<td>0.149 (0.507)</td>
<td>-0.025 (0.914)</td>
<td>-0.179 (0.426)</td>
<td>-0.217 (0.332)</td>
</tr>
<tr>
<td>Median signal change (%)</td>
<td>-0.212 (0.344)</td>
<td>0.048 (0.831)</td>
<td>-0.225 (0.314)</td>
<td>-0.247 (0.269)</td>
<td>-0.255 (0.252)</td>
</tr>
<tr>
<td>Median Delta pO2max (mmHg)</td>
<td>-0.309 (0.162)</td>
<td>-0.221 (0.323)</td>
<td>-0.326 (0.138)</td>
<td>-0.407 (0.060)</td>
<td>-0.177 (0.431)</td>
</tr>
<tr>
<td>Median oxygen wash-in time (min)</td>
<td>0.431* (0.045)</td>
<td>0.251 (0.260)</td>
<td>0.424* (0.049)</td>
<td>0.058 (0.798)</td>
<td>0.392 (0.071)</td>
</tr>
<tr>
<td>Median oxygen wash-out time (min)</td>
<td>0.105 (0.642)</td>
<td>0.242 (0.278)</td>
<td>0.169 (0.453)</td>
<td>0.201 (0.369)</td>
<td>0.201 (0.369)</td>
</tr>
</tbody>
</table>

*Spearman’s co-efficient (p), * significant at p>0.05

It is worth considering the similarities between a single value expression of lung function (e.g. median oxygen wash-in time) measured via MRI and the single value outputs of clinically established tests. These single measure outputs do not make use of the main advantage of imaging-based quantification of respiratory function – its ability to measure regional lung function, as opposed to merely whole lung level function.
As would be expected, measurement of respiratory dynamics via MRI is far less accurate that that possible via measurement via mass spectrometry or ultrasonic flow devices employed in multiple breath wash-out tests (LCI). Spearman’s Rho between nitrogen washout time via the Exhalyzer D, used to calculate LCI in our cohort, compared to oxygen wash-in time via OE-MRI (i.e. measurement of the same process – both use oxygen washout, but the Exhalyser D is measuring reducing nitrogen concentration rather than increasing oxygen concentration measured via MRI) was only 0.520 (p=0.033) (good but a way off excellent) – see the graph below.
The read out of exhaled nitrogen concentration on the Exhalyzer-D is essentially real time and the length of time of the MBW test is guided by the display of this measurement. By contrast, the MRI values of regional oxygen concentration are calculated by post-processing after the examination is complete and exported for analysis, meaning that an arbitrary wash-in time of 5 minutes has been chosen for ease of scanning.

This theory is supported by the Bland-Altman plot of the above data (below).

Nitrogen wash-out (by oxygen wash-in) time is consistently underestimated by the MRI (the mean difference is 3.21 minutes) with increasing underestimation as nitrogen wash-out time increases (i.e. the worse your airways disease, the less accurate the MRI data will be).

Whilst raw summary values (e.g. median) of whole lung oxygen uptake times and gas trapping may not be so promising in their current form, the
spatially-registered nature of the MRI measurements offers more interesting possibilities.

Measures of data distribution (skew and kurtosis) numerically account for spatial variability in MRI outputs (i.e. voxel level rather than whole lung level data) in a way that is not possible via current clinically established techniques.

<table>
<thead>
<tr>
<th>CFCT summary score</th>
<th>CFCT bronchiectasis score</th>
<th>CFCT mucus plugging score</th>
<th>CFCT Peribronchial thickening</th>
<th>CFCT parenchymal score</th>
<th>CFCT Hyperinflation score</th>
</tr>
</thead>
<tbody>
<tr>
<td>OE-MRI output</td>
<td>Skew</td>
<td>Kurtosis</td>
<td>Skew</td>
<td>Kurtosis</td>
<td>Skew</td>
</tr>
<tr>
<td>Signal change (%)</td>
<td>0.362 (0.098)</td>
<td>0.365 (0.095)</td>
<td>0.213 (0.341)</td>
<td>0.228 (0.307)</td>
<td>0.407 (0.060)</td>
</tr>
<tr>
<td>Delta pO2max (mmHg)</td>
<td>0.258 (0.247)</td>
<td>0.155 (0.490)</td>
<td>0.246 (0.269)</td>
<td>0.235 (0.292)</td>
<td>0.280 (0.207)</td>
</tr>
<tr>
<td>Oxygen wash-in time (min)</td>
<td>-0.034 (0.879)</td>
<td>-0.054 (0.812)</td>
<td>0.082 (0.718)</td>
<td>0.074 (0.745)</td>
<td>-0.088 (0.696)</td>
</tr>
<tr>
<td>Oxygen wash-out time (min)</td>
<td>0.712** (&lt;0.001)</td>
<td>0.697** (&lt;0.001)</td>
<td>0.633** (0.002)</td>
<td>0.659** (0.001)</td>
<td>0.640** (0.001)</td>
</tr>
</tbody>
</table>

Spearman’s co-efficient \( (p) \), * significant at \( p<0.05 \), **significant at \( p<0.01 \)

<table>
<thead>
<tr>
<th>Age</th>
<th>LCI_{2.5}</th>
<th>PO and IV antibiotic courses</th>
<th>Contemporaneous FEV_{1} (%predicted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OE-MRI output</td>
<td>Skew</td>
<td>Kurtosis</td>
<td>Skew</td>
</tr>
<tr>
<td>Signal change (%)</td>
<td>-0.128 (0.559)</td>
<td>-0.079 (0.720)</td>
<td>0.252 (0.328)</td>
</tr>
<tr>
<td>Delta pO2max (mmHg)</td>
<td>0.361 (0.091)</td>
<td>*<em>0.433</em> (0.039)</td>
<td>0.061 (0.815)</td>
</tr>
<tr>
<td>Oxygen wash-in time (min)</td>
<td>0.228 (0.295)</td>
<td>0.246 (0.258)</td>
<td>-0.125 (0.633)</td>
</tr>
<tr>
<td>Oxygen wash-out time (min)</td>
<td><strong>0.635</strong> (0.001)</td>
<td><strong>0.641</strong> (0.001)</td>
<td><strong>0.583</strong> (0.014)</td>
</tr>
</tbody>
</table>

Spearman’s co-efficient \( (p) \), * significant at \( p>0.05 \)

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Measures of regional heterogeneity of MRI-based oxygen wash-out time correlated very well with all CT structural scores apart from the parenchymal score. Correlation with the parenchymal score would not be expected as this score accounts for areas of collapse or consolidation which will not contribute to ventilation. There was strong correlation with LCI_{25}, but not with spirometry or disease stability as measured by frequency in antibiotic use.
Figure 14 - 14 year old girl with CF and an LCI of 16.4. a) The CT scan demonstrates bronchial wall thickening and mucus plugging in the upper lobes. b) One of the 6 colour maps of oxygen wash-out times on a scale from blue (rapid wash-out) to red (slow wash-out). c) The histogram of voxel wash-out times over all 6 coronal sections demonstrates this patient had the highest skew (49.7) and kurtosis (2617.7) of the cohort (standard deviation 219).

Figure 15 – 16 year old girl with CF and an LCI of 10.8 (i.e. less severe disease than the patient above. a) The CT demonstrates some mosaic attenuation, but minimal large airways disease. b) One of the 6 coronal oxygen wash-out time maps demonstrating more homogeneously rapid oxygen washout (note there are fewer voxels of calculated wash-out time on the left, likely the result of cardiac motion artefact and partial voluming of the heart at the left base on this section). c) The histogram of voxel wash-out times demonstrates fewer values distant from the mean with a greater difference between voxel counts at the median compared to the extreme of the distribution – ie. Less skew (lighter tail) and lower kurtosis (thinner tail). Skew 29.2, kurtosis 962, SD 15.5 (note the significant difference in y-axis scale compared to the histogram in figure 14).
6.3.1 Matrix-Pencil Decomposition Imaging –

Summaries of the results from matrix pencil decomposition imaging in the 22 patients who underwent this technique are below.

### 6.3.1.1 Ventilation Fraction

<table>
<thead>
<tr>
<th></th>
<th>% normal ventilation</th>
<th>% impaired ventilation (to any degree)</th>
<th>% unventilated</th>
<th>% severely impaired ventilation</th>
<th>% moderately impaired ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>72.52</td>
<td>27.85</td>
<td>4.14</td>
<td>8.85</td>
<td>14.06</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>67.79 – 78.49</td>
<td>21.51 – 32.21</td>
<td>1.89 – 6.16</td>
<td>5.87 – 11.68</td>
<td>12.72 – 15.05</td>
</tr>
</tbody>
</table>

Correlation with clinical measures is on the following page.
<table>
<thead>
<tr>
<th>Spearman's Coefficient (p)</th>
<th>Fraction normal ventilation</th>
<th>Fraction impaired ventilation (to any degree)</th>
<th>Fraction unventilated</th>
<th>Fraction severely impaired ventilation</th>
<th>Fraction moderately impaired ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.450* (0.036)</td>
<td>0.450* (0.036)</td>
<td>0.162 (0.471)</td>
<td>0.422 (0.051)</td>
<td>0.605** (0.003)</td>
</tr>
<tr>
<td>LCI_{2.5}</td>
<td>-0.768** (0.001)</td>
<td>0.768** (0.001)</td>
<td>0.574* (0.020)</td>
<td>0.771** (&lt;0.001)</td>
<td>0.609* (0.012)</td>
</tr>
<tr>
<td>LCI Nitrogen washout time (s)</td>
<td>-0.838** (&lt;0.001)</td>
<td>0.838** (&lt;0.001)</td>
<td>0.609* (0.012)</td>
<td>0.818** (&lt;0.001)</td>
<td>0.615* (0.011)</td>
</tr>
<tr>
<td>Number of IV and PO antibiotics courses</td>
<td>-0.210 (0.257)</td>
<td>0.210 (0.361)</td>
<td>-0.121 (0.603)</td>
<td>0.149 (0.520)</td>
<td>0.322 (0.154)</td>
</tr>
<tr>
<td>Contemporaneous FEV_{1} (% predicted)</td>
<td>0.260 (0.255)</td>
<td>-0.260 (0.255)</td>
<td>-0.092 (0.691)</td>
<td>-0.321 (0.156)</td>
<td>-0.120 (0.606)</td>
</tr>
<tr>
<td>Contemporaneous FVC (%predicted)</td>
<td>0.220 (0.339)</td>
<td>-0.220 (0.339)</td>
<td>-0.240 (0.294)</td>
<td>-0.264 (0.248)</td>
<td>0.184 (0.425)</td>
</tr>
<tr>
<td>Contemporaneous FEV_{1}/FVC</td>
<td>0.281 (0.217)</td>
<td>-0.281 (0.217)</td>
<td>-0.112 (0.630)</td>
<td>-0.366 (0.103)</td>
<td>-0.231 (0.315)</td>
</tr>
<tr>
<td>Bespoke cluster based low attenuation CT (%)</td>
<td>-0.479* (0.028)</td>
<td>0.479* (0.028)</td>
<td>0.252 (0.271)</td>
<td>0.534* (0.013)</td>
<td>0.325 (0.150)</td>
</tr>
<tr>
<td>CT summary score</td>
<td>-0.685** (0.001)</td>
<td>0.685** (0.001)</td>
<td>0.360 (0.109)</td>
<td>0.650** (0.001)</td>
<td>0.635** (0.002)</td>
</tr>
<tr>
<td>CT bronchiectasis score</td>
<td>-0.611** (0.003)</td>
<td>0.611** (0.003)</td>
<td>0.377 (0.092)</td>
<td>0.593** (0.005)</td>
<td>0.563** (0.008)</td>
</tr>
<tr>
<td>CT mucus plugging score</td>
<td>-0.731** (&lt;0.001)</td>
<td>0.731** (&lt;0.001)</td>
<td>0.464* (0.034)</td>
<td>0.717** (&lt;0.001)</td>
<td>0.615** (0.003)</td>
</tr>
<tr>
<td>CT peribronchial thickening score</td>
<td>-0.472* (0.031)</td>
<td>0.472* (0.031)</td>
<td>0.168 (0.468)</td>
<td>0.409 (0.066)</td>
<td>0.536* (0.012)</td>
</tr>
<tr>
<td>CT parenchymal score</td>
<td>-0.287 (0.207)</td>
<td>0.287 (0.207)</td>
<td>0.190 (0.410)</td>
<td>0.357 (0.112)</td>
<td>0.125 (0.589)</td>
</tr>
<tr>
<td>CT hyperinflation score</td>
<td>-0.534* (0.013)</td>
<td>0.534* (0.013)</td>
<td>0.181 (0.432)</td>
<td>0.466* (0.029)</td>
<td>0.590** (0.005)</td>
</tr>
</tbody>
</table>

Spearman’s coefficient (p value), *p<0.05, **p<0.01

There is very good correlation between matrix pencil decomposition ventilation fractions and LCI and CT structural scores, particularly the mucus plugging score.
### Perfusion Fraction

<table>
<thead>
<tr>
<th></th>
<th>Fraction normal perfusion</th>
<th>Fraction impaired perfusion (to any degree)</th>
<th>Fraction un-perfused</th>
<th>Fraction severely impaired perfusion</th>
<th>Fraction moderately impaired perfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median</strong></td>
<td>69.60</td>
<td>30.45</td>
<td>3.24</td>
<td>10.46</td>
<td>16.34</td>
</tr>
<tr>
<td><strong>Interquartile range</strong></td>
<td>64.79 – 76.59</td>
<td>23.41 – 35.21</td>
<td>1.46 – 4.23</td>
<td>6.66 – 13.85</td>
<td>14.76 – 17.16</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>61.16 – 81.91</td>
<td>18.09 – 38.84</td>
<td>0.67 – 9.59</td>
<td>3.08 – 15.93</td>
<td>12.81 – 20.27</td>
</tr>
</tbody>
</table>

Correlation with clinical measures is summarised on the following page.
<table>
<thead>
<tr>
<th>Spearman's Coefficient (p)</th>
<th>Fraction normal perfusion</th>
<th>Fraction impaired perfusion (to any degree)</th>
<th>Fraction unperfused</th>
<th>Fraction severely impaired perfusion</th>
<th>Fraction moderately impaired perfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.356 (0.104)</td>
<td>0.356 (0.104)</td>
<td>0.253 (0.256)</td>
<td>0.421 (0.051)</td>
<td>0.543** (0.009)</td>
</tr>
<tr>
<td>LCI2.5</td>
<td>-0.544* (0.029)</td>
<td>0.544* (0.029)</td>
<td>0.444 (0.085)</td>
<td>0.662** (0.005)</td>
<td>0.424 (0.165)</td>
</tr>
<tr>
<td>LCI Nitrogen washout time (s)</td>
<td>-0.682** (0.004)</td>
<td>0.682** (0.004)</td>
<td>0.662** (0.005)</td>
<td>0.747** (&lt;0.001)</td>
<td>0.362 (0.169)</td>
</tr>
<tr>
<td>Number of IV and PO antibiotics courses</td>
<td>-0.391 (0.080)</td>
<td>0.391 (0.080)</td>
<td>0.120 (0.605)</td>
<td>0.208 (0.366)</td>
<td>0.318 (0.159)</td>
</tr>
<tr>
<td>Contemporaneous FEV1 (% predicted)</td>
<td>0.383 (0.086)</td>
<td>-0.383 (0.086)</td>
<td>-0.194 (0.401)</td>
<td>-0.474* (0.030)</td>
<td>-0.026 (0.911)</td>
</tr>
<tr>
<td>Contemporaneous FVC (%predicted)</td>
<td>0.287 (0.208)</td>
<td>-0.287 (0.208)</td>
<td>-0.238 (0.298)</td>
<td>-0.329 (0.145)</td>
<td>0.212 (0.357)</td>
</tr>
<tr>
<td>Contemporaneous FEV1/FVC</td>
<td>0.440* (0.046)</td>
<td>-0.440* (0.046)</td>
<td>-0.318 (0.160)</td>
<td>-0.548* (0.010)</td>
<td>-0.032 (0.889)</td>
</tr>
<tr>
<td>Bespoke cluster based low attenuation CT (%)</td>
<td>-0.418 (0.059)</td>
<td>0.418 (0.059)</td>
<td>0.180 (0.435)</td>
<td>0.390 (0.081)</td>
<td>0.316 (0.163)</td>
</tr>
<tr>
<td>CT summary score</td>
<td>-0.688** (0.001)</td>
<td>0.688** (0.001)</td>
<td>0.477* (0.029)</td>
<td>0.710** (&lt;0.001)</td>
<td>0.572** (0.007)</td>
</tr>
<tr>
<td>CT bronchiectasis score</td>
<td>-0.608** (0.003)</td>
<td>0.608** (0.003)</td>
<td>0.510* (0.018)</td>
<td>0.671** (0.001)</td>
<td>0.396 (0.075)</td>
</tr>
<tr>
<td>CT mucus plugging score</td>
<td>-0.692** (0.001)</td>
<td>0.692** (0.001)</td>
<td>0.481* (0.027)</td>
<td>0.737** (&lt;0.001)</td>
<td>0.626** (0.075)</td>
</tr>
<tr>
<td>CT peribronchial thickening score</td>
<td>-0.429 (0.052)</td>
<td>0.429 (0.052)</td>
<td>0.284 (0.212)</td>
<td>0.442* (0.045)</td>
<td>0.518* (0.016)</td>
</tr>
<tr>
<td>CT parenchymal score</td>
<td>-0.469* (0.032)</td>
<td>0.469* (0.032)</td>
<td>0.138 (0.552)</td>
<td>0.378 (0.091)</td>
<td>0.388 (0.082)</td>
</tr>
<tr>
<td>CT hyperinflation score</td>
<td>-0.594** (0.005)</td>
<td>0.594** (0.005)</td>
<td>0.428 (0.053)</td>
<td>0.592** (0.005)</td>
<td>0.326 (0.149)</td>
</tr>
</tbody>
</table>

*Spearman's coefficient (p value), *p*<0.05, **p*<0.01

Again there was significant correlation with LCI and CT structural disease severity scores, although correlation was generally more significant with the ventilation fraction than with the perfusion fraction.
The formation of ventilation and perfusion maps also allows the calculation of ventilation perfusion (VQ) mismatch (i.e. the discrepancy between ventilated fraction and perfused fraction).

<table>
<thead>
<tr>
<th>VQ discrepancy (Q/fraction – V/fraction)</th>
<th>Median</th>
<th>Interquartile range</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>-2.19</td>
<td>-4.12 – -0.26</td>
<td>-7.72 – 4.34</td>
</tr>
</tbody>
</table>

There was no statistically significant correlation between the size of VQ discrepancy and any of the clinical markers of disease severity. 5 patients had a positive discrepancy (i.e. the perfusion defect was greater than the ventilation defect), but these 5 patients did not demonstrate a different clinical phenotype to those with larger or matched ventilation: perfusion fractions.
Figure 16 – An 8 year old boy with a CFCT hyperinflation score of 28.8%. a) CT demonstrates mosaic attenuation and mucus plugging. b) Matrix pencil decomposition ventilation map demonstrating reduced respiratory motion (blue) in the low attenuation areas of lung on CT. c) Identifying voxels falling under 75% of the median signal amplitude (shown in blue) allows quantification of ‘poorly’ ventilation lung fraction. d) Matrix pencil decomposition perfusion map demonstrating perfusion defects in the regions of ventilation defects and low attenuation areas. e) A mask can be formed of all voxels falling below a 75% median signal amplitude (shown in red) to quantify poor perfusion.

