Cystic Fibrosis

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KEY POINTS

Proton MRI is able to visualize the major changes in CF lung disease in a similar way to CT albeit there will be shortcomings in the detection of more subtle or smaller abnormalities. Further studies are warranted to determine whether the additional structural detail provided by CT is necessary for the evaluation of the severity and progression of CF lung disease. At the same time, proton and hyperpolarized gas MRI provide a broad spectrum of additional functional information in CF lung diseases which was previously not available to patients and clinicians. It is currently unknown whether the benefits derived from functional information about perfusion and/or ventilation by MRI will finally prevail over the mere structural information provided by CT in the clinical assessment of CF. It is conceivable that MRI and CT will be complementary as they have different advantages and disadvantages in elucidating the structure/function relationships. The MRI techniques to be applied in CF lung disease are novel and further development and studies are required to fully implement and assess their potential impact in CF.

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10.1 Introduction

Cystic fibrosis (CF) is an autosomal recessive disorder caused by gene mutations of the long arm of chromosome 7. This gene codes for the Cystic Fibrosis Transmembrane Regulator-Protein (CFTR), which functions as an anion channel. The impaired CFTR function causes aberrations of volume and ion composition of airway surface fluid, leading to viscous secretions with the consequence of bacterial colonization, chronic lung infection, air way obstruction and consecutive destruction of the lung parenchyma (Gibson et al. 2003). Despite improved understanding of the underlying pathophysiology and the introduction of new therapies, CF remains one of the most life-shortening inherited diseases in the Caucasian population. The median survival of CF-patients is up to 37.4 years in Germany (Stern et al. 2008) and 36.8 years in the USA in 2005 (Beall et al. 2005). Although CF affects most body systems, the majority of morbidity and mortality in CF-patients is due to chronic progressive lung disease.

The standard clinical tool for monitoring CF lung disease is pulmonary function testing. Pulmonary function tests provide a global measure of airflow obstruction and/or restriction, but provide no regional information about the lung function or information about lung structure. Although extremely useful, pulmonary function tests are known to be relatively insensitive to early lung disease and to small changes in the course of the disease. Furthermore, pulmonary function tests are dependent upon the effort and compliance of the patient, and are difficult for young children to perform. Yet pulmonary function tests remain one of the primary outcome measures in cystic fibrosis (CF) lung disease. A decrease of Forced Expiratory Volume in one second (FEV_1) was shown to be the most important prognostic factor for the course of the disease and the most significant predictor of mortality in a study of 673 patients with CF (Kerem et al. 1992). However, a more sensitive test that is not effort dependent and can be done by young children would be highly desirable for the assessment of cystic fibrosis lung disease.

The standard radiological tools for monitoring of lung disease in CF-patients are chest X-ray and thin-section computed tomography, evaluated using different scoring systems, e.g. the Chrispin-Norman Score (Chrispin and Norman 1974) for chest X-ray and the Bhalla or in a modified form the Helbich-Score (Bhalla et al. 1991; Helbich et al. 1999) for thin-section CT.

Chest CT provides submillimeter resolution images of lung structure and has been proposed as a possible outcome measure for CF lung disease (Brody et al. 1999, 2005; Robinson 2004). CT has been shown to be more sensitive to early CF lung disease than pulmonary function testing, likely due to the regional nature of the information obtained (Brody et al. 2005). Despite the promising early studies related to the use of CT scanning in CF, a major drawback remains the radiation exposure associated with CT (Brenner 2002, 2004; Frush et al. 2003; Huda and Vance 2007). Radiation safety concerns may ultimately limit the utility of CT in CF lung disease for applications in which multiple CT scans are required.

MRI of the chest has already been proposed as a potential imaging alternative in CF-patients in the late 1980s (Fiel et al. 1987). However, at this time, MRI technology was not able to produce comparable results to CT (Carr et al. 1995) or an adequate clinical input. Recently, new strategies have been implemented, ready to overcome the inherent difficulties of MRI of the lung, making this technique (morphological and functional MRI of the lung) especially attractive for imaging CF-patients. Recent studies compared low field MRI and chest X-ray or CT (Aboulmaali et al. 2002; Hebestreit et al. 2004). Other studies compared CT, chest X-ray and proton MRI at 1.5 T (Puderbach et al. 2007 a, b). Further studies used functional MRI techniques like oxygen enhanced MRI (Jakob et al. 2004), hyperpolarized helium (^{3}He)-MRI (Donnelly et al. 1999; Koumellis et al. 2005; Mentore et al. 2005) or contrast enhanced MR perfusion (Eichinger et al. 2006) to judge the functional impairment of the lung.