Figure 17 – Compare this 14 year old with CF to the figure above. a) CT demonstrated no structural lung disease (CFCT score 0, LCI 8.6). The matrix pencil ventilation (b and c) and perfusion (d and e) maps demonstrate far smaller, less segmental appearing ventilation and perfusion defects.
6.4 Discussion and Conclusions:

Principal findings

All 22 participants successfully completed the full MRI protocol with the resulting images all of sufficient quality for post-processing, again suggesting that this protocol is clinically feasible.

Significant T1 shortening was demonstrated on ufSSFP imaging following the administration of 100% oxygen, but no significant correlation was demonstrated between the degree of enhancement and any clinical measure of disease severity.

Both dynamic techniques did, however, show significant correlation with clinical measures. Both the ventilation and perfusion fractions calculated from matrix pencil decomposition imaging demonstrated strong statistically significant correlation with LCI\(_{2.5}\) (\(r=0.838, p=0.001\) for ventilation vs. \(r=0.544, p=0.029\) for perfusion) and with all CFCT component scores with the exception of the parenchymal score (\(r=\) up to 0.731, \(p<0.001\) for ventilation and \(r=\) up to 0.692, \(p=0.001\) for perfusion).

Significant correlation was demonstrated between the median oxygen wash-in time and LCI\(_{2.5}\) (\(r=0.60, p=0.011\)), CFCT summary score (\(r=0.431, p=0.045\)) and CFCT mucus plugging score (\(r=0.424, p=0.049\)), but not with any other clinical measures. Collection of MBW data on the same day as the MRI allowed direct comparison of gas wash-out times via the Exhalyser D
and via OE-MRI demonstrating only moderate correlation (r=0.52, p=0.033) with increasing underestimation of wash-in time by MRI as time increases. This is perhaps not surprising, as the timing of the dynamic oxygen enhanced protocol is an arbitrary 5 minutes for each phase and as wash-in or wash-out time increases up to and beyond 5 minutes, the protocol will not allow regional oxygen concentration to reach its peak or nadir and the numeric output will rely more on extrapolation from preceding data points.

Whilst single values expressing wash-in or-out times and degrees of enhancement at a whole lung level did not show particularly strong correlations, there were significant correlations between clinical measures and oxygen wash-out times when the spatial distribution of disease was assessed via expression of ventilation heterogeneity as skew or kurtosis of wash-out time values at a voxel level. Moderate to strong, statistically significant correlation was demonstrated between skew and kurtosis of wash-out time with CT measures (r= up to 0.718, p<0.001) and LCI_{2.5} (r=0.591, p=0.013). In fact, as with the matrix pencil data above, the only CT structural lung disease score which did not correlate significantly with wash-out time heterogeneity was the parenchymal score. This is reassuring as this is the only score that should not affect oxygen wash out (areas of collapse or consolidation should not contribute to ventilation).

As explained in the introduction to this chapter, in the context of this thesis, both skew and kurtosis are measures of heterogeneity, with increasing skew and kurtosis both representing increasingly heterogeneous local lung
function across an individual’s lungs. The fact that the skew and kurtosis of outputs correlates best with MBW and CT findings is relevant as it is evidence that the spatial registration of the lung function data is the most significant output, rather than whole lung level measurements more akin to MBW testing or spirometry.

Formation of ventilation and perfusion maps from the matrix pencil decomposition technique enables calculation of ventilation mismatch by simple subtraction of one fraction from the other. Median difference was -2.19 (more perfused lung than ventilated lung), but with a range from -7.72 to +4.34. The size of the discrepancy did not correlate with any clinical measure and the 5 patients whose discrepancy was reversed (i.e. more perfusion defect than ventilation defect) did not have a different clinical phenotype than the rest of the cohort. People with CF often have long-term vascular access devices and there is a risk of pulmonary embolism as a result, but more data will be required to investigate the possibility of mismatched perfusion defects being secondary to thromboembolic events as opposed to the matched perfusion defects from reflex vasoconstriction and redistribution of pulmonary blood away from areas of poor ventilation.

**Strengths and weaknesses**

The combination of multiple methods of ventilation imaging by simple 2-part oxygen enhancement, dynamic oxygen enhancement and matrix pencil decomposition imaging is a particular strength of this study. No published studies currently available compare the use of these different approaches
and, as discussed before, the collection of MBW data, including unadjusted nitrogen washout times in seconds has been particularly useful in examining the accuracy of OE-MRI based calculation of oxygen wash-in times.

The most significant weakness is arguably the presence of only single time point data. This limits us to whole lung level assessment, rather than enabling the tracking of individual areas of altered lung function over time. The lack of longitudinal data also likely explains the lack of significance in correlation of single outputs of lung function from dynamic OE-MRI. Whilst the spatial information contained within skew and kurtosis are encouraging, both are very blunt measures of generalised heterogeneity. Both suffer from non-linear responses as disease significance increases – as a lung moves from completely normal to increasingly abnormal, skew and kurtosis will increase in line with increasing heterogeneity. However, there comes a point when as much lung is diseased as is healthy and as disease progresses beyond this point, it is feasible that worsening disease will result in a reduction in skew and kurtosis as the lungs become more homogeneous diseased. Therefore, neither output is ideal for longitudinal follow up into adulthood. The tracking of OE-MRI measures over time in regions chosen visually is likely to offer far more clinically important information (for example following function in an area of focal exacerbation over treatment).
Strengths and weaknesses in relation to other studies and discrepant results

Martini et al correlated outputs from the exactly the same dynamic oxygen enhanced MRI protocol to CT and spirometry in a cohort of 21 older patients (20 – 40 years old, median 25). Interestingly they found strong correlation between CT total disease summary scores and delta pO2 max \( r = -0.741, p<0.001 \) where we found none \( r = -0.309, p=0.162 \) and significant correlation between CT bronchiectasis scores and almost all OE-MRI outputs. Martini et al also found no significant correlation between OE-MRI outputs and CT hyperinflation scores, whereas I found significant correlation between hyperinflation and the skewness of oxygen wash-out times \( r=0.543, p=0.009 \). The significant differences in results is likely, at least in part, secondary to the significant differences in populations – my cohort was much younger and, as discussed in the first results chapter, has a predominance of small airways disease and far less severe bronchiectasis than Martini’s cohort. This is particularly significant going forward, as the introduction of highly effective modulator therapies is likely to greatly reduce disease severity in people with CF. My study also has considerable strength in design compared to that of Martini et al, in that all CT, MRI and MBW testing was performed within a single hospital attendance, with a maximum between test interval of 5 days (most on the same day) whereas the study of Martini et al relied on retrospective collection of data with up to 275 days between MRI and CT and up to 125 days between MRI and spirometry with no inclusion of MBW testing [226].
Nyilas et al published a study using exactly the same matrix pencil decomposition technique as my study, in a similar population (40 children with CF, from 6-18 years old, median 12) and found very similar correlation between ventilation fraction and LCI (r=0.76, p=<0.001 compared to our findings r=0.768, p<0.001). They didn’t however compare to structural disease on CT, instead comparing to an Eichinger score from structural MRI – performed using fat suppressed T2 BLADEs and T2 HASTEs. The exact details of the structural MR imaging are not given, but structural imaging took a mean of 11.2 minutes with a maximum time of 17.7 minutes and likely therefore included both respiratory triggering and repeats of sequences where image quality was deemed to be insufficient for scoring. Since their study, the further division of ventilation and perfusion defects into “moderate”, “severe” and “non” -functioning groups has been added with stronger correlation between LCl2.5 and severely impaired ventilation fraction than moderately impaired ventilation fraction (r=0.771, p<0.001 vs. r=0.609, p=0.012 respectively) [160].

More recently, the same group have published reproducibility data on the matrix pencil decomposition technique demonstrating good reproducibility between two scans 24 hours apart (ICC 0.6 in CF, 0.9 in healthy controls) and a limit of agreement for fractional ventilation of -4.4% to +3.7% (compared to -2.6 to 3 for LCI)[227].
Meaning of the study

Oxygen enhanced and matrix pencil decomposition imaging of lung function can be successfully implemented in children and young people, right down to the age of 6 years, with no need for repeated acquisitions in our cohort and good tolerance of the necessary imaging time and breath holds as described in the previous chapters.

Matrix pencil decomposition based ventilation and perfusion fractions correlate well with LCI 2.5 and CT measures of disease severity, but in oxygen enhanced imaging, the homogeneity of ventilation appears to be more significant than whole lung measures of ventilation efficiency and longitudinal trends in local lung function are likely to be of more interest than single time point measures of lung function.

Unanswered questions and future research

Nyilas et al have provided short term reproducibility data for the matrix pencil decomposition technique, but short term reproducibility data in CF is still required for the dynamic OE-MRI protocol and medium to long term variability data is required for both techniques, both in times of disease stability and over periods of acute exacerbation. A recently successful grant application will allow us to employ both techniques in the longitudinal imaging follow up of people with CF over a 3 year period with a side arm for extra imaging over times of exacerbation. The most exciting prospect from this future project is the ability to track local changes lung function rather
than relying on whole lung measures of function therefore fully utilising the spatial registration of function which MRI enables.

As discussed above, the arbitrary timings of the OE-MRI technique limit its application to more severe disease, and it may be necessary to plan OE-MRI timings using MBW prior to the MRI. An additional study of the effects of lying supine during lung function testing would also be interested to assess the possible role of positioning and breathing pattern on discrepancy between imaging-based and more conventional measures of lung function.
Chapter 7 – MRI Assessment of Extra-Thoracic Disease Associated with Chronic Suppurative Lung Diseases (Paranasal Sinus and Liver Disease)

7.1 Introduction:

As mentioned in the introductory chapter, the suppurative lung diseases studied in this cohort form part of multisystem disorders. In addition to airways disease, cystic fibrosis causes paranasal sinus disease, liver disease, exocrine and endocrine pancreatic disease (leading to malabsorption and diabetes), intestinal disease (e.g. meconium ileus and distal intestinal obstruction syndrome – DIOS) and male infertility (absence of the vas deferens). Likewise, in addition to bronchiectasis, PCD causes chronic otitis media, paranasal sinus disease, congenital cardiac anomalies, disordered abdominal situs (including asplenia in the setting of right atrial isomerism, albeit rarely) and infertility (disordered sperm motility and increased incidence of ectopic pregnancy)[228]. Whilst the application of MRI to the assessment of lung and airways disease is still largely within a research setting, MRI assessment of the paranasal sinuses and abdominal viscera is commonplace in a clinical setting.

Paranasal sinus disease is of particular interest within the study of chronic suppurative lung disease syndromes, with the formation of the well known “unified airways hypothesis” – that microorganisms which colonise or infect the upper respiratory tract (including the paranasal sinuses) may transit to
the lower respiratory tract or vice versa with possible advantages of adaptation to the host environment prior to translocation from upper to lower respiratory tract compartments. As discussed in the introductory chapter, bespoke CF-specific imaging scoring systems exist for the quantification of paranasal sinus disease, however, most clinical sinus imaging is via CT, with better depiction of bone and better guidance of surgical intervention compared to MRI. In order to minimise unnecessary exposure to ionising radiation, sinus imaging is generally only considered appropriate once the degree of symptoms suggest surgical intervention may be necessary. The use of MRI to follow up gross large airways disease opens the opportunity to track longitudinal change in paranasal sinus disease in asymptomatic patients in a single MRI appointment, thus potentially identifying significant, but clinically occult disease. Following on from the work of Eggesbo et al, MRI signal abnormalities may also correlate with the presence of certain micro-organisms within sinus mucus.

Many of the MRI acquisitions our protocol uses for lung imaging also include at least part of the upper abdomen. This includes two different methods of quantitative signal mapping (T1 via IR-HASTE and ufbSSFP and T2 via ufbSSFP) potentially allowing simultaneous quantitative assessment of liver parenchymal quality.

**Aims and objectives** –

The aims of this chapter are to (i) explore the use of quantitative MRI in assessment of paranasal sinus disease as part of a multisystem CF MRI
protocol and (ii) to explore any associations between sinus disease and lung disease, either supporting the unified airways hypothesis or providing extrathoracic surrogate markers of disease severity.

There are established liver MRI mapping techniques already in use, both in research and clinical care, but their addition to this multisystem MRI protocol would take the total examination time well over an hour and limit the protocols applicability to paediatric cohorts. As such, the third aim of this chapter is to assess the utility of the T1 and T2 maps obtained for quantitative lung imaging, in the assessment of liver disease.

**Hypotheses:**

**Primary** -

Quantification of paranasal sinus and liver disease via MRI during the same examination as MRI lung assessment is feasible (i.e. the extra required examination time well tolerated by the patient and the images are of adequate quality for analysis).

**Secondary** -

MRI-derived measures of paranasal sinus disease and the presence of signal abnormalities suggestive of sinus infection/colonisation correlate with lung disease severity supporting the unified airways hypothesis.

MRI measures of liver disease correlate with clinical markers such as liver function tests and ultrasound elastography.
7.2 Methods:

7.2.1 Paranasal Sinus Imaging –

The MRI protocol is described in full in the methods chapter. In brief, T1 and T2 images were obtained coronal plane and the resulting images manually segmented using the Aquarius image viewer (iNtuition, Terarecon) to provide sinus volume, volume of sinus mucosa and volume of sinus mucus. Susceptibility weighted imaging was acquired in axial plane to assess for the presence or absence of artefact suggesting infection with significant micro-organisms and diffusion weighted (DWI) images acquired in axial plane. Mucosa and mucus were then segmented in Horos (version 2.2.0) and exported to ImageJ (version 1.49v. NIH, USA) for conversion into histograms of ADC values (using the “display pixel values” macro).

Figure 18 – Sinus ROI workflow. a) The raw ADC map is examined and sinus mucosa and mucus differentiated. b) a region of interest is drawn free-hand around the sinus mucosa and c) the voxels outside of the region of interest removed (value set to ‘0’). d) ImageJ is used to export the individual voxel values into excel where the surrounding ‘0’ values and halo of negative voxels around the mucosa (mostly susceptibility artefact from adjacent bone) can be removed. The remaining values can then be used for calculation of mean, median, mode, skew, kurtosis and various centiles.
Each measure was correlated with structural lung disease scores from CT (CFCT score), quantitative CT low attenuation values, quantitative ventilation MRI outputs and clinical data including LCI\textsubscript{2.5}, spirometry and number of courses of PO and IV antibiotics in the 6 months preceding MRI.

### 7.2.2 Liver Imaging –

Six regions of interest, each 10 mm in diameter, were placed in the portion of the liver included on each of the lung mapping images, taking care to avoid hepatic vasculature. Results were then correlated with the presence of absence of liver disease as per patient electronic records, evidence of portal hypertension on ultrasound (increased splenic craniocaudal length and reduced or reversed portal venous flow) and quantitative ultrasound measures of hepatic fibrosis (ultrasound sheer wave elastography performed on a GE LogiQ E10 with velocities classified using both the Ishak and Metavir classification systems [198]).

### 7.3 Results:

#### 7.3.1 Demographics and Clinical Data –

The demographics, clinical data from the previous chapters (exacerbations, spirometry, LCI\textsubscript{2.5} and CT structural lung disease scores) are summarised in the table over the page.
<table>
<thead>
<tr>
<th>Summary of demographics and clinical data from previous chapters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
</tr>
<tr>
<td>n=22</td>
</tr>
<tr>
<td>12 male (54.5%)</td>
</tr>
<tr>
<td>Median age 14 (range 6 – 35, 18 patients under 20 years)</td>
</tr>
<tr>
<td>PCD 3 (2x 9 years old, 1x 13 years old)</td>
</tr>
<tr>
<td>All others CF</td>
</tr>
<tr>
<td><strong>Exacerbations</strong></td>
</tr>
<tr>
<td><strong>Median</strong></td>
</tr>
<tr>
<td>IV antibiotic courses in prior 6 months</td>
</tr>
<tr>
<td>PO antibiotic courses in prior 6 months</td>
</tr>
<tr>
<td>Combined IV and/or PO antibiotic courses in prior 6 months</td>
</tr>
<tr>
<td><strong>Spirometry (% predicted)</strong></td>
</tr>
<tr>
<td><strong>Median</strong></td>
</tr>
<tr>
<td>FEV₁</td>
</tr>
<tr>
<td>FVC</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
</tr>
<tr>
<td><strong>LCI₂.₅</strong></td>
</tr>
<tr>
<td>n=16</td>
</tr>
<tr>
<td><strong>Median</strong></td>
</tr>
<tr>
<td>11.19</td>
</tr>
<tr>
<td><strong>Structural lung disease on CT</strong></td>
</tr>
<tr>
<td><strong>Median</strong></td>
</tr>
<tr>
<td>CFCT score</td>
</tr>
<tr>
<td>Total score</td>
</tr>
<tr>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>Mucus plugging</td>
</tr>
<tr>
<td>Peribronchial thickening</td>
</tr>
<tr>
<td>Parenchymal disease</td>
</tr>
<tr>
<td>Hyperinflation</td>
</tr>
</tbody>
</table>
### Table

<table>
<thead>
<tr>
<th>CT low attenuation volume calculation</th>
<th>Median</th>
<th>Range</th>
<th>Correlation with age (Spearman’s, p)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10.2%</td>
<td>0 – 61.8%</td>
<td>-0.045, 0.844</td>
</tr>
</tbody>
</table>

§% predicted
^% of maximal score
*significant at p<0.05
**significant at p<0.001

#### 7.3.2 Sinus Imaging

All patients completed the whole protocol, including imaging of the paranasal sinuses, with adequate image quality for analysis and segmentation.

Within our cohort, the total maxillary sinus volume ranged from 5.99 cm$^3$ to 41.00 cm$^3$ (median 21.24 cm$^3$) with no significant correlation between volume and age, likely reflecting the relatively tight age distribution within the cohort (Spearman’s -0.034, p=0.879).
There were only 2 patients (9% of the cohort) with no maxillary sinus disease (mucus or mucosal thickening) – a 13 year old boy with PCD and a 15 year old boy with CF (DF508/p.Gly551ASP) and one patient with mucosal thickening but no mucus (patient 1 – a 14 year old girl with CF) all other patients had a degree of both mucosal thickening and mucus. The volume of maxillary sinus mucus and mucosal thickening is summarised in the table over the page.
<table>
<thead>
<tr>
<th>Maxillary sinus mucus</th>
<th>Maxillary sinus mucosal thickening</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Feature present</strong></td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>19/22 (86%)</td>
</tr>
<tr>
<td>Unilateral</td>
<td>5/22 (22.7%)</td>
</tr>
<tr>
<td>20/22 (91%)</td>
<td></td>
</tr>
<tr>
<td>14/22 (63.6%)</td>
<td>18/22 (81.8%)</td>
</tr>
<tr>
<td>15/22 (68.2%)</td>
<td>5/22 (22.7%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease volume</th>
<th>Median</th>
<th>Range</th>
<th>Correlation with age (Spearmans, p)</th>
<th>Median</th>
<th>Range</th>
<th>Correlation with age (Spearmans, p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (ml)</td>
<td>6.2</td>
<td>0 – 17</td>
<td>0.089, 0.695</td>
<td>12.4</td>
<td>0 – 24.6</td>
<td>-0.134, 0.553</td>
</tr>
<tr>
<td>Volume expressed as % of total sinus volume (i.e. both sinuses)</td>
<td>20.1%</td>
<td>0 – 57.6%</td>
<td>0.249, 0.263</td>
<td>64.8%</td>
<td>0 – 93.9%</td>
<td>-0.110, 0.626</td>
</tr>
<tr>
<td>Mean % volume (mean of each side)</td>
<td>22.0%</td>
<td>0 – 57.6%</td>
<td>0.285, 0.198</td>
<td>65.2%</td>
<td>0 – 93.4%</td>
<td>-0.140, 0.536</td>
</tr>
<tr>
<td>Worst side % (individually)</td>
<td>30.5%</td>
<td>0 – 92.1%</td>
<td>0.193, 0.390</td>
<td>71.3%</td>
<td>0 – 100%</td>
<td>-0.143, 0.526</td>
</tr>
</tbody>
</table>

**Susceptibility artefact within mucus**
- Present in 20/21 (95.2%)^  
- Bilateral in 14/21 (66.7%)^  
- Unilateral 5/21 (23.8%)^  

^One patient had significant motion artefact on the STIR images making assessment for susceptibility artefact impossible
As above, the majority of patients had maxillary sinus disease, most bilaterally, but much of the sinus opacification by percentage of sinus volume was by thickened sinus mucosa rather than by mucus. This is an important finding as CT is not generally able to distinguish mucosal thickening from mucus (the attenuation of both is very similar). Susceptibility artefact was demonstrated within the mucus of all but one patient with successful STIR imaging (one patient, the youngest of our cohort at 6 years of age, produced too much motion artefact on this single sequence for assessment). There were no significant associations between volumes of mucus or mucosal thickening and patient age (see table below).