Currently, research with MRI in CF lung disease lags behind that with CT. In the following, we review the common findings of CF lung disease on conventional proton MRI and discuss some of the newer MRI techniques that provide functional information about CF lung disease.

10.2 Structural Changes of CF Lung Disease on Proton-MRI

Using common proton-MRI sequences, it is possible to visualize the structural changes of CF lung disease including bronchial wall thickening, mucus plugging, bronchiectasis, air fluid levels, consolidation and segmental/lobar destruction, albeit with lower spatial and temporal resolution than with CT (Puderbach et al. 2007a). Although not yet proven, it seems likely that the lower spatial and temporal resolution of MRI will mean

that MRI is less sensitive than CT to specific imaging features such as distal bronchiectasis. However, this does not necessarily mean that MRI will provide less useful information about CF since sensitivity to these imaging features may not be critical for the assessment of the overall burden of disease (Puderbach et al. 2007b).

10.2.1 Bronchial Wall Thickening

The visualization of bronchial wall thickening is dependent on bronchial size, bronchial wall thickness and bronchial wall signal. In MRI studies of normal lung, only the central airways to the level of lobar bronchi are routinely visualized, and some segmental bronchi can be identified. This is in contrast to CT in which the sixth to eighth generation bronchi can be identified. However in CF patients, bronchial wall thickening of small airways enhances their detectability by MRI so that small airways with thick walls can be visualized in the lung periphery (Fig. 10.1) (Puderbach et al. 2007a). Interestingly, the T2 weighted signal of the thickened bronchial walls in CF varies from high intensity to low intensity. Since water and edema produce a high T2 weighted signal, it would not be surprising if the high bronchial wall signal is due to edema possibly caused by active inflammation. This is a phenomena not observed in CT. A T1 weighted sequence allows for evaluation of the contrast enhancement of the bronchial wall. In CF, different patterns of bronchial wall contrast enhancement have been observed. In some lung regions, bronchi demonstrate striking enhancement while in other regions weak contrast enhancement is observed. This phenomenon may also be related to inflammatory activity within the bronchial wall, but further studies are required to improve our understanding of these phenomena (Fig. 10.2).

10.2.2 Mucus Plugging

Mucus plugging is well visualized by MRI due to the high T2 weighted signal of its fluid content (Fig. 10.1). Mucus plugging in central large bronchi and peripheral small bronchi can be visualized on MRI. In central mucus plugging, there is high T2 weighted signal filling the bronchus within its course. Peripheral mucus plugging shows a grape like appearance of small T2 weighted high intensity areas, similar to the "tree in bud" phenomena in small airway inflammation on CT. Mucus plugging does not show contrast enhancement, thus mucus and bronchial wall thickening can be differentiated by the combination of T2 weighted and contrast enhanced sequences. In CT, these two pathologic entities can not be reliably distinguished because the CT attenuation of mucus and soft tissue are similar.

Depending on the stage of disease, CF patients have an increased risk of hemoptysis. The localization of the origin of bleeding can be crucial for the outcome of the patient. With CT, mucus and blood are similar in attenuation and cannot be distinguished. On MRI, using the combination of T1 and T2 weighted and contrast enhanced sequences, mucus and fresh blood can be distinguished. Mucus has a high T2 weighted and low T1 weighted signal, while fresh blood has a low T2 weighted and T1 weighted signal.

10.2.3 Bronchiectasis

The MRI appearance of bronchiectasis is dependent on: bronchial level, bronchial diameter, wall thickness, wall signal and the signal within the bronchial lumen. Central bronchiectasis is well visualized on MRI independent of wall thickening or wall signal because of the anatomically thicker wall of the central bronchi. Peripheral bronchi starting at the third to fourth generation are poorly visualized by MRI except when they are pathological with bronchial wall thickening and/or mucus plugging.

10.2.4 Air Fluid Levels

Air fluid levels are indicative of active infection and occur in saccular or varicose bronchiectasis. Bronchial air fluid levels can be visualized by MRI because of the high T2 weighted signal from the fluid. However, discriminating between a bronchus with an air fluid level and one with a partial mucus plug or a severely thickened wall can be difficult. However, by evaluating the signal characteristics on T1 and T2 weighted, and contrast enhanced sequences, air fluid levels can frequently be differentiated (Fig. 10.2).