7.3.2.1 Correlation with Clinical Status –
There was no statistically significant difference in markers of lung disease severity between those with and without sinus disease (see table below). A near significant difference was, however, demonstrated in CFCT scores of structural lung disease severity. Given MRI’s ability to distinguish mucus from mucosal thickening, the presence or absence of each was also assessed individually, with the same trend toward significance demonstrated in the difference in CFCT scores in those with or without mucosal thickening, a significant difference in the degree of CFCT hyperinflation score (small airways disease) between those with or without sinus mucus and a near significant difference in the rate of exacerbations requiring antibiotics.
<table>
<thead>
<tr>
<th>Clinical marker</th>
<th>Sinus disease y/n</th>
<th>Sinus mucosal thickening y/n</th>
<th>Sinus mucus y/n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>21.00, 1.000</td>
<td>21.00, 1.000</td>
<td>30.00, 0.929</td>
</tr>
<tr>
<td>LCI$_{2.5}$</td>
<td>18.00, 0.600</td>
<td>18.00, 0.600</td>
<td>20.00, 1.000</td>
</tr>
<tr>
<td><strong>Exacerbations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>22.00, 0.866</td>
<td>22.00, 0.866</td>
<td>31.50, 0.787</td>
</tr>
<tr>
<td>PO</td>
<td>34.50, 0.104</td>
<td>34.50, 0.104</td>
<td><strong>48.00, 0.069</strong></td>
</tr>
<tr>
<td>IV and PO</td>
<td>34.00, 0.139</td>
<td>34.00, 0.139</td>
<td><strong>47.50, 0.069</strong></td>
</tr>
<tr>
<td><strong>Contemporaneous spirometry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV$_1$</td>
<td>10.00, 0.312</td>
<td>10.00, 0.312</td>
<td>19.00, 0.408</td>
</tr>
<tr>
<td>FVC</td>
<td>11.00, 0.364</td>
<td>11.00, 0.364</td>
<td>21.00, 0.523</td>
</tr>
<tr>
<td>FEV$_1$/FVC</td>
<td>12.00, 0.424</td>
<td>12.00, 0.424</td>
<td>18.00, 0.356</td>
</tr>
<tr>
<td><strong>CFCT scores</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total summary score</td>
<td><strong>36.50, 0.052</strong></td>
<td><strong>36.50, 0.052</strong></td>
<td>39.50, 0.308</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>33.00, 0.173</td>
<td>33.00, 0.173</td>
<td>35.00, 0.586</td>
</tr>
<tr>
<td>Mucus plugging</td>
<td><strong>36.00, 0.078</strong></td>
<td><strong>36.00, 0.078</strong></td>
<td>36.50, 0.464</td>
</tr>
<tr>
<td>Peribronchial thickening</td>
<td><strong>36.00, 0.078</strong></td>
<td><strong>36.00, 0.078</strong></td>
<td>41.00, 0.265</td>
</tr>
<tr>
<td>Parenchymal score</td>
<td>28.50, 0.364</td>
<td>28.50, 0.364</td>
<td>29.50, 0.929</td>
</tr>
<tr>
<td>Hyperinflation</td>
<td>34.00, 0.139</td>
<td>34.00, 0.139</td>
<td><strong>49.50, 0.040</strong>*</td>
</tr>
</tbody>
</table>

Test statistic (Mann-Whitney U), p
Bold=near significant * p<0.05
Simple scatter of number of antibiotic courses (IV and PO) by presence of maxillary sinus mucus

Simple Scatter of CFCT hyperinflation score (%) by presence vs absence of maxillary sinus mucus
### 7.3.2.1.1 Volume of Mucus and Thickened Mucosa

Correlation of the various methods of quantifying sinus disease on a continuous scale against established clinical measures of lung disease severity are summarised below (Spearman’s correlation coefficient, p value).

<table>
<thead>
<tr>
<th>Clinical measure</th>
<th>Mucosal disease</th>
<th>Mucus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean %</td>
<td>% total bilateral volume</td>
</tr>
<tr>
<td><strong>Spirometry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contemporaneous</td>
<td>-0.284, 0.201</td>
<td>-0.321, 0.145</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; (%) predicted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contemporaneous</td>
<td>-0.286, 0.197</td>
<td>-0.315, 0.154</td>
</tr>
<tr>
<td>FVC (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contemporaneous</td>
<td>-0.192, 0.392</td>
<td>-0.219, 0.327</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 month lowest</td>
<td>-0.415, 0.055</td>
<td>-0.447*, 0.037</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; (%) predicted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 month lowest</td>
<td>-0.247, 0.267</td>
<td>-0.264, 0.235</td>
</tr>
<tr>
<td>FVC (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 month lowest</td>
<td>-0.396, 0.068</td>
<td>-0.437*, 0.042</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LCl&lt;sub&gt;2.5&lt;/sub&gt;</strong></td>
<td>-0.075, 0.782</td>
<td>-0.060, 0.824</td>
</tr>
</tbody>
</table>

**Exacerbations**

<table>
<thead>
<tr>
<th></th>
<th>IV antibiotic courses</th>
<th>PO antibiotic courses</th>
<th>Combined IV&amp;PO antibiotic courses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Courses</td>
<td>Mean %</td>
<td>Mean %</td>
<td>Mean %</td>
</tr>
<tr>
<td></td>
<td>0.127, 0.572</td>
<td>0.099, 0.662</td>
<td>0.224, 0.316</td>
</tr>
<tr>
<td></td>
<td>0.155, 0.491</td>
<td>0.105, 0.641</td>
<td>0.249, 0.263</td>
</tr>
<tr>
<td></td>
<td>0.008, 0.972</td>
<td>0.191, 0.394</td>
<td>0.193, 0.389</td>
</tr>
<tr>
<td></td>
<td>0.044, 0.846</td>
<td>0.278, 0.211</td>
<td>0.303, 0.170</td>
</tr>
<tr>
<td></td>
<td>0.051, 0.820</td>
<td>0.110, 0.625</td>
<td>0.138, 0.541</td>
</tr>
<tr>
<td></td>
<td>-0.138, 0.541</td>
<td>0.160, 0.477</td>
<td>-0.001, 0.996</td>
</tr>
<tr>
<td></td>
<td>-0.105, 0.643</td>
<td>0.093, 0.680</td>
<td>0.214, 0.338</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical measure</td>
<td>Mucosal disease</td>
<td>Mucus</td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean %</td>
<td>% total bilateral volume</td>
<td>Maximum % (worst side)</td>
</tr>
<tr>
<td>CFCT scores (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total lung summary score</td>
<td>0.163, 0.180, 0.468</td>
<td>0.164, 0.465</td>
<td>0.092, 0.684</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>0.071, 0.080, 0.752</td>
<td>0.139, 0.536</td>
<td>-0.131, 0.561</td>
</tr>
<tr>
<td>Mucus plugging</td>
<td>0.129, 0.140, 0.568</td>
<td>0.146, 0.515</td>
<td>0.162, 0.472</td>
</tr>
<tr>
<td>Peribronchial thickening</td>
<td>0.042, 0.054, 0.854</td>
<td>0.046, 0.838</td>
<td>0.128, 0.571</td>
</tr>
<tr>
<td>Parenchymal score</td>
<td>0.180, 0.194, 0.422</td>
<td>0.149, 0.507</td>
<td>0.022, 0.921</td>
</tr>
<tr>
<td>Hyperinflation</td>
<td>0.250, 0.266, 0.262</td>
<td>0.242, 0.279</td>
<td>0.262, 0.238</td>
</tr>
</tbody>
</table>

Spearman's correlation coefficient, \( p \)
*statistically significant at \( p<0.05 \)

Somewhat disappointingly, the only statistically significant relationship between continuous measures of sinus disease and clinical measures of lung disease severity within our small cohort was a moderate correlation between maxillary sinus mucosal thickening, expressed as a percentage of total maxillary sinus volume, with the lowest FEV\(_1\) and FEV\(_1\)/FVC from the 6 months preceding MRI (-0.447, \( p=0.037 \) and -0.437, \( p=0.042 \) respectively).

All but one patient (P15 - the youngest patient at only 6 years old) had exacerbations requiring antibiotics in the 6 month preceding MRI. Whilst no significant linear correlation is demonstrated between sinus disease and exacerbation frequency, on plotting the amount of sinus mucosal thickening
against the number of courses of antibiotics (PO and IV) in the preceding 6 months, it becomes clear that those with opacification of around 50% or more of their sinus volume by mucosal thickening had more courses. In fact, taking a cut off of >47% opacification identifies all patients with more than 2 recent courses of antibiotics.

Fisher's exact test, using a cut off of 50% sinus opacification by mucosal thickening, shows an increased incidence of requirement of >2 courses of
antibiotics (PO or IV), nearing statistical significance (p=0.074) with an unadjusted odds ratio of 6.875 (95% CI 0.931 – 50.782). Statistical significance is gained on adjusting the threshold to 47% opacification by mucosal thickening (p=0.005, unadjusted OR 4.250, 95% CI 1.804 – 10.013).

The same relationship between volume of sinus thickening and exacerbations requiring antibiotic courses does not hold true with volume of sinus mucus (see graph below).

7.3.2.1.2 Susceptibility and Diffusion-Weighted Imaging

Whilst volume of sinus mucus shows no meaningful relationship with respiratory disease status (see previous table for correlation coefficients
and p values), our protocol includes two sequences for the assessment of mucus quality – a susceptibility-weighted sequence to assess for the presence of micro-organisms which sequester iron and other metals, and a diffusion weighted sequence to assess for mucus thickness.

Apparent diffusion coefficients from regions of interest drawn around mucus within the maxillary sinuses are summarised in the table below with values expressed as summary statistics from both sinuses or of the highest/lowest unilateral sinus (i.e. the extremes within each individual). 90th and 10th centile measures are included as used in certain situations in nuclear medicine to express extremes of distribution with a slight reduction in the effect of any marked outliers (in this case, often single figure pixel values from partial voluming effects with adjacent bone at the lower end of the distribution).

Mucus ADC measurement was not possible in 2 patients - the DWI images for patient 8 were too badly affected by motion for accurate delineation of mucus from the mucosa and there was too much susceptibility artefact in patient 10 (majority of values were “0”). Those with no maxillary sinus mucus (n=3) were also excluded from analysis (entering 0 values would effect summary statistics and correlation coefficients).
Correlation of mucus ADC values with clinical markers of lung disease severity are summarised in the table below (Spearman's correlation coefficient, p).

<table>
<thead>
<tr>
<th>Descriptive statistics across the cohort</th>
<th>Median mucus ADC of both sinuses (mm²/s)</th>
<th>Mode of both sinuses mucus ADCs (mm²/s)</th>
<th>90th centile of highest side (mm²/s)</th>
<th>10th centile of lowest side (mm²/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (/22)</td>
<td>17</td>
<td>12</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>433.41 (183.41)</td>
<td>405.33 (187.15)</td>
<td>700.89 (211.78)</td>
<td>230.08 (169.27)</td>
</tr>
<tr>
<td>Median (25th – 75th quartile)</td>
<td>412.00 (295.75 – 490.50)</td>
<td>435.50 (310.00 – 506.00)</td>
<td>258.50 (524.60 – 842.80)</td>
<td>208.60 (141.10 – 265.00)</td>
</tr>
<tr>
<td>Minimum</td>
<td>151.00</td>
<td>1.00</td>
<td>443.00</td>
<td>1.70</td>
</tr>
<tr>
<td>Maximum</td>
<td>827.00</td>
<td>694</td>
<td>1205.00</td>
<td>265.00</td>
</tr>
</tbody>
</table>

**Correlation coefficients**

<table>
<thead>
<tr>
<th>(Spearman's coefficient, p)</th>
<th>Median mucus ADC of both sinuses</th>
<th>Mode of both sinuses mucus ADCs</th>
<th>90th centile of highest side</th>
<th>10th centile of lowest side</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spirometry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contemporaneous FEV₁ (%) predicted</td>
<td>0.354, 0.163</td>
<td>0.168, 0.602</td>
<td>0.130, 0.619</td>
<td>0.174, 0.504</td>
</tr>
<tr>
<td>Contemporaneous FVC (%) predicted</td>
<td>0.053, 0.841</td>
<td>0.098, 0.762</td>
<td>-0.261, 0.311</td>
<td>0.123, 0.639</td>
</tr>
<tr>
<td>Contemporaneous FEV₁/FVC</td>
<td><strong>0.434, 0.082</strong></td>
<td>0.084, 0.795</td>
<td>0.402, 0.110</td>
<td>0.142, 0.586</td>
</tr>
<tr>
<td><strong>LCI&lt;sub&gt;2.5&lt;/sub&gt;</strong></td>
<td>0.137, 0.689 (n=11)</td>
<td>0.607, 0.148 (n=7)</td>
<td>-0.082, 0.811 (n=11)</td>
<td>0.300, 0.370 (n=11)</td>
</tr>
</tbody>
</table>

**Exacerbations**

<p>| | | | | |
|                                |                                  |                                 |                             |                             |
|--------------------------------|----------------------------------|---------------------------------|                             |                             |
| IV antibiotic courses          | 0.198, 0.445                     | <em><em>0.581</em>, 0.048</em>*               | -0.226, 0.382              | 0.251, 0.330               |
| PO antibiotic courses          | 0.298, 0.245                     | 0.056, 0.862                    | 0.081, 0.757               | 0.036, 0.891               |
| Combined IV&amp;PO antibiotic courses | 0.339, 0.183                     | 0.379, 0.224                    | 0.016, 0.950               | 0.106, 0.658               |</p>
<table>
<thead>
<tr>
<th>(Spearman’s coefficient, p)</th>
<th>Median mucus ADC of both sinuses</th>
<th>Mode of both sinuses mucus ADCs</th>
<th>90th centile of highest side</th>
<th>10th centile of lowest side</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CFCT scores (%)</strong></td>
<td><strong>Total lung summary score</strong></td>
<td>0.384, 0.128</td>
<td><em><em>0.692</em>, 0.013</em>*</td>
<td>-0.060, 0.918</td>
</tr>
<tr>
<td></td>
<td><strong>Bronchiectasis</strong></td>
<td>0.166, 0.525</td>
<td>0.463, 0.130</td>
<td>-0.174, 0.504</td>
</tr>
<tr>
<td></td>
<td><strong>Mucus plugging</strong></td>
<td>0.353, 0.218</td>
<td><em><em>0.633</em>, 0.019</em>*</td>
<td>-0.136, 0.602</td>
</tr>
<tr>
<td></td>
<td><strong>Peribronchial thickening</strong></td>
<td><em><em>0.498</em>, 0.042</em>*</td>
<td><strong>0.744</strong>, <strong>0.006</strong></td>
<td>0.123, 0.638</td>
</tr>
<tr>
<td></td>
<td><strong>Parenchymal score</strong></td>
<td>-0.137, 0.600</td>
<td>0.197, 0.539</td>
<td><em><em>-0.522</em>, 0.032</em>*</td>
</tr>
<tr>
<td></td>
<td><strong>Hyperinflation</strong></td>
<td>0.366, 0.149</td>
<td><strong>0.519, 0.084</strong></td>
<td>0.161, 0.538</td>
</tr>
</tbody>
</table>

NB. As explained previously, not all patients underwent LCI. For LCI correlation n is included in parentheses.

Spearman’s correlation coefficient, p  
*significant at p<0.05  
**significant at p<0.01

Exclusion of those cases with no sinus disease and those whose DWI images could not be assessed has a significant effect on sample size. For better visual analysis, the scatter plots below include the cases with no sinus mucus coded as ADC=0 (clearly the ADC will not be 0, there is no mucus ADC to measure in these cases, hence exclusion from the above analysis).

The box plots still exclude these cases.

Whilst no significant linear association is demonstrated between mucus ADC and LCI2.5, plotting them on a scatter chart demonstrates that all of the
patients with an LCI over 14 (approximately 2 x the upper limit of normal) have a median sinus mucus ADC of over 300mm$^2$/s.

Using this mucus threshold ADC of 300mm$^2$/s, Fisher's exact test nears significance (p=0.077) with an unadjusted odds ratio of 2.00 (95%CI 1 – 3.999).
Visually, there is also a trend toward a high number of exacerbations requiring IV antibiotics and the mode of sinus mucus ADC values. This is shown in the plots below (again, the scatter plot includes patients with no mucus coded as 0, whilst the box plot has 0 values removed).
NB. There was a single patient with 3 courses of IV antibiotics in the preceding 6 weeks, but this patient (patient 8) had too much motion artefact on DWI for calculation of mucus ADC.

Independent samples Kruskal-Wallis test shows no statistically significant difference in the mode of the mucus ADC in those with 0, 1 or 2 IV antibiotic courses in the preceding 6 months (test statistic 4.15, degrees of freedom=2, p=0.125), but if the dependant variable is dichotomised into those who did or didn’t have IV antibiotics in the preceding 6 months (i.e. any exacerbations) then the relationship nears significance (Mann-Whitney U=24.0 p=0.064). Clearly a larger cohort is needed to further investigate any
association, in particular, more cases with stable disease and less frequent courses of antibiotics are required.

To allow inclusion of those cases with no sinus mucus, the ADC data can be dichotomised using the same cut off ADC of 300mm²/s used above.

Although those with a mucus ADC>300mm²/s were generally within the group who received antibiotics, n is too small (particularly the number with no mucus or mucus with ADC values under 300mm²/s) and no statistically significant difference could be demonstrated (p=0.525).

Statistically significant linear correlation was demonstrated between sinus mucus ADC values and structural lung disease scores on CT (see table above). Again, it was the most frequent ADC value within an individual patient’s mucus (the mode) that correlated most closely, but peribronchial
thickening scores also demonstrated significant correlation with median ACD values. As seen with other clinical markers of disease severity it was higher mucus ADC values that were associated with higher lung disease severity scores (see graphs below).
In addition to continuous measures of diffusion within mucus, the presence or absence of susceptibility artefact was recorded as present or absent and,
if present, as unilateral or bilateral. As above, patient 15 (our youngest patient) was excluded as there was too much motion artefact on the susceptibility-weighted imaging.

<table>
<thead>
<tr>
<th>Susceptibility artefact present?</th>
<th>19/21 (90.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral</td>
<td>5</td>
</tr>
<tr>
<td>Bilateral</td>
<td>14</td>
</tr>
</tbody>
</table>

Comparison of distributions within the absent, unilateral and bilateral groups with clinical markers of lung disease severity by independent sample Kruskal-Wallis test is summarised in the table below. Intergroup comparison for those with significant independence is demonstrated in the subsequent graphs (box and scatter charts) with Bonferroni corrected p values for multiple comparisons.

<table>
<thead>
<tr>
<th>Clinical measure vs presence of susceptibility artefact</th>
<th>Test statistic (degrees of freedom)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.168(2)</td>
<td>0.558</td>
</tr>
<tr>
<td>LCI&lt;sub&gt;2.5&lt;/sub&gt;</td>
<td>1.881(2)</td>
<td>0.391</td>
</tr>
<tr>
<td>Exacerbations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>5.333(2)</td>
<td>0.069*</td>
</tr>
<tr>
<td>PO</td>
<td>3.758(2)</td>
<td>0.154</td>
</tr>
<tr>
<td>IV +/- PO</td>
<td>7.103(2)</td>
<td>0.029*</td>
</tr>
<tr>
<td>Contemporaneous spirometry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;(%)</td>
<td>1.395(2)</td>
<td>0.498</td>
</tr>
<tr>
<td>FVC (%)</td>
<td>2.133 (2)</td>
<td>0.344</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC</td>
<td>0.849 (2)</td>
<td>0.654</td>
</tr>
<tr>
<td>CFCT structural disease scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total summary score</td>
<td>6.938(2)</td>
<td>0.031*</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>2.574(2)</td>
<td>0.276</td>
</tr>
<tr>
<td>Mucus plugging</td>
<td>5.767(2)</td>
<td>0.056</td>
</tr>
<tr>
<td>Peribronchial thickening</td>
<td>6.027(2)</td>
<td>0.049*</td>
</tr>
<tr>
<td>Parenchymal score</td>
<td>1.050(2)</td>
<td>0.592</td>
</tr>
<tr>
<td>Hyperinflation</td>
<td>9.478(2)</td>
<td>0.009**</td>
</tr>
</tbody>
</table>
Comparison | p          | Bonferroni corrected p |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.029*</td>
<td></td>
</tr>
<tr>
<td>None - Unilateral</td>
<td>0.540</td>
<td>1.000</td>
</tr>
<tr>
<td>None - Bilateral</td>
<td>0.044*</td>
<td>0.131</td>
</tr>
<tr>
<td>Unilateral - Bilateral</td>
<td>0.036*</td>
<td>0.107</td>
</tr>
</tbody>
</table>
### Comparison of CFCT Total Lung Score (%)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>p</th>
<th>Bonferonni corrected p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.031</td>
<td></td>
</tr>
<tr>
<td>None - Unilateral</td>
<td>0.345</td>
<td>1.000</td>
</tr>
<tr>
<td>None - Bilateral</td>
<td>0.027*</td>
<td>0.082</td>
</tr>
<tr>
<td>Unilateral - Bilateral</td>
<td>0.066*</td>
<td>0.198</td>
</tr>
</tbody>
</table>
Comparison | p       | Bonferonni corrected p
-----------|---------|---------------------
Overall    | 0.049*  |                     
None - Unilateral | 0.317   | 0.951              
None - Bilateral  | 0.034*  | 0.101              
Unilateral - Bilateral | 0.106   | 0.317              

Simple Scatter of CFCT Total Lung Score by Maxillary Sinus Artefact

Simple Boxplot of CFCT Peribronchial Thickening Score (%) by Sinus Mucus Artefact
<table>
<thead>
<tr>
<th>Comparison</th>
<th>p</th>
<th>Bonferonni corrected p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.009**</td>
<td></td>
</tr>
<tr>
<td>None - Unilateral</td>
<td>0.686</td>
<td>1.000</td>
</tr>
<tr>
<td>None - Bilateral</td>
<td>0.034*</td>
<td>0.103</td>
</tr>
<tr>
<td>Unilateral - Bilateral</td>
<td>0.009**</td>
<td>0.028*</td>
</tr>
</tbody>
</table>
Significant differences were demonstrated in the severity of small airways disease (hyperinflation score) on CT, and near significant differences in the total CFCT summary score depending on the presence and degree of susceptibility artefact within maxillary sinus mucus.

Of course, the diffusion-weighted imaging quantifies diffusion of water within the sinus mucosa as well as in the mucus. As summarised in the table at the beginning of this results section, maxillary sinus mucosal thickening was demonstrated in all but two patients. As above, one patient (patient 8) caused too much motion artefact for analysis, therefore, the total cohort with sinus mucosa to analyse consisted of 19 patients. The distribution of ADC values within the mucosa of individuals within the cohort is summarised in the table below.
Correlation of clinical markers of lung disease severity with mucosal diffusion coefficients and their distributions is summarised below.

<table>
<thead>
<tr>
<th>Descriptive statistics across the cohort</th>
<th>Median mucosal ADC of both sinuses (mm²/s)</th>
<th>10th centile of both sinuses mucosal ADCs (mm²/s)</th>
<th>Median of lowest side (i.e. unilateral)</th>
<th>10th centile of lowest side</th>
<th>Mode of lowest side</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N (/19)</strong></td>
<td>19</td>
<td>19</td>
<td>19</td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td><strong>Mean (SD)</strong></td>
<td>2072.37 (236.90)</td>
<td>1707.75 (430.69)</td>
<td>1942.21 (309.75)</td>
<td>1630.98 (480.02)</td>
<td>1818.71 (775.17)</td>
</tr>
<tr>
<td><strong>Median (25th – 75th quartile)</strong></td>
<td>2025.00 (1865.00-2269.50)</td>
<td>1837.10 (1452.00-1984.40)</td>
<td>1949.00 (1768.50-2150.00)</td>
<td>1763.50 (1373.00-1900.00)</td>
<td>1977.00 (1523.00-2330.00)</td>
</tr>
<tr>
<td><strong>Minimum</strong></td>
<td>1677.00</td>
<td>299.00</td>
<td>1144.00</td>
<td>229.50</td>
<td>248.00</td>
</tr>
<tr>
<td><strong>Maximum</strong></td>
<td>2503.50</td>
<td>2170.20</td>
<td>2503.50</td>
<td>2170.20</td>
<td>2635.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(Spearman’s coefficient, p)</th>
<th>Median mucosal ADC of both sinuses (mm²/s)</th>
<th>10th centile of both sinuses mucosal ADCs (mm²/s)</th>
<th>Median of lowest side (i.e. unilateral)</th>
<th>10th centile of lowest side</th>
<th>Mode of lowest side (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>-0.537*, 0.018</td>
<td>-0.584*, 0.009</td>
<td>-0.579**, 0.009</td>
<td>-0.551*, 0.015</td>
<td>-0.286, 0.535</td>
</tr>
<tr>
<td><strong>Spirometry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contemporaneous FEV₁ (% predicted)</td>
<td>0.093, 0.705</td>
<td>0.082, 0.737</td>
<td>-0.025, 0.920</td>
<td>0.093, 0.705</td>
<td>0.071, 0.879</td>
</tr>
<tr>
<td>Contemporaneous FVC (% predicted)</td>
<td>-0.003, 0.991</td>
<td>-0.092, 0.708</td>
<td>-0.146, 0.552</td>
<td>-0.116, 0.637</td>
<td>-0.036, 0.939</td>
</tr>
<tr>
<td>Contemporaneous FEV₁/FVC</td>
<td>0.081, 0.743</td>
<td>0.139, 0.571</td>
<td>0.019, 0.937</td>
<td>0.161, 0.509</td>
<td>-0.036, 0.939</td>
</tr>
<tr>
<td>(Spearman’s coefficient, ( p ))</td>
<td>Median mucosal ADC of both sinuses (mm(^2)/s)</td>
<td>10(^{th}) centile of both sinuses mucosal ADCs (mm(^2)/s)</td>
<td>Median of lowest side (i.e. unilateral)</td>
<td>10(^{th}) centile of lowest side</td>
<td>Mode of lowest side</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>---------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>------------------------------------------</td>
<td>---------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>LCI(_{2.5}) ((n))</td>
<td>-0.236, 0.437</td>
<td>-0.264, 0.384</td>
<td>-0.407, 0.168</td>
<td>-0.242, 0.426</td>
<td>0.400, 0.600</td>
</tr>
<tr>
<td>Exacerbations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV antibiotic courses</td>
<td>-0.256, 0.289</td>
<td>-0.462*, 0.046</td>
<td>-0.398, 0.092</td>
<td>-0.437, 0.061</td>
<td>-0.179, 0.701</td>
</tr>
<tr>
<td>PO antibiotic courses</td>
<td>0.174, 0.477</td>
<td>0.244, 0.315</td>
<td>0.237, 0.328</td>
<td>0.203, 0.403</td>
<td>0.289, 0.530</td>
</tr>
<tr>
<td>Combined IV&amp;PO antibiotic courses</td>
<td>-0.004, 0.988</td>
<td>-0.050, 0.837</td>
<td>-0.015, 0.950</td>
<td>-0.069, 0.780</td>
<td>0.000, 1.000</td>
</tr>
</tbody>
</table>

**CT**

**CFCT scores (%)**

<table>
<thead>
<tr>
<th>Total lung summary score</th>
<th>-0.345, 0.148</th>
<th>-0.468*, 0.043</th>
<th>-0.477*, 0.039</th>
<th>-0.454, 0.051</th>
<th>-0.143, 0.760</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiectasis</td>
<td>-0.542*, 0.017</td>
<td>-0.542*, 0.017</td>
<td>-0.541*, 0.017</td>
<td>-0.543*, 0.016</td>
<td>-0.107, 0.819</td>
</tr>
<tr>
<td>Mucus plugging</td>
<td>-0.183, 0.454</td>
<td>-0.297, 0.218</td>
<td>-0.322, 0.178</td>
<td>-0.284, 0.239</td>
<td>-0.018, 0.969</td>
</tr>
<tr>
<td>Peribronchial thickening</td>
<td>-0.332, 0.166</td>
<td>-0.427, 0.069</td>
<td>-0.482*, 0.037</td>
<td>-0.380, 0.109</td>
<td>-0.357, 0.432</td>
</tr>
<tr>
<td>Parenchymal score</td>
<td>0.112, 0.647</td>
<td>0.030, 0.904</td>
<td>0.107, 0.663</td>
<td>-0.041, 0.866</td>
<td>-0.357, 0.432</td>
</tr>
<tr>
<td>Hyperinflation</td>
<td>-0.239, 0.324</td>
<td>-0.381, 0.108</td>
<td>-0.354, 0.137</td>
<td>-0.376, 0.112</td>
<td>-0.847*, 0.016</td>
</tr>
<tr>
<td>Low attenuation % (semi-automated bespoke threshold cluster analysis)</td>
<td>-0.070, 0.775</td>
<td>-0.161, 0.509</td>
<td>-0.200, 0.412</td>
<td>-0.204, 0.403</td>
<td>-0.107, 0.819</td>
</tr>
</tbody>
</table>

*Spearman’s coefficient, \( p \)

\*\( p < 0.05 \), **\( p < 0.001 \)
There was no correlation between mucosal volume or degree of sinus opacification by mucosa and age (Spearman's coefficient -0.134 p=0.553 and -0.140 p=0.536 respectively), but there was a significant correlation between age and mucosal diffusion coefficients. The trend is towards lower ADC values, i.e., more restricted diffusion, with age. In other organ systems, restricted tissue diffusion is associated with increased cellularity (e.g., in tumours or abscesses) or oedema (for example in cerebral infarction). There was statistically significant correlation between mucosal ADC values and exacerbations requiring IV antibiotics and structural lung disease severity, particularly total CFCT scores and both the bronchiectasis and bronchial wall thickening sub-scores, with decreasing ADC (increasingly restricted diffusion) associated with worse lung disease. The strongest correlation was between the lowest unilateral ADC mode (i.e., the lowest of the two modes obtained within an individual – one per sinus), but it is worth noticing that unlike sinus mucus where larger regions of interest could be drawn, the volume of mucosa that could be segmented was significantly smaller with only 7 patients with a recordable mucosal ADC mode. This adds significant bias with those with less thickening more likely to be excluded from analysis.
It is clear from the scatter plot above that any association between ADC values and IV antibiotic courses would be better assessed considering
antibiotic courses as an ordinal rather than a continuous variable. There is an apparent trend toward lower values (more restricted diffusion) in those with more frequent antibiotic usage which nears significance by Kruskal-Wallis, see table below.

(NB: as was the case for the mucus ADC analysis above, the 2 cases with no sinus mucosal disease are included on the scatter chart as ADC=0, but are excluded from the Kruscal-Wallis test and box plot).

<table>
<thead>
<tr>
<th>Mucosal ADC measure</th>
<th>Test statistic (d.f.)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest median (unilateral)</td>
<td>3.726(2)</td>
<td>0.155</td>
</tr>
<tr>
<td>10th centile (bilateral)</td>
<td>5.200(2)</td>
<td>0.074</td>
</tr>
<tr>
<td>Lowest 10th centile (unilateral)</td>
<td>4.812(2)</td>
<td>0.090</td>
</tr>
</tbody>
</table>

Simple Boxplot of Lowest (Unilateral) 10th centile Mucosal ADC by Number of IV Antibiotic Courses in the Preceding 6 Months
As above, it is worth highlighting that the small volume of sinus mucosa results in insufficient segmented pixels to yield an ADC mode.
Given we have seen correlations between higher mucus ADC values and lung disease severity and between lower mucosal ADC values and worsening disease severity, it is tempting to investigate the relationship between mucosal disease and mucus.

<table>
<thead>
<tr>
<th>ADC measures</th>
<th>Mucus median</th>
<th>Mucus mode</th>
<th>Mucus 90th centile</th>
<th>Mucus highest 90th centile</th>
<th>Mucus 25th centile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosal median</td>
<td>-0.272, 0.290</td>
<td>-0.438, 0.112</td>
<td>-0.135, 0.606</td>
<td>-0.039, 0.881</td>
<td>-0.500*, 0.041</td>
</tr>
<tr>
<td>Mucosal 10th centile</td>
<td>-0.302, 0.239</td>
<td>-0.699*, 0.011</td>
<td>-0.113, 0.667</td>
<td>0.007, 0.978</td>
<td>-0.498*, 0.042</td>
</tr>
<tr>
<td>Mucosal lowest 10th centile</td>
<td>-0.297, 0.247</td>
<td>-0.664*, 0.018</td>
<td>-0.098, 0.708</td>
<td>0.000, 1.000</td>
<td>-0.419, 0.086</td>
</tr>
<tr>
<td>Mucosal 25th centile</td>
<td>-0.315, 0.218</td>
<td>-0.720**, 0.008</td>
<td>-0.120, 0.646</td>
<td>-0.002, 0.993</td>
<td>-0.520*, 0.033</td>
</tr>
</tbody>
</table>

There are some interesting correlations with trends toward high mucus ADCs (more watery mucus) in those with lower mucosal ADCs (potentially more inflamed mucosa).
7.3.2.2 Correlation with Experimental Quantitative Lung MRI Outputs

Although the outputs of the quantitative MRI sequences remain experimental, correlation of sinus disease with MRI measures of lung disease yields interesting results:

<table>
<thead>
<tr>
<th>Mucus</th>
<th>Mucosal thickening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median mucus ADC</td>
<td>Mucus ADC mode</td>
</tr>
<tr>
<td>Simple mapping –</td>
<td></td>
</tr>
<tr>
<td>Median baseline T1&lt;sup&gt;†&lt;/sup&gt;</td>
<td>-0.048 (0.840)</td>
</tr>
<tr>
<td>Skew of T1&lt;sup&gt;†&lt;/sup&gt;</td>
<td>0.200 (0.399)</td>
</tr>
<tr>
<td>Mean baseline T2</td>
<td><strong>-0.650</strong> (0.003)</td>
</tr>
</tbody>
</table>

**Dynamic Oxygen Enhanced Imaging**

<table>
<thead>
<tr>
<th>Enhancement fraction</th>
<th>Median baseline T1&lt;sup&gt;†&lt;/sup&gt;</th>
<th>Median SI change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.280 (0.232)</td>
<td><strong>-0.466</strong> (0.080)</td>
<td>-0.214 (0.365)</td>
</tr>
<tr>
<td><strong>-0.527</strong>* (0.044)</td>
<td>-0.090 (0.705)</td>
<td><strong>-0.387</strong> (0.075)</td>
</tr>
<tr>
<td><strong>-0.466</strong>* (0.045)</td>
<td>-0.317 (0.161)</td>
<td><strong>-0.002</strong> (0.992)</td>
</tr>
</tbody>
</table>

Spearman’s coefficient (p), *p<0.05, **p<0.005

NB. Matrix pencil normal and abnormal ventilation fractions are inverse fractions of each other and therefore correlation coefficients are identical for each but with inverted signs. Coefficients given are for ‘normal fraction’

<sup>†</sup>= T1 from IR-HASTE method (there was no significant correlation with ufbSSFP T1 values

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Increased mucosal thickening and lower mucosal ADC values significantly correlated with higher lung T1 values (higher median values and higher skew) i.e. more lung disease. There was also a strong correlation between sinus disease and lung T2 values. As described in a previous chapter, again this was in the reverse of the expected relationship, with a trend toward lower lung T2 values in those with higher sinus mucus ADC values, likely reflecting decreased perfusion rather than increased mucus plugging or bronchial oedema.

Dynamic oxygen enhanced MRI and matrix pencil decomposition ventilation:perfusion MRI outputs also correlated with sinus disease with increasing mucus ADCs associated with decreases in the fraction of normally ventilated and perfused lung (OE MRI enhancement fraction and matrix pencil ventilation and perfusion fractions).

After further validation work has been performed on these novel lung imaging methods, MRI will become a particularly interesting tool in the assessment of links between sinonasal and pulmonary disease in chronic suppurative lung disease research.
**Figure 19** – An 18 year old female with CF. a) Coronal T2 weighted MRI demonstrated mucosal thickening occupying 76% of the maxillary sinus volume. This was associated with high CFCT scores (total 20.5%, bronchiectasis 28.8%, mucus plugging 33.3%, peribronchial wall thickening 19.4% and hyperinflation 20.4%). b) Structural MRI demonstrated high bronchiectasis (50%) and mucus plugging (50%) scores and matrix pencil decomposition c) demonstrated significant ventilation defects (impaired ventilation fraction 0.35).

**Figure 20** – A 16 year old girl with CF. a) Coronal T2 weighted MRI demonstrates significant mucosal thickening. b) ADC map from diffusion weighted imaging - This patient had the lowest mucosal ADC and the highest mucus ADC mode. c) CFCT demonstrated significant peribronchial thickening (13%) and hyperinflation (16.7%) and matrix pencil decomposition imaging d) demonstrated a ventilation impairment fraction of 0.27.
7.3.3 Liver imaging –

The clinical measures of liver disease within the cohort are summarised below.

<table>
<thead>
<tr>
<th>Liver disease y/n</th>
<th>2/22 (9.1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ultrasound</strong></td>
<td></td>
</tr>
<tr>
<td>Interval between MRI and ultrasound (days)</td>
<td>52</td>
</tr>
<tr>
<td>Sheer wave velocity (ms)</td>
<td>1.245</td>
</tr>
<tr>
<td>ISHAK score (0 – 6)</td>
<td>2</td>
</tr>
<tr>
<td>Metavir score (0 – 4)</td>
<td>1</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>3/20 (13.6%)</td>
</tr>
</tbody>
</table>

All patients had adequate data on EPR for classification of the presence or absence of liver disease, with two patients classed as having CF liver disease. 14 patients had sheer wave elastography results with a median time between MRI and ultrasound of 52 days, but a large range. Two patients were missing ultrasound data regarding spleen size.

All but one patient had T1 maps to assess (patient one was imaged before ufbSSFP imaging was set up on the scanner).