10.2.5 Consolidation

Consolidation in CF is mainly caused by alveolar filling with inflammatory fluid. The visualization of consolidation in MRI is based on the high T2 weighted signal

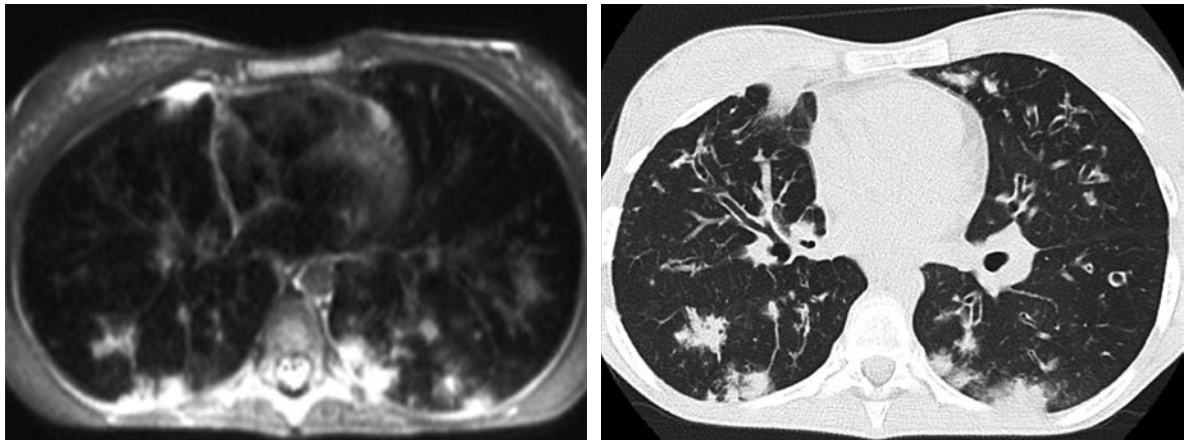

Fig. 10.1a,b. Transverse MR T2 weighted (HASTE) image (**a**) and corresponding CT image (**b**) of a 14 years old female with CF. In both images bronchial wall thickening, bronchiectasis, peripheral mucus plugging and dorsal consolidations are demonstrated. (Reprint with permisson. Altes TA, Eichinger M, Puderbach M (2007) Magnetic Resonance Imaging of the Lung in Cystic Fibrosis. Proceedings of the American Thoracic Society 4:322–325)

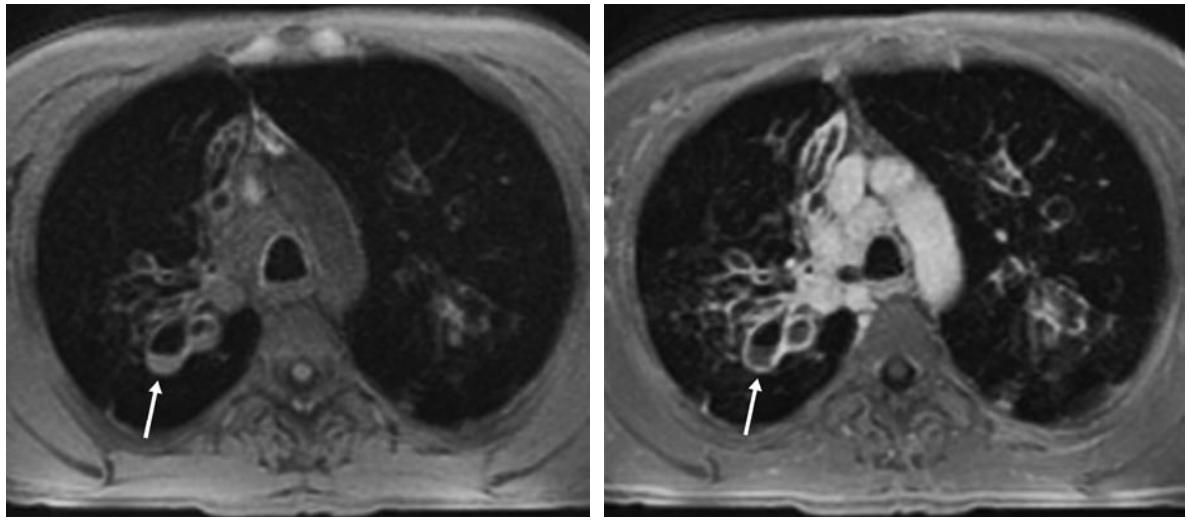

Fig. 10.2. T1 weighted MR images of a 43-year-old CF-patient (**a**) pre- and (**b**) post contrast media: contrast enhancement. The post contrast images demonstrate extensive bronchial wall enhancement and permit differentiation of a thickened wall from intrabronchial secretions, with intrabronchial fluid having an air fluid level (arrow). (Reprint with permisson. Altes TA, Eichinger M, Puderbach M (2007) Magnetic Resonance Imaging of the Lung in Cystic Fibrosis. Proceedings of the American Thoracic Society 4:322–325)

from the inflammatory fluid. Comparable to CT, MRI is able to visualize air bronchograms as low signal areas following the course of the bronchi within the consolidation (Eibel et al. 2006; Rupprecht et al. 2002). With disease progression, complete destruction of lung segments or of a complete lung lobe can occur and these destructed lung areas have a similar appearance on MRI as CT (Fig. 10.3).