<table>
<thead>
<tr>
<th>Liver T1 mapping</th>
<th>Via IR-HASTE (ms)</th>
<th>Via ufbSSFP (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td>609.43</td>
<td>698.70</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>606.20</td>
<td>692.07</td>
</tr>
<tr>
<td><strong>25th – 75th Centile</strong></td>
<td>565.05 – 643.54</td>
<td>692.07 – 724.46</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>496.53 – 803.63</td>
<td>492.74 – 974.80</td>
</tr>
</tbody>
</table>
By Shapiro-Wilk test, the IR-HASTE T1 values are normally distributed (0.944(20), p=0.281), but the ufbSSFP values are not (0.888(20), p=0.025). Correlation between the two methods of calculating liver T1 is strong, but far from perfect (Spearman's correlation coefficient 0.776, p<0.001). The green line is $y=x$ and the Bland-Altman plot is shown below.
As was the case when comparing lung T1 values via the two methods, there is a systematic error between the two with consistently higher values obtained by the ufbSSFP method compared to the IR-HASTE method. The magnitude of the difference, however, is considerably smaller in the liver than was demonstrated in the lung (mean lung T1 909ms vs 1477ms, compared to a mean liver T1 of 609ms vs 699ms). As before there are several differences between acquisitions (ufbSSFP was acquired during a single breath hold, IR-HASTE during free-breathing with subsequent non-rigid registration and averaging over time. Further more, T1 was measured via the placement of 6 ROIs in the liver, away from any vasculature, but placement of the ROI may have differed between sequences. Linear correlation was demonstrated between age and T1 values, but not with shear wave velocity on ultrasound or resulting ISHAK or Metavir score.
<table>
<thead>
<tr>
<th></th>
<th>Liver T1 by IR-HASTE</th>
<th>Liver T1 by ufbSSFP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spearman’s (p)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.745** (&lt;0.001)</td>
<td>0.501* (0.021)</td>
</tr>
<tr>
<td><strong>Ultrasound shear wave elastography</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shear wave velocity (m/s)</td>
<td>0.052 (0.865)</td>
<td>0.102 (0.741)</td>
</tr>
<tr>
<td>ISHAK score</td>
<td>0.006 (0.986)</td>
<td>0.129 (0.675)</td>
</tr>
<tr>
<td>Metavir score</td>
<td>0.314 (0.295)</td>
<td>0.369 (0.218)</td>
</tr>
</tbody>
</table>

Spearman’s correlation coefficient (p value)
By simple logistic regression, no significant relationship could be demonstrated between T1 measurement and the presence of liver disease (IR-HASTE - Wald 0.281, p=0.596; ubbSSFP - Wald 0.001, p=0.975).

**7.4 Discussion and Conclusions:**

**Principal findings**

All recruits completed the full hour-long MR protocol. There was one failed analysis of susceptibility artefact (a 6 year old with CF with too much motion artefact) and scans from 2 people failed DWI analysis (one secondary to the presence of extensive susceptibility artefact within the sinus mucus and one from too much motion – the same 6 year old whose susceptibility-weighted imaging was not of sufficient quality for analysis). The sinus imaging was the very last part of the protocol and therefore the
most likely to be affected by motion as participants became restless. It is however notable that all competed the protocol and imaging of the other 6 year old within the cohort was of sufficient quality.

Interestingly, and unexpectedly, there was no significant correlation between sinus volume and age. Also interestingly much of the sinus opacification demonstrated was secondary to mucosal thickening rather than mucus, a finding which would be difficult to make via CT where differentiation of mucus and mucosa is often not possible.

There was no significant difference in clinical markers of disease severity in those with vs those without sinus disease, but near significant differences were demonstrated in the CFCT hyperinflation scores and rate of pulmonary exacerbations (both worse in those with sinus mucus).

Quantification of mucus and mucosa allowed suggestion of an association between sinus opacification of >50% by mucosal thickening with increased pulmonary exacerbation frequency (no participant with <47% opacification by mucosa had more than 2 exacerbations compared to 13 with >47% opacification). Further investigation with a larger cohort and more varied range of sinus disease severity is clearly required for confirmation.

The presence of susceptibility artefact within sinus mucus was associated with a significant increase in CFCT hyperinflation score (p=0.028) and there was a more interesting relationship between sinus mucus and mucosal
diffusion and lung disease. My data suggests the two are linked with strong correlation between mucus ADC mode (likely a measure of mucus quality) and lower mucosal ADC values (10\textsuperscript{th} and 25\textsuperscript{th} centiles) (r= -0.720 to -0.0664, p=0.008 to 0.018) i.e. more watery mucus appears to be associated with more restricted diffusion within the adjacent mucosa. Elsewhere within the body, diffusion restriction (low ADC values) is associated with inflammation and increased cellularity (for example within tumours). My hypothesis is that mucosal inflammation is being measured by sinus DWI either resulting from or resulting in more watery mucus. Of interest when considering the unified airways hypothesis, more watery mucus (high mucus ADC mode) correlated moderately to strongly with exacerbation frequency (0.581, p=0.048), CFCT peribronchial thickening score (0.744, p=0.006), mucus plugging score (r=0.633, p=0.019) and hyperinflation score (r=0.519, p=0.084). Lower mucosal ADC values also correlated strongly with CFCT hyperinflation scores (r=-0.847, p=0.016) and moderately with CFCT bronchiectasis and peribronchial thickening scores (r=-0.542, p=0.017 and r=-0.427, p=0.069 respectively).

Strong correlation was also demonstrated between sinus disease measures and the experimental MRI-based lung function outputs. Strong correlation was demonstrated between mucus ADC mode and ventilation fraction (-0.722, p=0.004), perfusion fraction and T2 (-0.632 and -0.660, p=0.010 and 0.015), with the same trend toward worse lung disease with more watery mucus. Weak to moderate correlation was then also demonstrated between mucosal thickening (%) and T1 skew and OE-enhancement (r=0.560 and -
0.383, p=0.007 and 0.075 respectively). Clearly correlation is not synonymous with causation and collection of longitudinal data and ideally a future interventional trial will add considerably to the results presented here.

Only two patients with liver disease were recruited with a median time of 52 days between MRI and quantitative ultrasound. Liver T1 measured using the lung mapping sequences demonstrated a significant correlation between age and T1, but no significant correlation between T1 and clinical markers of liver disease.

**Strengths and weaknesses**

This is the first study to report the combination of lung imaging, imaging-based lung function testing and extra thoracic imaging all within the same examination. The fact that all of these quantitative measures were achieved in a high proportion of the cohort, despite the inclusion of two 6 year olds is notable. The collection of contemporaneous CT and MBW data is a considerable strength, as is the availability of sheer wave elastography in the cohort. Although this was collected retrospectively from examinations performed as part of clinical care, the median time interval of 52 days is not particularly high and again, the addition of MBW and sheerwave elastography to a comparative study of multisystem MR to standard of care is not something that has been reported previously.
Whilst recruitment of a population at an age of considerable clinical interest and successful completion by most of the cohort is a strength, the lack of patients without sinus disease (n=2) and the small number with liver disease (n=2) is a weakness that severely limits interpretation. There was also only a single patient (one of the 6 year olds) who had experienced no pulmonary exacerbations in the preceding 6 months. Given the high incidence of sinus disease in people with CF and PCD, it is likely that future studies will require some normal subject data for comparison.

We also lack reproducibility data (single time point and short, medium and long term) in the same way as discussed for the lung imaging chapters previously. This is particularly relevant in sinus imaging given the well-known phenomenon of the nasal cycle whereby the nasal mucosa on each side alternates between congestion and decongestion in health. Alterations in sinus mucosal volume and ADC will be required to study normal variation before either method can be applied as a measure of CF or PCD disease severity or treatment response[229]. Furthermore the segmentation of sinus mucus and mucosa and the subsequent extraction of voxel data for histogram analysis was extremely labour-intensive and, as such, was only performed by a single observer. Inter and intra-observer variability data is still required.
Strengths and weaknesses compared to other studies (and discrepant results)

The multiparametric sinus MRI included in my protocol allows far more advanced analysis of sinus disease compared to CT, but the study of Sheikh et al of 12 patients before and after 1 year's treatment with Ivacaftor has a far more powerful message – 11 of the 12 demonstrated significant improvement in sinus disease following ivacaftor therapy [230]. The addition of extra time points and ideally, a therapeutic intervention would be a far better test of my suggested protocol than our current single time-point cohort study.

On a similar theme, and as discussed in the Introduction chapter, Graham et al using serial MR imaging to track sinus disease in 5 people with CF (ages 25 to 39) undergoing aminoglycoside lavage; with images obtained 6 times in a 180 day period, demonstrated a reduction in disease with therapy. The number in the study were small, images analysed via semiquantitative visual scoring rather than computational volume analysis and the protocol did not include susceptibility or diffusion weighted imaging, but the inclusion of multiple time points is a considerable strength of their study.

As discussed in the introduction Eggesbo et al first described the ‘black hole sign’ of susceptibility artefact, linking the appearance to micro-organisms present within the mucus. They did this via CT and MR imaging of the sinuses with contemporaneous collection of sinus mucus samples via endoscopic sinus aspirates[231]. We have a larger cohort than Eggesbo et al
(22 vs only 10), but do not have sinus mucus aspirates for confirmation of mucus infection and further characterisation of the sinus microbiome of our cohort.

A very recently published paper by Sommerburg et al used MRI to examine the paranasal sinuses of 67 infants and young children with CF and 30 healthy controls, from 0 – 6 years of age, demonstrating prevalent disease in the CF group (mucosal swelling in 83%, mucopyoceles in 75%, polyps in 26%) [232]. Although they used sedation and general anaesthesia, their data clearly shows that this technique has the spatial resolution required to image the sinuses of people with chronic suppurative lung disease, even from birth. Interestingly, contrary to prior beliefs, they also demonstrated no significant difference in aerated sinus volume between infants and young children with and without CF. Again, however, the omission of susceptibility and diffusion-weighted sinus imaging and contemporaneous lung imaging is a considerable short coming compared to our protocol.

The best practice guidance of Debray et al for diagnosis of CF-associated liver disease mentions both MRI and ultrasound, but not any quantitative read out of either (i.e. no mapping techniques and no sheer wave elastography), instead relying on morphologic features such as nodularity of the liver contour[233]. Quantitative liver MRI is however, well established in a non-CF research setting. Mojtahed et al studied 1037 adults (40 to 60 years old) deemed to be at low risk of non-alcoholic fatty liver disease, using a Shortened Modified Look Locker Inversion (ShMOLLI)-
based T1 mapping technique; suggesting normal values of T1 ranging from 573 to 852ms (median 666ms). None of our cohort had a liver T1 of over 852ms by IR-HASTE mapping and only one had a T1 over 852ms by ufbSSFP[234].

Poetter-Lang et al investigated the ability of structural MRI to diagnose CF liver disease (CFLD) using altered gall bladder morphology, periportal tracking and periportal fat deposition as signs of CFLD with a resulting sensitivity of 94.1% and specificity of 84.6% compared to clinical symptoms, lab tests and the Debray criteria but did not include any mapping technique. The only quantitative measure included that had statistically significant univariate association with CFLD was splenic volume [235]. Although spleen volume was not measured in my cohort, spleen length was included, with only 3 participants demonstrating splenomegaly and no statistically significant association between the presence of splenomegaly and liver T1 values.

Most liver T1 mapping in the published literature uses the Modified Look-Locker inversion recovery (MOLLI) or Shortened version (ShMOLLI) technique as used in the study of Mojtabah et al. Extra sequences were not included in our protocol to keep the imaging time as low as possible, so as to include the multiple quantitative lung imaging techniques described in the previous chapters. It is however possible that a ShMOLLI based mapping sequence could be added to a future protocol as it is reported to only require 3 minutes[236]. Furthermore, a free breathing MOLLI
technique has recently been validated for T1 mapping of the liver in children and young adults by Cho et al [237]. Once our protocol has been rationalised, perhaps removing the static pre and post oxygenation mapping portion, this could potentially be added in its place.

**Meaning of study**

It is possible to include full multiparametric MRI assessment of the paranasal sinuses in a respiratory MRI protocol with good patient tolerance. Whilst the liver is included in lung T1 maps, further data is required to determine the appropriateness of use of liver T1 values derived from lung T1 maps; specifically, this will require recruitment of more patients with CF liver disease.

Interesting relationships between sinus and lung disease have been observed, but again further research is required to better elucidate any meaningful connection between sinus and lung disease. Short, medium and long -term reproducibility studies, follow-up studies over periods of disease stability and of exacerbation and studies of the effect of interventions such highly effective modulator therapies on sinus and liver disease are required to further investigate the possible role of a multisystem quantitative MRI protocol in long term chronic suppurative lung disease surveillance and as a potential source of surrogate outcomes in future clinical trials.
Unanswered questions and future research

It is clear than in the case of both sinus and liver disease imaging, what we need most is more participants with more heterogeneous disease (particularly those with less sinus disease and those with CF liver disease). As above the other area of significant interest is short, medium and long term variability in outputs and the effect of treatment. These can be explored as part of the planned and recently funded project described in the previous chapter following people with CF over a 3 year period of disease stability and additionally through times of exacerbation. The protocol will need to be optimised, but given sinus imaging only required 10 extra minutes of scanning and liver imaging was acquired as part of the lung imaging it seems reasonable to include both in the proposed trial protocol.
Chapter 8 – Discussion and Conclusions

This chapter reiterates the original aims, objectives and hypotheses of the thesis and then summarises the principal findings relating to each of the hypotheses. I assess the successes and shortcomings of the thesis as a whole and discuss future plans to build on the data presented.

Aims objectives and hypotheses –

Aims and objectives

1. To set up a clinically feasible, multisystem (lung, sinonasal and upper abdominal visceral) quantitative MRI examination for the investigation and follow up of chronic suppurative lung disease

2. To evaluate novel imaging biomarkers of CF and PCD disease severity

Hypotheses

1. Combined structural and quantitative MRI assessment of the thorax can provide comparable information to CT such that follow up imaging via CT could be replaced with MRI.

2. Quantitative MR measures of ventilation correlate with established clinical measures of ventilation (LCI and FEV$_1$) and provide additional spatial information.
3. A multisystem MRI assessment can provide new extra-thoracic imaging biomarkers of CF and PCD disease severity whilst being better tolerated by patients than current multimodality imaging follow up.

*Aim 1 – setting up a clinically feasible multisystem quantitative MRI examination for CF and PCD*

*Aim 2 – evaluation of novel imaging biomarkers of CF and PCD disease severity*

**Principal findings**

The investigated protocol included sequences for structural lung disease assessment, multiple quantitative MRI measures of structural lung disease (T1 and T2 mapping), multiple imaging measures of lung function (oxygen-enhanced and matrix pencil decomposition imaging), upper abdominal imaging (included in thoracic imaging) and multiparametric MRI of the paranasal sinuses all in a single protocol taking up to, but not over, an hour of time in the scanner. This protocol was successfully completed by the full cohort with ages all the way down to 6 years, without any anaesthetic/sedation and with no scans needing to be terminated for claustrophobia etc. Following the MRI a third of participants said they would choose long term follow up via MRI over CT despite two thirds
reporting that the MRI took too long compared to CT. There are several different methods of assessing the same feature of disease severity built into the protocol (e.g. two different forms of oxygen enhancement) and it would be possible to shorten the protocol to around 40 minutes for increased participant comfort. I believe our results show that it is clear that MRI surveillance is at least feasible from the perspective of patient experience and tolerance.

The other aspect of clinical feasibility is the scanner itself, its staff and the financial implications of starting a surveillance program.

The Royal Brompton has 5 MRI scanners, mostly used for cardiac MR imaging (in the region of 10,000 CMR examinations a year) and our lung MR protocol is similar in length to a clinical cardiac MRI protocol. We have around 950 children and adults with CF alone and 950 hours of additional MR scanning per year for annual surveillance would be a considerable undertaking. Furthermore, NHS funding for CF care is ‘bundled’ meaning that each patient registered is associated with a set income to the hospital to be used for their care. There is no separate budget for imaging so the £170 cost of an MRI comes out of the same budget as a standard CT (£114) or chest radiograph (£40). Setting up the oxygen enhanced ventilation imaging required purchase of a low flow gas mixer and flow regulator and a supply of bottled oxygen and medical air at a cost of around £1000 up front and in the order of £2 – £3 per bottle of gas, and uses standard MR sequences likely to be available on all NHS MRI scanners. The only part of
our protocol which would be harder to implement more widely is the matrix pencil decomposition imaging, which requires non-proprietary sequences. Both ventilation MRI methods also require extensive post processing performed by research teams off site. Whilst this works well in research, implementation of in-house analysis will be an important milestone in making the techniques available clinically. Whilst the protocol is acceptable to people with CF and PCD, there is a lot more work to do before it becomes clinically implementable on a wider scale.

In addition to previously described imaging based markers of disease severity (e.g. structural lung disease Eichinger scores), my protocol provided a number of very recently developed MRI measures of lung function (OE-MRI based wash-in and wash-out times, matrix pencil decomposition ventilation and perfusion fractions) and a number of completely novel quantitative outputs not previously published in the medical literature (lung T2, matrix pencil decomposition ventilation and perfusion fractions sub-divided into moderate, severe and non-functioning fractions, sinus mucus volume and diffusion coefficient, sinus mucosal volume and diffusion coefficient). In fact, by the time of thesis submission each patient had 141 MR imaging based metrics across all areas of interest for analysis against clinical markers of disease severity.
Strengths and weaknesses

The biggest single strength of this study is the inclusion of multiple methods of functional lung imaging alongside structural lung, quantitative liver and structural and quantitative sinus imaging. The other particular strength is the inclusion of the participant experience questionnaire which has subsequently helped to design MR protocols for other studies (on-going studies of functional lung MRI in adult pulmonary hypertension and dynamic airways collapse).

Our age range is relatively small with the vast majority of patients around the age of transition from paediatrics to adult care (range 6 – 35 years, median 14, but only 4 patients over the age of 20). This time period is particularly important, with significant life changes and a well-recognised decline in lung function demonstrated through the teenage years across multiple registry datasets [7,207,208](this may be multifactorial but decreased treatment adherence is a significant factor[209,210]).

In my opinion, the biggest weakness is probably the inclusion of only a single time point with no scope for investigation of changes in metrics in line with clinical features of disease stability or decline.

Strengths and weaknesses compared to other studies and discrepant results

Whilst there are many studies comparing the use of MRI and CT in structural lung disease imaging and fewer more recent studies comparing
functional lung imaging to conventional lung function, there has been no previously published study of a multisystem MR examination for CF or PCD.

The most complete CF assessment via MR that I am aware of is the VIPS protocol, under evaluation by a multicentre international trial group [161]. This protocol includes structural, ventilation and perfusion imaging but no extrathoracic imaging and has a number of disadvantages compared to my protocol. VIPS stands for Ventilation, Inflammation, Perfusion and Structure. Ventilation is assessed via Fourier decomposition imaging, but many centres involved also use hyperpolarised gas MR for ventilation imaging. As discussed in the introduction chapter and the discussion section of chapter 6, hyperpolarised gases allow hugely powerful analyses of ventilation and alveolar diffusion, but like Fourier decomposition and matrix pencil decomposition the technique is not widely available and is unlikely to reach clinical care outside of dedicated research centres in the near future. By comparison, oxygen enhanced imaging is extremely easy to implement. Inflammation is imaged via diffusion weighted imaging (DWI). We did not include this in our protocol. Whilst diffusion may represent inflammation (as we were intending it to be used in sinus imaging) it will be also be dependant on the availability of water (protons) within the imaged tissue and is likely to suffer the same limitations as we found in T2 mapping of the lungs where much of the signal likely reflect altered perfusion rather than inflammation. Perfusion imaging in the VIPS protocol is via dynamic contrast enhanced MR which requires cannulation and delivery of contrast media. We wanted to devise an MR protocol which did not impose any new
risks or discomforts compared to CT, to people with CF (particularly the younger children involved). We do not use contrast in CT imaging for CF or PCD outside of cases of bronchial artery embolization and as such did not want to include contrast imaging in our MR protocol. The structural imaging in VIPS is via a HASTE sequence (Half Fourier Acquisition TurboSpin Echo - A fast sequence, but more susceptible to motion artefact and with lower spatial resolution than the BLADE sequence we used). As discussed in the structural imaging chapter (chapter 4) HASTE is of considerably lower spatial resolution and is more impacted by respiratory and cardiac motion compared to BLADE imaging.

**Hypothesis 1** – Combined structural and quantitative MRI assessment of the thorax can provide comparable information to CT such that follow-up imaging via CT could be replaced with MRI.

**Principal findings**

Structural lung MR imaging via T2 BLADE and assessed via Eichinger scoring, correlated strongly / very strongly with CT appearances assessed via CFCT (r=0.729-0.857, p<0.001) with equivalent interobserver variability (ICC=0.877-0.965 vs 0.877-0.992 respectively); however, there was a tendency of MRI scores to exaggerate disease extent compared to CT scores. Sensitivity of MRI to individual features of large airways disease was high, but interpretation of specificity was limited by the small numbers of patients without disease features. As such, my data supports the use of MRI for structural disease surveillance, but not for primary diagnosis. In fact,
since the study closed, the same structural imaging has been adopted for clinical use in specific circumstances, when follow up imaging is required at a frequency which would be deemed inappropriate for CT (see figure 21).

**Figure 21** – a) CT demonstrating a thick-walled debris containing cavity in the left upper lobe of an adult with chronic pulmonary aspergillosis. b) MRI on the same day as the CT. c) and d) MRI follow up of the infected cavity at monthly intervals whilst on therapy demonstrating loss of the internal septation, but no significant change in cavity size and slight increase in cavity wall thickening – i.e. there was no treatment response to the dose of antifungal therapy given. Serial imaging allows up-titration of dose or change of therapeutic strategy whilst minimising interval exposure to hepatotoxic medication where no pulmonary disease benefit is demonstrated.

MRI scores of bronchiectasis/wall thickening, mucus plugging and parenchymal disease all correlate well with CT, but a viable replacement for the CFCT hyperinflation score is notably absent from structural MRI assessment. Simple T1 and T2 mapping did not demonstrate significant correlation with CT hyperinflation score, but there is moderate correlation between CT hyperinflation scores and the skew and kurtosis of the oxygen wash-out times from OE-MRI (r=0.543 and 0.521, p=0.009 and 0.013
respectively) and with the matrix pencil decomposition ventilation and perfusion fractions (r=-0.534 and -0.594, p=0.013 and 0.005 respectively). I do, therefore, feel that MRI can be an entirely appropriate replacement for CT imaging in the context of regular disease surveillance (for example as part of an annual surveillance program).

**Strengths and weaknesses**

The limited time required for structural imaging via breath hold BLADEs and the lack of any need for repeated imaging in our cohort shows that this approach is easily implementable clinically. In fact, the short time required means that structural imaging alone could be performed in a similar time frame to structural CT, removing some of the barriers to implementation mentioned above. As discussed in chapter 4, there may be a need to add some T1 weighted imaging to exclude T2 signal null mucus plugs in the setting of ABPA. From personal experience, T1 BLADE images are not of the same quality as T2 BLADE images, but a simple breath hold HASTE in axial plane would likely suffice whilst only adding a minute or two to the protocol.

As discussed before, the main limitation to the assessment of the use of this MRI protocol as a disease surveillance test is the single time point imaging acquired as part of this study. It was our original plan to not only perform MRI scans at the time of CT, but to also repeat the MRI in participants admitted for treatment of exacerbation, thus examining the ability of MRI to demonstrate response to treatment. However, it quickly became clear that
the CTs were generally timed for the end of two week admissions for IV antibiotics and that a follow up MRI would therefore involve bringing a child back to hospital after an inpatient stay. The MRI scans were performed off site at a private imaging centre with no provision for research lung MRI on the main hospital campus and it was not felt that transfer for research imaging was feasible, or indeed safe, in a patient admitted for an infective exacerbation, before a treatment response had been observed. Now we have shown considerable correlation between CT and MRI appearances alongside the extra information made possible by ventilation MRI follow up studies no longer need to include the requirement for CT imaging at recruitment.

The other weakness of this study, when it comes to more generalised surveillance of disease severity, is the lower age limit of 6 years. Advances in technology have significantly reduced the radiation doses required for diagnostic CT with an increasing uptake of ultra-low dose CT protocols specifically for the follow up of people with cystic fibrosis. These are low dose, but also low detail CT scans [238]. Some teams now consider ‘low dose’ CT to be part of a CF general check up with scans on an annual or biennial basis from as early as 2 years of age [239]. The CF Trust Standards of Care document advises ‘regular’ monitoring of lung function with spirometry from 5-6 years of age and annual monitoring via chest radiography. Additionally, liver ultrasound is advised on alternate years throughout childhood to screen for CF liver disease [240]. We do not use surveillance CT imaging in the UK, following the CF Trust recommendation
that “CT scanning should be carried out when appropriate and not routinely” and it is relatively rare to need to CT someone with CF under the age of 6. However, it is notable that there are studies examining the use of lung MRI in the assessment of neonatal lung disease. Whilst many rely on general anaesthesia and/or sedation and transfer of neonates from NICU to an imaging department, several report the use of small footprint MRI scanners situated specifically on NICUs optimised for free breathing neonatal imaging [241,242]. It is well recognised in paediatric radiology that with the right environment, time and preparation, awake non-sedated imaging is quite possible until the age of around 18-24 months and again from 5-6 years. It is therefore quite possible that an MRI surveillance program for appropriate lung diseases could start with initial imaging in infancy, a pause until the age of 5 or 6 and then regular follow up from that point onwards.

**Strengths and weaknesses compared to other studies and discrepant results**

As discussed in chapter 4, from a structural disease imaging standpoint we imaged fewer patients than Ciet et al, but the addition of ventilation imaging techniques rather than just structural imaging delivers an MRI equivalent of the hyperinflation score from CT [110]. As shown in chapter 2, at a young age this feature predominates over bronchiectasis, wall thickening and mucus plugging and has the greatest association with exacerbation frequency (r=0.642, p=0.001) and significant correlation with spirometry
(r=-0.444 to 0.510, p=0.015 to -0.038) and LCI (r=0.599, p=0.024). Martini et al combined structural imaging and the same dynamic oxygen enhanced protocol into a lung MRI examination, but in an older cohort with more severe disease and with up to 125 days between CT and MRI likely explaining the discrepancy between our results and with no MBW testing for evaluation of imaging and conventional lung function testing correlation [226] and whilst Nyilas et al examined the same matrix pencil decomposition technique with conventional lung function tests (including MBW) with similar levels of correlation, they did not include CT in their study [160].

Hypothesis 2 - Quantitative MR measures of ventilation correlate with established clinical measures of ventilation (LCI and FEV1) and provide additional spatial information.

Principal findings

There was no significant correlation between MRI outputs and spirometry values, but strong correlation was demonstrated between oxygen wash-in time by MRI and LCI2.5 (r=0.600, p=0.011) and very strong correlation between nitrogen wash-out time (measured using the Exhalyser-D) and impaired ventilation fraction measured via matrix pencil decomposition MRI (r=0.838, p,0.001).

Whilst no significant correlation was demonstrated between whole lung median oxygen washout time and LCI2.5, there was statistically significant
correlation between oxygen washout heterogeneity (skew and kurtosis) and LCI_{2.5}, suggesting that the spatial localisation of MRI and its resulting ability to measure focal lung function is of additional benefit.

**Strengths and weaknesses and comparison with other studies**

All participants in my study who consented to LCI measurement had this performed within 2 hours of MRI, at a reference centre for MBW testing in clinical research, to a strictly controlled protocol. Since this study closed to recruitment, Nyilas et al have published a short-term reproducibility study including MBW testing in 23 patients with MRI and LCI on the same day and repeated 24 hours later, resulting in limits of agreement for matrix pencil ventilation fraction of -4.4% to +3.7% (compared to -2.6 to 3 for LCI) [227]. Medium- and longer- term variability data is still required for both matrix pencil decomposition and dynamic oxygen enhanced imaging.

A strength of our MRI protocol is its rapid applicability at any centre with an MRI scanner with no non-proprietary sequences required for the oxygen enhanced imaging. The biggest weakness, as described previously, is likely the lack of follow up data and this will be addressed in a follow up study (discussed below).
Hypothesis 3 – A multisystem MRI assessment can provide new extrathoracic imaging biomarkers of CF and PCD disease severity whilst being better tolerated by patients than current multimodality imaging follow up.

Principal findings

As discussed previously, by the end of analysis, each patient had 141 quantitative outputs from a single MRI examination, many relating to extrathoracic sites of CF and PCD related disease. The two measurements of liver T1 relaxation time and the single measure of liver T2 relaxation time did not correlate with liver disease as defined by blood tests, splenic size on ultrasound or shear wave ultrasound elastography; however this was likely impacted by the very few recruits with liver disease. It is well known that MRI can demonstrate signs of CF liver disease and further work will be required to assess the utility of lung T1 maps for simultaneous liver T1 mapping.

The presence of sinus susceptibility artefact and opacification of over half the maxillary sinus with thickened mucosa were associated with increased exacerbation frequency and increased CT hyperinflation scores. A novel association was also suggested between increasingly watery mucus and a possible increase in sinus mucosal inflammation, an association that warrants further investigation.
The patient feedback questionnaire showed that breath holds were not a significant problem for a young cohort with CF or PCD and although many reported the protocol took too long and staying still was difficult compared to CT, all participants completed the whole examination with all lung imaging successfully post processed and only one recruit (a 6 year old) producing too much motion artefact for complete quantitative assessment of the paranasal sinuses.

Strengths and weaknesses

The simultaneous assessment of lung, sinus and liver disease has not been reported previously in the medical literature and very much highlights the strength of MRI as a multisystem/whole-body imaging tool. The lack of requirement for injected contrast media and use of non-sedated awake imaging means that the only objective disadvantage of MR surveillance over CT surveillance is the longer time required.

Whilst the feedback questionnaire gives us important insights into scan length and the impact of breath holds etc, the “better tolerated than” “multimodality imaging follow up” part of the hypothesis is far hard to test. Many do not undergo the full yearly follow up of chest radiograph, liver ultrasound and LCI all on the same day so comparing an all-in-one MRI to standard of care equivalents is not currently possible. It is notable though that there are studies currently recruiting which specifically aim to rationalise CF medications attempting to reduce the burden of care on the
lives of people with CF. It is easy to see that an equivalent approach to rationalising investigations could be needed in the near future.

**Strengths and weaknesses compared to other studies and discrepant results**

As stated above, this is the first report of an all-in-one, multisystem MRI examination designed specifically for patients with chronic suppurative lung diseases. Fitting complete structural and functional lung imaging, liver and sinus imaging into a single examination in under one hour which is tolerable even to 6 year olds is a significant step toward instigating MRI based surveillance of CF and PCD disease severity.

There are, however, other systems which suffer pathology related to CF and PCD which were not imaged within our protocol. Ng et al used MRI to measure the transit time of a food bolus from the mouth to the caecum as a measure of gut motility in people with CF, imaging the abdomen at regular intervals over a 6 hour time period[243]. Whilst an additional 6 hours of scanning is not practical, it would be possible to add some very basic small bowel imaging to our protocol, perhaps when specific gut motility questions are asked.

Chiang et al showed better demonstration of the vas deferens by MRI than ultrasound in a cohort of 14 men with presumed congenital absence of the vas deferens [244]. Whilst follow up imaging of the vas deferens is not likely to be of interest, a single study in male patients classed as CFSPID – cystic fibrosis screen positive inconclusive diagnosis may be of diagnostic
relevance. CFSPID refers to the situation where mutations of unknown significance are found in the CFTR gene with a clinical phenotype that is not that of definite cystic fibrosis, but may include a slightly elevated sweat chloride or similar suggestive feature. These patients are particularly difficult to treat as the diagnosis is not definite. Understandably there is often a high level of worry in these patients and their families and extra clues from multisystem MRI such as the presence of both vas deferens, homogeneous ventilation and the absence of any paranasal sinus disease may be of significant reassurance [192, 245–248].

There is also a recognised association between primary ciliary dyskinesia and disordered cerebrospinal fluid regulation with resulting hydrocephalus [249]. None of our 3 recruits with PCD had hydrocephalus, but the coronal imaging of the paranasal sinuses demonstrates the intracranial CSF spaces well. The same images also demonstrate the middle and inner ear and could be used to assess chronic otitis media, also a common feature of PCD (again not seen in our cohort). The inclusion of more participants with PCD or ideally a separate study with addition of more neuroimaging would add significant weight to the argument for MR surveillance in PCD.

**Meaning of the thesis as a whole**

Multisystem MRI offers a feasible surveillance imaging test for lung and associated extrathoracic disease in CF, and likely also for PCD. It is capable of replacing the surveillance CTs used to regularly follow lung disease in many countries and of adding an acceptable method of lung disease surveillance to standard care in the UK. With future work, MRI may be able
to rationalise CF and PCD diagnostics in such a way that all imaging and lung function measures can be obtained in a single short visit to an imaging centre rather than multiple attendances to different departments on different occasions. Furthermore, the use of oxygen-enhanced imaging as opposed to hyperpolarised gas MR demonstrates that functional lung imaging is already possible to implement on every MRI scanner in the country, albeit with significant organisational and resource challenges.

**Unanswered questions and future research**

A successful application for funding to the CF Foundation, supported by the data from this thesis, will drive a longer term follow up study of quantitative MRI outputs in people with CF. This will assess short and long term repeatability of MR outputs in people with CF and a small number of controls, long term directional change in outputs compared to changes in conventional measures of disease state and the impact of highly effective modulator therapies on disease severity.

Short-term reproducibility will be assessed between two scans performed over a 2-4 week period to assess variability in people with CF compared to that in healthy controls. Subsequent follow up will be performed at 6-month intervals over a 2 year period of disease stability (assessed via questionnaire in advance of imaging). There will then be a side arm whereby people initial recruited but experiencing a period of infective exacerbation will be rescanned at the start and end of IV antibiotic therapy with assessment of the responsiveness of MRI outputs to therapy and
comparison of long term recovery from an acute exacerbation on return to
the original longitudinal follow up arm of the trial.

The above study will enable further assessment of the value of liver T1
measurements from lung T1 maps as the cohort will be larger and may
include individuals with a clinically evident decline in liver function, and
may, depending on time constraints, also allow assessment of variability
and longitudinal directional change in sinus disease both during times of
clinical stability and over the course of an infective exacerbation.

Further future work will include the guidance of oxygen enhanced imaging
protocol timing via MBW testing, ideally including real time measurement
of exhaled nitrogen at the time of imaging. This will require significant input
from the manufacturers of the Exhalyser D as the equipment is not MRI
compatible and any solution to this problem is likely to require
modification of the traditional configuration of MBW equipment to include a
long extension tube with significant resulting ‘dead space’. An interesting
aside, without the need for further MR imaging, would be an investigation of
the effects of measuring LCI in a supine position compared to the
conventional upright position as any difference in resultant breathing
pattern or implied ventilation inhomogeneity will be very relevant to the
interpretation of future oxygen enhanced MRI studies.

With at least 141 possible outputs from our pilot data, it is clear there is still
a lot of research to contemplate!
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### Appendix 1 - Patient Characteristics

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## Appendix 2 – CFCT Scoring Proforma

**CFCT scoring sheet**

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<td>Segmental or larger</td>
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</table>
Appendix 3 – Participant Experience Feedback Questionnaire

Trial participant identifier

General questions before your examination

1. Did you fill in this questionnaire on your own?
   Yes ☐
   No ☐ I was helped by .................................................................

2. Have you had a CT examination before?
   Yes ☐
   No ☐

3. Have you had an MRI examination before?
   Yes ☐
   No ☐

4. Are you worried about having an imaging test today?
   Yes ☐
   No ☐

If yes, what are you worried about?
5. Are you worried about having a CT scan?

Yes ☐
No ☐

If yes, what is your main worry?

6. Are you worried about having an MRI scan?

Yes ☐
No ☐

If yes, what is your main worry?

(If you want, we can discuss any worries you have before your scan. It will help us to better understand your experience if you write any worries here before your scan)
The MRI examination

7. The time spent on the MRI scanner felt...
(Please circle one answer)

- Far too long
- A little too long
- About right
- A bit too short
- Far too short

8. The MRI machine was...
(Circle one)

- Far too noisy
- A little too noisy
- Not too noisy

9. Staying still for the MRI was...

- Easy
- Easy enough
- Not too difficult
- Quite difficult
- Far too difficult

10. I found holding my breath for the MRI scan was...

- Easy
- Easy enough
- Not too difficult
- Quite difficult
- Far too difficult

11. The MRI scanner made me feel

- Very claustrophobic
- A bit claustrophobic
- Not claustrophobic
The CT examination

12. The time spent on the CT scanner felt...
(Please circle one answer)

Far too long  A little too long  About right  A bit too short  Far too short

13. The CT machine was...
(Circle one)

Far too noisy  A bit too noisy  Not too noisy

14. Staying still for the CT was...

Easy  Easy enough  Neither easy nor difficult  Quite difficult  Too difficult

15. I found holding my breath for the CT scan was...

Easy  Easy enough  Not too difficult  Quite difficult  Too difficult

16. The CT scanner made me feel

Very claustrophobic  A bit claustrophobic  Not claustrophobic
17. If in the future you were given a choice of CT or MRI for imaging your lungs, which would you choose? (Please circle one)

CT

MRI

18. The main reason for my choice is...

☐ Length (time) of examination
☐ Ability / need to remain still
☐ Breath holding requirements
☐ Noise
☐ Claustrophobia
☐ Other (please write below)
Appendix 4 – Ethics Committee Approved Trial Protocol

[Amended protocol 21st November 2016. Amendments in bold and red]

Study Title

A Pilot Study to assess the use of MRI in the assessment of patients with cystic fibrosis and primary ciliary dyskinesia

Short Study Title/Acronym: MRI in cystic fibrosis and primary ciliary dyskinesia

REC Reference: 16/YH/0351
Research Office Reference: 2016LI002B

CHIEF INVESTIGATOR:

Dr A Devaraj
Consultant Radiologist
Radiology Department
The Royal Brompton Hospital, Sydney Street, London

Phone: 02073528121
Email: A.Devaraj@rbht.nhs.uk
Fax:

SPONSOR REPRESENTATIVE:

Patrik Pettersson
Royal Brompton and Harefield NHS Foundation Trust (RB&HFT)
Royal Brompton Hospital (RBH)
Research Office
Chelsea Wing, Level 2
Sydney Street
London SW3 6NP

Phone: 0207 352 8121 ext. 2610
Email: p.pettersson@rbht.nhs.uk
Fax: 020 8725 0794
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11.2 Radiology or any other procedure(s) Clinically indicated chest CT scan: 361
As is our routine practice, this will be performed using our low dose, non-contrast CT chest protocol with individualised scanning protocols for children of different sizes and adults.

Research MRI scan:
20 – 40 minute scan performed using a standardised protocol including images of the lungs, paranasal sinuses, pulmonary arterial system and upper abdominal organs.

11.3 Definition of the End of Trial

12. Safety Reporting
12.1 Definitions
12.2 Recording Adverse Events (AEs)
12.3 Reporting SAEs
12.4 The Type and Duration of the Follow-up of Subjects after AEs
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14.2 Endpoints
  14.2.1 Primary endpoints
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14.3 Statistical Analysis Plan
  14.3.1 Primary endpoint analysis
  14.3.2 Secondary endpoint analysis
14.4 Randomisation
14.5 Interim Analysis (if applicable)

15. Committees in Involved in the Study

16. Direct Access to Source Data

17. Ethics and Regulatory Requirements

18. Finance

19. Insurance and Indemnity

20. Publication Policy

21. Statement of Compliance
# 1. LIST OF ABBREVIATIONS

(Commonly used abbreviations; please add/delete as appropriate. Please delete this sentence as well.)

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AE</td>
<td>Adverse Event</td>
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<tr>
<td>AR</td>
<td>Adverse Reaction</td>
</tr>
<tr>
<td>ASR</td>
<td>Annual Safety Report</td>
</tr>
<tr>
<td>CI</td>
<td>Chief Investigator</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>DMC</td>
<td>Data Monitoring Committee</td>
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<tr>
<td>EXACT</td>
<td>Exacerbations of Chronic Pulmonary Disease Tool</td>
</tr>
<tr>
<td>GAfREC</td>
<td>Governance Arrangements for NHS Research Ethics</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>HRA</td>
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<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
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<td>ISF</td>
<td>Investigator Site File</td>
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<tr>
<td>ISRCTN</td>
<td>International Standard Randomised</td>
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<tr>
<td>MUST</td>
<td>Malnutrition Universal Screening Tool</td>
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<tr>
<td>NHS R&amp;D</td>
<td>National Health Service Research &amp; Development</td>
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<tr>
<td>NIMP</td>
<td>Non-Investigational Medicinal Product</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>PIS</td>
<td>Participant Information Sheet</td>
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<tr>
<td>QA</td>
<td>Quality Assurance</td>
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<tr>
<td>QC</td>
<td>Quality Control</td>
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<td>RCT</td>
<td>Randomised Control Trial</td>
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<td>REC</td>
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<td>SAR</td>
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<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SDV</td>
<td>Source Document Verification</td>
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<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
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<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
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<td>SSA</td>
<td>Site Specific Assessment</td>
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<td>TMG</td>
<td>Trial Management Group</td>
</tr>
<tr>
<td>TSC</td>
<td>Trial Steering Committee</td>
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2. STUDY PERSONNEL AND FACILITIES

**Principal Investigator (PI):** Dr A Devaraj, The Royal Brompton Hospital, Radiology department, Sydney Street, London

  **E-mail:** A.Devaraj@rbht.nhs.uk  
  **Phone:** 02073528121

**Statistician:** Not applicable

  **E-mail:**  
  **Phone:**  
  **Fax:**

**Medical Expert:** Dr Simon Padley

  **E-mail:** s.padley@rbht.nhs.uk  
  **Phone:** 0207 352 8121 x2943  
  **Fax:**

**Routine local laboratories:** Not applicable

  **E-mail:**  
  **Phone:**  
  **Fax:**

**Central Laboratory:** Not applicable

  **E-mail:**  
  **Phone:**  
  **Fax:**

**Pharmacy:** Not applicable

  **E-mail:**  
  **Phone:**  
  **Fax:**
# 3. STUDY SYNOPSIS

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<td>MRI in cystic fibrosis and primary ciliary dyskinesia</td>
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<td><strong>Study drug (s):</strong></td>
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<td><strong>Chief Investigator:</strong></td>
<td>Dr A Devaraj</td>
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<tr>
<td><strong>Medical condition/disease under investigation:</strong></td>
<td>Cystic Fibrosis (CF) and Primary Ciliary Dyskinesia (PCD)</td>
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<td><strong>Study duration:</strong></td>
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<td><strong>Primary Objective:</strong></td>
<td>Can MRI perform at least as well as CT in cystic fibrosis / primary ciliary dyskinesia disease assessment?</td>
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<tr>
<td><strong>Secondary Objective:</strong></td>
<td>Is MRI as acceptable to the patient and hospital as CT? Can MRI produce any novel, clinically useful biomarkers of disease severity in CF or PCD?</td>
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<td><strong>Study population:</strong></td>
<td>Approximately 50 CF and PCD patients referred for CT from outpatient clinics or inpatient admissions</td>
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<td>Small prospective pilot / feasibility study</td>
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<td><strong>Eligibility criteria:</strong></td>
<td><strong>Inclusion criteria:</strong> Known CF or PCD clinically assessed and referred for CT assessment during the trial period</td>
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<td><strong>Exclusion criteria:</strong> Contraindication to MRI (pacemaker etc) Inability to remain still for an MRI investigation Inability to undergo MRI within 7 days of CT (e.g. due to patient or machine availability)</td>
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<tr>
<td><strong>Study treatment:</strong></td>
<td>(i.e. dose and mode of the study drug administration if applicable): No study treatment given.</td>
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4. INTRODUCTION

4.1 BACKGROUND

Cystic fibrosis (CF) is one of the most common inherited fatal diseases in Caucasians and causes a progressive lung disease. At birth the lungs are normal, but over time the airways dilate and become thick walled with progressive loss of functioning of lung tissue. Primary ciliary dyskinesia (PCD) is a group of different inherited conditions that cause similar lung changes, albeit often more mild.

Currently the best imaging technique for demonstrating the rate and extent of lung changes is computed tomography (CT). However, this involves exposure to ionising radiation and there is concern that repeated exposures, particularly early in life, increase the risk of certain cancers later in life.

Advances in treatments have improved life expectancy in CF and PCD patients, thus increasing the importance of minimising any risk from repeated CT examinations.

Whilst lung involvement remains the most common cause of life limiting disease, life expectancy has significantly increased and extra-pulmonary disease is becoming an important consideration (Elborn. Cystic Fibrosis. Lancet 2016).

4.2 PRE-CLINICAL DATA/CLINICAL DATA

Recent technological advances have led to better visualisation of the lungs via MRI, producing diagnostic quality images with the advantage of not using ionising radiation and the potential to acquire additional functional data not currently obtainable via CT (Eichinger, European Journal of Radiology 2012 and Dournes, Radiology 2015).

Rhinosinusitis is experienced by around 60% of CF patients, reduces quality of life (Habib. Ann Am Thorac Soc 2015), and is associated with a higher frequency of pulmonary exacerbations (Umetsu D Lancet 1990). MRI offers the potential to measure sinus opacification, mucosal oedema and diffusion coefficients of mucus and sinus mucosa (White. Clin Imaging 2008) at times also providing signs of superadded infection (Som Radiology 1990 and Eggesbo Acta Radiol 1999).

Pulmonary–systemic shunting is a recognised feature of severe chronic lung disease. The development of hypertrophied bronchial arteries as a result
can cause life-threatening haemoptysis. The degree of shunting (Qp:Qs) and pulmonary flow velocity can be measured indirectly via validated cardiac MRI techniques (Fleck. Pediatr Radiol 2013).

MRI offers a robust method of both structural and functional assessment of abdominal viscera. Structural pancreatic and hepatic detail is well demonstrated using established commercially available sequences regularly employed throughout the NHS. Additionally, more research stage sequences, including T1 mapping techniques, have been used to estimate liver function and fibrosis (Zhang. Magn Reson Imaging 2016 and Chen Quant Imaging Med Surg. 2016).

4.3 STUDY RATIONALE AND RISK/BENEFIT ANALYSIS

We wish to examine the possibility of replacing CT assessment of CF/PCD lung disease with MRI assessment thus reducing radiation exposure, and the possible role of MR imaging of other structures (sinuses, pulmonary arteries and upper abdominal organs) in the assessment of disease progression.

As long as the standard safety questionnaire has been completed, MRI is considered a safe examination. There will, therefore, be no added risk to the patient.

Whilst the study will be of no immediate benefit to its participants, depending on the trial outcome, benefit may come later when numerous follow up CT scans may potentially be replaced with follow up MRI thus reducing lifetime cumulative radiation dose.

The discovery of new biomarkers of disease severity may, if incorporated into regular follow up protocols, further aid the clinical teams in the risk stratification and management of these patients.

4.4 MANAGEMENT OF POTENTIAL STUDY RISKS

The risks are those which contra-indicate examination via MRI. These are assessed via a standard safety checklist, completed routinely by anyone attending the imaging department for an MRI examination. If contra-indications to MRI are present, the patient will not be enrolled into the study.
5. STUDY OBJECTIVES

5.1 PRIMARY OBJECTIVE

To determine whether MRI can produce sufficiently diagnostic images of the lungs of patients with CF and PCD to allow the replacement of CT imaging follow up.

5.2 SECONDARY OBJECTIVES

To determine whether MRI is as acceptable to patients with CF or PCD as CT.
To investigate the feasibility of using other MRI parameters (pulmonary blood flow velocity, sinus disease and abdominal organ characteristics) as markers of disease severity.

6. TRIAL DESIGN

6.1 OVERALL DESIGN

Small prospective pilot / feasibility study.

We aim to recruit approximately 50 patients over the age of 6 years, with CF or PCD.

Patients will be identified in routine clinic appointments or at inpatient admission for investigation or treatment. If they are referred for CT examination, the respiratory clinician will ask if the patient is willing to participate in this study. If so, they will undergo their clinical CT but will also undergo a research MRI examination within 7 days of the CT scan (on the same day where possible). A smaller number of patients may later be asked if they would consent to undergoing a second scan at the end of their inpatient or acute outpatient treatment. The CT will not be repeated.

The MRI scans will be anonymised and reported by a radiologist, blinded to the CT findings. The report will then be compared to the report from the standard CT to assess concordance between the modalities. The images will also be scored using standard research scoring tools (Eichinger Lung MRI score for the MRIs and Brody2 and Eichinger scores for the CTs) to assess inter and intra observer variability. Linked-anonymised imaging data will also be analysed by collaborating teams in Basel, Switzerland and Manchester, England.

Patients or their carers will also be asked to fill in a short questionnaire comparing their experience of the CT and MRI examinations to assess
relative acceptability. The cost (time, resources etc) of each examination will be calculated and compared.

6.2 Treatment and rationale

No treatment is given as part of this imaging study.

6.3 Schematic of trial design

The clinical (blue) and research (green) components run in parallel (i.e. the research MRI and patient experience questionnaires are additional to, not in place of the standard clinical care).
7. ELIGIBILITY CRITERIA

7.1 INCLUSION CRITERIA

Age of 6 years or over
Established diagnosis of CF or PCD
Referred for clinical CT chest

7.2 EXCLUSION CRITERIA

Contraindication to MRI (pacemaker or other metallic implant etc. as assessed by standard MRI safety checklist).

Inability to remain still for an MRI examination of 20 – 40 minutes.

Inability to undergo MRI examination within 7 days of the CT scan (e.g. due to patient or machine availability).
7.3 DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS AND STOPPING RULES

For the majority of patients this study will involve a single extra imaging examination in addition to standard investigation. A small number of patients scanned as inpatients, or as outpatients undergoing acute treatment, may be asked if they would consent to a single follow up MRI at the end of their admission (the CT will not be repeated).

For the MRI data to be reasonably compared to the CT they should ideally be performed on the same day. If not possible, the scan can be performed within 7 days. If an MRI cannot be performed within 7 days for whatever reason, the patient will not be recruited to the study. Their standard of care investigations (including their CT) and treatment will continue as normal outside of the trial.

The MRI machine is quite large and loud and patients need to lie very still for the examination. If a patient becomes claustrophobic or wants to stop the examination for any reason, the operator performing the scan will be in constant contact with via a microphone built into the scanner and the scan can be stopped at any time.

Patients who terminate a scan early will be asked if they would fill in a short questionnaire to assess whether MRI is tolerated less well than CT and, if so, how.

8. SUBJECT/PATIENT RECRUITMENT PROCESS

There will be single centre involvement (The Royal Brompton). Recruitment will be via the respiratory physicians in clinic. Once referred for CT, the patients will be given the information sheet and asked if they would consent to trial enrolment.

Patient recruitment at a site will only commence once the trial team has ensured that the following approval/essential documents are in place:

1. The main REC approval,
2. Final sponsorship and/or R&D approval (NHS Permission),
3. Local Site Delegation of Duties and Signature Log is completed.
All subjects who wish to enter the study will be fully screened and consented by the Chief Investigator (CI), or one of the qualified clinicians involved in the study as the Principal Investigator (PI).

9. STUDY PROCEDURES

9.1 INFORMED CONSENT

Informed consent will be obtained by the Chief Investigator (CI), Principal Investigator (PI) and/or a nominated deputy as recorded on Sponsor’s Delegation of Responsibilities Log. All individuals taking informed consent will have received consent training.

Consent to enter this study will be obtained after a full account has been provided of its nature, purpose, risks, burdens and potential benefits, and the patient has had the opportunity to deliberate. The patient will be allowed to specify the time they wish to spend deliberating, usually up to 24 hours.

Periods shorter than 24 hours will be permitted if the patient feels that further deliberation will not lead to a change in their decision, and provided the person seeking consent is satisfied that the patient has fully retained, understood and deliberated on the information given. This provision has been made with the support of our patient advisory group.

Likewise, periods longer than 24 hours will be permitted should the patient request this. The Investigator or designee will explain that the patients are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason. A copy of the signed Informed Consent Form (ICF) along with a copy of the most recent approved Patient Information Sheet (PIS) will be given to the study participant. The original signed consent form will be retained at the study site (one filed in the medical notes and one filed in the Trial Master File (TMF)). A copy of the consent form will also be given to the patient.

9.2 RANDOMISATION PROCEDURE

There will be no randomisation.

10. STUDY ASSESSMENTS

10.1 SCREENING ASSESSMENTS
None.

### 10.2 Baseline Assessments

Clinical CT chest and standardised, routinely performed annual outpatient follow-up investigations (this includes clinical history, pulmonary function testing and blood tests).

### 10.3 Trial Assessment

A single MRI examination, lasting between 20 and 40 minutes, involving imaging of the lungs, paranasal sinuses, pulmonary arterial system and upper abdominal organs. Intravenous contrast material will not be administered. 100% oxygen **will** be inhaled for part of the lung assessment.

### 10.4 Subsequent Assessments

A small number of patients admitted from outpatients or undergoing acute outpatient treatment may be asked if they would consent to a single follow up MRI examination at the end of their inpatient stay / outpatient treatment. The CT will not be repeated.

### 10.5 Summary Chart of Study Assessments

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Day of clinic visit</th>
<th>Within 7 days of CT</th>
<th>At end of in-patient stay / outpatient treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Routine clinic visit</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Routine investigations (clinical history, lung function testing, blood tests)</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Routine clinical chest CT</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Trial consent form</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. MRI safety checklist</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>6. MRI examination</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>7. Patient experience questionnaire</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>8. Repeat MRI (in a small group of inpatients and outpatients undergoing acute treatment)</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>
Methods

11.1 Laboratory Procedures

Not applicable.

11.2 Radiology or any other procedure(s)

Clinically indicated chest CT scan:

As is our routine practice, this will be performed using our low dose, non-contrast CT chest protocol with individualised scanning protocols for children of different sizes and adults.

Research MRI scan:

20 – 40 minute scan performed using a standardised protocol including images of the lungs, paranasal sinuses, pulmonary arterial system and upper abdominal organs.

- Is ARSAC licence required?

No.

- Tools

Bespoke post-scan questionnaire to assess patient experience.

Standard MRI safety checklist
Standardised MRI and CT scoring tools (Eischinger and Brody2 / CFCT scores)

11.3 Definition of the End of Trial

Last patient, last visit once imaging questionnaire filled out.

12. Safety Reporting

12.1 Definitions

Adverse Event (AE) — any untoward medical occurrence in a patient or clinical trial subject who is administered a treatment and which does not necessarily have a causal relationship with this treatment (i.e. any unfavourable or unintended change in the structure (signs), function (symptoms), or chemistry (lab data) in a subject to whom a treatment/study procedure has been administered, including occurrences unrelated to that product/procedure/device).
**Serious Adverse Event (SAE)** – is defined as an untoward occurrence that:

- Results in death; or
- Is life-threatening (places the subject, in the view of the Investigator, at immediate risk of death)
- Requires hospitalization or prolongation of existing hospitalization (hospitalisation is defined as an inpatient admission, regardless of length of stay; even if it is a precautionary measure for observation; including hospitalisation for an elective procedure, for a pre-existing condition)
- Results in persistent or significant disability or incapacity (substantial disruption of one’s ability to conduct normal life functions)
- Consists of a congenital anomaly or birth defect (in offspring of subjects or their parents taking the study drug regardless of time of diagnosis)
- Is otherwise considered medically significant by the investigator.

Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the outcomes listed in the definition of serious will also be considered serious.

### 12.2 Recording Adverse Events (AEs)

All Adverse Events will be recorded in the hospital notes and Case Report Form (CRF).

If the Investigator suspects that the disease has progressed faster due to the administration of the study treatment/procedure, then he/she will report this as an unexpected adverse event to the Sponsor and the main REC as detailed in Section 12.3.

Clinically significant abnormalities in the results of objective tests (MRI) may be recorded as Adverse Events (these may have already been demonstrated on the routine chest CT). These will be communicated to the clinical team and any necessary further investigation or treatment discussed as per our routine departmental unexpected significant findings protocol.

### 12.3 Reporting SAEs

Principal Investigator (PI) at all sites must report all SAEs to the Chief Investigator (CI) or a delegated individual in the research team. The CI and his research team at RBH are responsible for reporting events to the
Research Office immediately and/or within 24 hours of becoming aware of the event using the Sponsor’s SAE Reporting Form.

All other AEs must be reported to the Sponsor by the research team in the Annual Progress Report (APR).

Classification and causality of Adverse Events (AEs) will be conducted by local PIs and reviewed by CI. The CI cannot downgrade the site PI’s classification and if there is disagreement which cannot be resolved during formal discussion then the assessment of the site PI will be accepted. The CI, can however, upgrade the seriousness of an event without consultation with the site PI.

All Adverse Events that are to be reported to the Research Office must be signed and dated and completed by the Investigator.

Information can be submitted in electronic format:

§ Email: safetyreporting@rbht.nhs.uk or

§ Fax: 0207 351 8829.

The research team also has the responsibility to report SAEs occurring in a certain period (28 days) after a patient completes the trial. Any SAEs reported to the Investigators during this phase must be documented in the patient’s medical notes and submitted via an SAE form

The Research Ethics Committee (REC) that gave a favorable opinion of the study (the ‘main REC’) should be informed where in the opinion of the CI/PI the event was:

• ‘related’: that is, it resulted from administration of any of the research procedures; and

• ‘Unexpected’: that is, the type of event is not listed in the protocol as an expected occurrence.

Reports of related and unexpected SAEs should be submitted within 15 days of the CI/PI becoming aware of the event, using the form below. The form should be completed in typescript and signed by the Chief Investigator.

• NRES Report of Serious Adverse Event Form, V3
The coordinator of the main REC will acknowledge receipt of the safety report.

12.4 The type and duration of the follow-up of subjects after AEs

As long as the routine safety procedures are followed, AEs related to MRI are extremely rare. Any necessary follow up will be provided as per current guidelines.

12.5 Pregnancy

MRI is normally avoided during pregnancy. This is assessed as part of the standard MRI safety checklist performed before every examination. Patients who are pregnant will not be recruited to the trial.

12.6 Annual Progress Reports (APRs)

The Chief Investigator will prepare the APR for the study. It will be reviewed by the RO and sent to the main REC by the CI within 30 days of the anniversary date on which the favourable opinion was given by the main REC, and annually until the trial is declared ended.

12.7 Reporting Urgent Safety Measures

The Sponsor and/or the Investigator may take appropriate urgent safety measures in order to protect the subjects of a clinical study against any immediate hazard to their health or safety. If safety measures are taken, the main REC approval is not required before the measure is taken.

The Investigator will immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the main REC and the study Sponsor of the measures taken and the circumstances giving rise to those measures.

In order to prevent any delays in the reporting timelines the Sponsor has delegated this responsibility to the CI/PI. Therefore the CI/PI must report any urgent safety measures to the main REC directly, and in parallel to the Sponsor. The REC coordinator will acknowledge receipt of urgent safety measures within 30 days.

13. Data Management and Quality Assurance

13.1 Confidentiality
All data will be handled in accordance with the Data Protection Act 1998, NHS Caldecott Principles, The Research Governance Framework for Health and Social Care, 2nd Edition (2005), and the condition of the main REC approval.

The Case Report Forms (CRFs) will not bear the subject’s name or other personal identifiable data. The subject’s Date of Birth (DOB) and trial Identification Number (ID), will be used for identification.

13.2 Data collection tool

Case Report Forms (CRF) will be designed by the CI and the final version will be reviewed and discussed with the study Sponsor. All data will be entered legibly in black ink with a ball-point pen. If the Investigator makes an error, it will be crossed through with a single line in such a way to ensure that the original entry can still be read. The correct entry will then be clearly inserted. The amendment will be initialled and dated by the person making the correction immediately. Overwriting or use of correction fluid will not be permitted.

It is the Investigator’s responsibility to ensure the accuracy of all data entered and recorded in the CRFs. The Delegation of Responsibilities Log will identify all trial personnel responsible for data collection, entry, handling and managing the database.

Anonymised MRI data will be stored on PACS (secure onsite clinical imaging archive). With patient consent, this will be stored long-term, otherwise it will be deleted at the end of the analysis.

Numerical data (imaging scores etc) will be stored in an excel database saved to the secure network drive of onsite NHS trust PCs. Patient questionnaires will be uploaded to the same folder on the NHS trust PC network drive.

13.3 Data handling and analysis

This is a small pilot study, with limited numeric data. Excel will be adequate for data entry. Statistical analysis will be performed using SPSS.

MRIs will be reported and re-reported by several different radiologists to provide inter and intra observer variability data.

Data will be stored on an NHS trust Network drive accessible via secure log in from both Royal Brompton Hospital Sites (Sydney St and Fulham Road buildings).

A single set of MRI data, linked-anonymised such that the patient will not be identifiable outside of the onsite Royal Brompton
research team, will be sent to Professor Oliver Bieri at an academic institution in Basal, Switzerland for computational analysis that cannot be performed elsewhere. Similar linked-anonymised imaging data will be sent to a Manchester-based advanced imaging analysis company called Bioxydyn for further analysis.

Data entry will primarily be performed by Dr T Semple (radiology fellow). Image reporting and scoring by Dr A Devaraj and Dr S Padley who will enter their own data. The datasets will be combined by Dr T Semple and further analysis also performed by Dr T Semple.

13.4 Archiving Arrangements

The study documents (including the Trial Master File (TMF), Case Report Forms (CRFs), Informed Consent Forms along with the trial database) will be kept for a minimum of five years. They will be stored in locked offices within the Royal Brompton and Harefield NHS Foundation Trust (RB&HFT). The CI is responsible for the secure archiving of trial documents. The trial database will also be kept electronically on the RB&HFT computer network, for a minimum of five years.

The approved repository for longer retention of local materials for studies that involve RB&HFT patients is Box-It Storage UK. The study documentation will be prepared for archiving by the research team in line with the Research Office Archiving SOP and the transfer will be arranged by the Research Office.

14. Statistical Design

This is a small limited pilot / feasibility study without the necessity for complex statistical analysis. If successful implementation is achieved, a larger study powered for statistical significance will be undertaken. Formal statistician involvement will be sought at this stage.

14.1 Sample Size and Recruitment

This is a small pilot / feasibility study consisting of approximately 50 patients recruited from outpatient appointments.

14.2 Endpoints

14.2.1 Primary endpoints
Numeric comparison of MRI and CT scores (Eischinger and Brody2 / CFCT) for each patient. Categorical comparison of clinical CT report with research MRI report.

14.2.2 Secondary endpoints

Categorical comparison of acceptability scores for CT and MRI. Multivariate analysis of MRI findings (pulmonary arterial blood flow velocity, sinus disease and abdominal organ tissue characteristics).

14.3 Statistical analysis plan

14.3.1 Primary endpoint analysis

Simple comparison of scores for each category within the Eichenger and Brody scoring systems (T test or Man-Whitney) with interclass correlation co-efficients / Kappa values for inter and intra observer variation calculations for each modality.

14.3.2 Secondary endpoint analysis

Simple analysis of questionnaire data (frequency of answers, mean and range of satisfaction scores etc.

Logistic regression analysis of novel potential MRI markers in relation to established markers of disease severity (lung clearance index, CT appearance, known cystic fibrosis genotype or form of primary ciliary dyskinesia).

14.4 Randomisation

There will be no randomisation.

14.5 Interim analysis (if applicable)

Not applicable.
15. COMMITTEES IN INVOLVED IN THE STUDY

Trail Management Group (TMG)

Dr A Devaraj (CI)
Dr S Padley
Dr T Semple
Prof J Davies
Dr C Hogg

16.1 DIRECT ACCESS TO SOURCE DATA

The Investigator(s)/institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

17. ETHICS AND REGULATORY REQUIREMENTS

The Sponsor will ensure that the trial protocol, Patient Information Sheet (PIS), Informed Consent Form (ICF), GP letter and submitted supporting documents have been approved by the Health Research Authority (HRA), prior to any patient recruitment taking place. The protocol and all agreed substantial protocol amendments, will be documented and submitted for HRA Approval prior to implementation.

Before site(s) can enrol patients into the trial, the PI must obtain Confirmation of capacity and capability. It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary approval. This does not affect the individual clinician’s responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

Within 90 days after the end of the trial, the CI and Sponsor will ensure that the main REC is notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply a final summary report of the clinical trial to the main REC and the Sponsor in parallel within one year after the end of the trial.
18. **FINANCE**

A pump-priming research grant has been obtained from The Royal College of Radiologists (£10,000).

19. **INSURANCE AND INDEMNITY**

NHS bodies are liable for clinical negligence and other negligent harm to individuals covered by their duty of care. NHS Institutions employing researchers are liable for negligent harm caused by the design of studies they initiate. The provision of such indemnity for negligent harm should be stated to the participant.

20. **PUBLICATION POLICY**

Data ownership rights will lie with the institution.

21. **STATEMENT OF COMPLIANCE**

The trial will be conducted in compliance with the protocol, Sponsor's Standard Operating Procedures (SOPs), GCP and the applicable regulatory requirement(s).

The study conduct shall comply with all relevant laws of the EU if directly applicable or of direct effect and all relevant laws and statutes of the UK country in which the study site is located including but not limited to, the Human Rights Act 1998, the Data Protection Act 1998, the Medicines Act 1968, and with all relevant guidance relating to medicines and clinical studies from time to time in force including, but not limited to, the ICH GCP, the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (2008 Version), the NHS Research Governance Framework for Health and Social Care (Version 2, April 2005).

This study will be conducted in compliance with the protocol approved by the main REC and according to RGF standards. No deviation from the protocol will be implemented without the prior review and approval of the Sponsor and the main REC except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the Sponsor and the main REC as soon as possible.
Appendix 5 – Presentations, Publications, Prizes and Grant Applications over the MDres Registration Period

Presentations given
(Respiratory imaging only)

“New-perspectives course” – The role of CT and MRI as part of Vertex sponsored Cystic Fibrosis Masterclass, Stockholm, May 2016

Brompton chest radiography course – Paediatric chest radiograph interpretation, October 2016

Paediatric respiratory updates – updates in paediatric thoracic imaging – Great Ormond Street, Nov 2016

Large airways collapse group national meeting – role of cine CT and MR techniques in large airways imaging – Royal Brompton Nov 2016

BSTI Case presentation - Relapsing Polychondritis case – London, Nov 2016

3rd John Price paediatric respiratory medicine course – King’s College Hospital, April 2017 - Childhood interstitial lung disease workshop

The London CF course – Imaging in CF – London Sept 2017

BIR/IPEM Dose Management in Contemporary Radiological Practice – The radiologist’s perspective – NEC Birmingham Oct 2017

RBH Grand round on lung MRI in practice – London Jan 2018

RBH Infection day: Is there a role for lung MRI – London Jan 2018

BEAT PCD Training School: 1.5 hour PCD imaging workshop – Lisbon Feb 2018

4th John Price paediatric respiratory medicine course – London April 2018
  • Neonatal lung disease imaging masterclass (part of the postgraduate course)
  • Personal practice session on imaging paediatric lung disease (part of the main conference)

BASIC course (PICU imaging) – May 2018

UK PCD support group – imaging in PCD presentation for AGM June 2018

CIPP XVII - Toledo – July 2018
  • Post-graduate course – paediatric respiratory radiology day
• Session on modern imaging of non-CF bronchiectasis

RCR18 Paediatric chest imaging session – Liverpool September 2018

London CF course – Imaging session – October 2018

Irish Thoracic Society Annual meeting (Belfast) – November 2018
  • Lung imaging outcome measures in CF

St Georges’ Hospital Paediatric Imaging Day – March 2019
  • Paediatric chest imaging

London CF course Imaging session – March 2019

BEAT PCD Training School: 1.5 hour PCD MRI imaging workshop – Pozan March 2019

Davos Diagnostic course 2019 Davos - April 2019
  • Childhood ILD workshop
  • Paediatric chest imaging workshop

RSM paediatric respiratory day – London May 2019
  • Case-based introduction to paediatric chest imaging

ESPR 2019 Helsinki – May 2019
  • Improvements in CT technology and impact on paediatric imaging

BASIC 2019 (PICU imaging) London – July 2019

ERS Paediatric Respiratory Infections Workshop Lisbon – Nov 2019

BTS Winter meeting London - December 2019 Assessment of lung disease in children

Royal Brompton and Royal College of Radiologists Thoracic Imaging Master class London – childhood ILD lecture – February 2020

John Price Paediatric Respiratory Conference London - March 2020 (online due to CoVID-19 outbreak) - The Future of Paediatric Respiratory Imaging. Joint lecture with Dr CM Owens
Papers and abstracts


M Zusag, SR Desai, T Semple, A Shah and E Angelini. SAPSAM – Sparsely Annotated Pathological Sign Activation Maps – A novel approach to train convolutional neural networks on lung CT scans using binary labels only. Accepted for ISBI 2019


Semple T, Ashworth M and Owens CM. Interstitial Lung Disease in Children Made Easier...well almost! Radiographics 2017. 37 (6) 1679-1703


**Book chapters** –
Kendig and Chernick’s Disorders of the Respiratory Tract in Children: Imaging chapter

Chapman and Nakielney’s Aids to Radiologic Differential Diagnosis (7e):
- Chest chapter
- Paediatrics chapter

Grainger and Alison’s Diagnostic radiology (8e)
- Lung MRI sub-chapter
- Current status of paediatric imaging
- Neonatal and paediatric chest

Encyclopaedia of respiratory medicine 2nd edition – Imaging the lung in childhood (chapter 10214) with Dr Alistair Calder

**Abstracts** –
(Relating to paediatric respiratory imaging only)

ESTI 2016
The role of fetal MRI in planning for the ex-utero intrapartum (EXIT) procedure

ESPR 2017
A Pictorial review of Congenital Lung Abnormalities

ECR 2017
Effect of new CT technology on paediatric CT dose (part of the Eurosafe initiative)

BSTI 2017 and ECR 2018
Motion capture based respiratory gating for neonatal thoracic CT

ESPR 2018
CT dose taskforce session and abstract

ESPR 2019
Imaging cystic fibrosis in the 21st century

ERS 2019
CT lung findings in proven aspiration

ECFS 2019
• MRI as the new gold standard in the assessment of CF lung disease severity? A bespoke CF-MRI protocol combining quantitative ventilation and structural MRI measures to replace CT
• The addition of sinus imaging to a quantitative CF lung MRI protocol demonstrates an association between sinus signal characteristics and lung disease severity

ECR 2020
Chronic aspiration in children – expansion of ERS project to include a second population

Awards and prizes
• 1st prize, poster presentation competition, NHLI Post Graduate Research Day 2017
• Presentation prize – BSTI – for motion capture-based respiratory gating for neonatal thoracic CT
• Travel grant – International Paediatric Radiology, Chicago May 2016
• ECFS abstract selected for German translation for Vertex report on top abstracts from ECFS 2019

Grants
Contributions toward successful applications for the following:
• CF Foundation funded follow up study using this thesis as pilot data – “Oxygen-enhanced MRI as an outcome measure in cystic fibrosis” (~$900k)
• Imperial BRC grant (£50k) – Quantitative lung MRI in diagnosis prognostication and assessment treatment effect in pulmonary hypertension
• Chiesi grant (£20k) – Quantitative MRI assessment of bronchial collateralisation and haemoptysis in cystic fibrosis and response to embolization
Appendix 6 – Published cystic fibrosis MRI abstracts in full

ECFS 2019

Title
MRI as the new gold standard in the assessment of CF lung disease severity? A bespoke CF-MRI protocol combining quantitative ventilation and structural MRI measures to replace CT

Authors and affiliations
T Semple1,2, C Edmondson1,2, B Rawal1,2, J Barnett1,2, C Short1,2, G Bauman3, O Pusterla3, O Bieri3, M Tibiletti4, GJM Parker4,5, S Carr1,2, C Hogg1,2, JC Davies1,2, S Padley1,2

1. The Royal Brompton Hospital, London, UK
2. National Heart and Lung Institute, Imperial College London, UK
3. Division of Radiological Physics, Department of Radiology, University of Basel Hospital, Basel, Switzerland
4. Bioxydyn Ltd, Manchester, UK
5. University of Manchester, UK

Objectives
Conventional MRI demonstrates the gross structural disease of CF but is insensitive to CT signs of small airways disease. We aimed to prove that the addition of ventilation MRI techniques resolves this shortcoming.

Methods
A bespoke quantitative CF MRI examination was designed combining rapid structural imaging (1 minute 2 seconds), oxygen-enhanced (OE-) and Fourier-decomposition (FD-) ventilation/perfusion MRI. This was trialled in a cohort of CF patients undergoing clinical CT.

Visual CT and MRI scores of bronchiectasis/wall thickening and mucus plugging were compared and ventilation MRI measures correlated with CT scores and clinical measures (spirometry, LCI and courses of IV antibiotics in prior 6 months).

Results
22 patients were scanned (median age 14 years, range 6–35).

ICC for interobserver variability in structural scores was similar in MRI to CT (0.877-0.965 vs 0.877-0.989).

There was very strong correlation between CT and MRI structural scores (table 1).
There was strong correlation between MRI ventilation/perfusion measures, CT scores and LCI2.5. No significant correlation was demonstrated with spirometry measures or courses of IV antibiotics (table 2).

**Conclusions**
MRI is now capable of providing equivalent structural information to CT with the additional benefit of clinically relevant quantitative measures of ventilation and pulmonary perfusion, without ionising radiation exposure.

Table 1 – CT/MRI component score correlation

<table>
<thead>
<tr>
<th>Measure</th>
<th>Pearson’s correlation co-efficient</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary score</td>
<td>0.864**</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bronchiectasis/wall thickening</td>
<td>0.819**</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mucus plugging</td>
<td>0.837**</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 2 – Correlation with clinical measures

<table>
<thead>
<tr>
<th>Clinical measure</th>
<th>FD-MRI perfusion fraction (Pearson’s co-efficient, p)</th>
<th>OE-MRI oxygen wash out time (skew) (Pearson’s co-efficient, p)</th>
<th>OE-MRI oxygen wash out time (kurtosis) (Pearson’s co-efficient, p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT summary score (i.e structural disease severity)</td>
<td>-0.725** &lt;0.001</td>
<td>0.675* 0.001</td>
<td>0.636* 0.001</td>
</tr>
<tr>
<td>CT hyperinflation score (%max)</td>
<td>-0.632* 0.002</td>
<td>0.561* 0.007</td>
<td>0.540 0.009</td>
</tr>
<tr>
<td>LCI2.5</td>
<td>-0.776* 0.001</td>
<td>0.712* 0.003</td>
<td>0.750* 0.001</td>
</tr>
</tbody>
</table>
ECFS 2019

The addition of sinus imaging to a quantitative CF lung MRI protocol demonstrates an association between sinus signal characteristics and lung disease severity

Authors and affiliations
T Semple1,2, C Edmondson,1,2 B Rawal1,2, J Barnett1,2, C Short1,2, G Bauman3, O Pusterla3, O Bieri3, M Tibiletti4, GJM Parker4,5, S Carr1,2, C Hogg1,2, JC Davies1,2, S Padley1,2

1. The Royal Brompton Hospital, London, UK
2. National Heart and Lung Institute, Imperial College London, UK
3. Division of Radiological Physics, Department of Radiology, University of Basel Hospital, Basel, Switzerland
4. Bioxydyn Ltd, Manchester, UK
5. University of Manchester, UK

Objectives
To explore potential relationships between maxillary sinus disease and CF lung disease.

Methods
Structural (T1, T2 and susceptibility weighted) MRI of the paranasal sinuses (10mins) was added to a quantitative CF-MRI examination. 3D segmentation software was used to quantify sinus mucosal and mucus volumes, (% of sinus volume). Susceptibility artefact (known to be associated with organisms including aspergillus and pseudomonas) was noted as present unilaterally or bilaterally.

These measures were compared with structural lung disease on CT, oxygen enhanced (OE-) and Fourier decomposition (FD-) MRI measures and clinical features (spirometry, LCI and frequency of antibiotics in the prior 6 months).

Results
22 patients were scanned (median age 14 years, range 6–35).

No significant correlation was seen between sinus mucus or mucosal volume and the above measures, but there were moderate to strong correlations between the presence and extent of sinus susceptibility artefact and bronchial wall thickening, mucus plugging and hyperinflation on CT, ventilation and pulmonary perfusion on MRI and the frequency of antibiotics (table 1).

Conclusions
Susceptibility artefact (suggesting the presence of aspergillus/pseudomonas) is associated with several indicators of worse lung disease.
Sinus MRI imaging is quick and can add value to lung protocols. Further work is needed to assess the clinical relevance of these findings.

Characters with spaces 1433 (tables count for 50 characters each row – 10 rows = 500) = total 1933

**Table 1** – Correlation between susceptibility artefact (absent, unilateral, bilateral) and clinical measures of CF lung disease severity

<table>
<thead>
<tr>
<th>Clinical measure</th>
<th>Spearman's R (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT bronchiectasis score</td>
<td>0.296 (0.181)</td>
</tr>
<tr>
<td>CT bronchial wall thickening score</td>
<td><em><em>0.522</em> (0.013)</em>*</td>
</tr>
<tr>
<td>CT mucus plugging score</td>
<td><em><em>0.508</em> (0.016)</em>*</td>
</tr>
<tr>
<td>CT hyperinflation score</td>
<td><strong>0.670</strong> <strong>(0.001)</strong></td>
</tr>
<tr>
<td>FD MRI perfusion defects</td>
<td><em><em>0.442</em> (0.045)</em>*</td>
</tr>
<tr>
<td>Lower quartile OE-MRI signal intensity change</td>
<td><em><em>-0.624</em> (0.002)</em>*</td>
</tr>
<tr>
<td>FEV₁ (%predicted)</td>
<td>-0.093 (0.681)</td>
</tr>
<tr>
<td>LCI₂.₅</td>
<td>0.169 (0.564)</td>
</tr>
<tr>
<td>IV and oral antibiotic courses in prior 6 months</td>
<td><em><em>0.581</em> (0.005)</em>*</td>
</tr>
</tbody>
</table>