10.2.6 Mosaic Pattern

On CT, a mosaic pattern of lung attenuation is a common finding in CF patients. This pattern can be observed on inspiratory scans as areas of relative hyperlucency, which can be due to air trapping or regional hypoperfusion (mosaic perfusion). These two entities can be distinguished on expiratory CT images since regions of air trapping will not change significantly in vol-

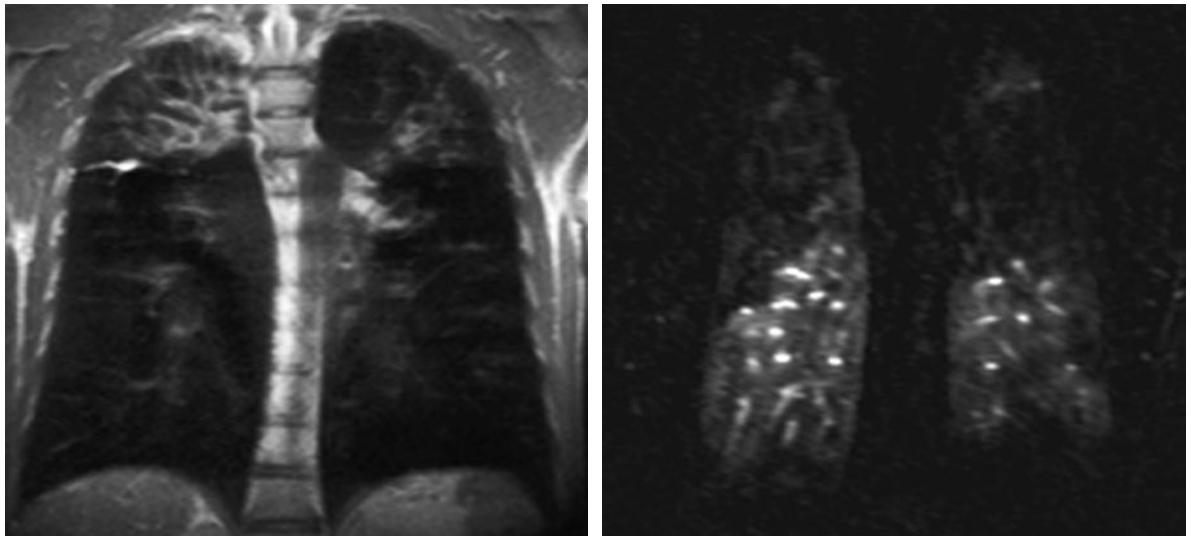

Fig. 10.3. **a** T2 weighted MR image of the patient shown in Fig 10.2 showing lobar destruction of the right upper lobe and severe bronchiectasis and wall thickening of the left lobe. **b** MR-Perfusion map of the corresponding lung region showing large perfusion defects in both upper lobes and an inhomogeneous perfusion in the peripheral lower lobe zones. (Reprint with permisson. Altes TA, Eichinger M, Puderbach M (2007) Magnetic Resonance Imaging of the Lung in Cystic Fibrosis. Proceedings of the American Thoracic Society 4:322–325)

ume and thus change little in measured CT attenuation. Conversely, in areas of hypoperfusion without air trapping, the lung attenuation will increase with expiration.

On MRI, the phenomena of air trapping is not typically apparent because even normal lung parenchyma has a very low signal, and an increase of the air content does not cause a detectable decrease in lung parenchymal signal. However, an approach to overcome this limitation might be the measurement of T1 relaxation times (Stadler et al. 2005). Mosaic perfusion also is not typically apparent on routine MR images, but MR-perfusion imaging has the potential to overcome this limitation (Eichinger et al. 2006).

10.3 Functional Lung MR Imaging

In addition to visualization of structural changes within the lung, MRI can provide functional assessment of pulmonary hemodynamics and ventilation. Pulmonary perfusion imaging typically requires the administration of gadolinium based intravenous contrast. An inhaled contrast agent, either oxygen or a hyperpolarized noble gas, is required for MR lung ventilation imaging.

10.3.1 Pulmonary Perfusion

In CF, regional ventilatory defects cause changes in regional lung perfusion due to the reflex of hypoxic vasoconstriction or tissue destruction. A variety of MRI methods have been employed to assess lung perfusion, including methods that rely on the endogenous signal from blood (Mai and Berr 1999) and others that require the administration of intravenous contrast (Hatabu et al. 1996; Levin and Hatabu 2004). Using a contrast-enhanced 3D MRI acquisition in 11 children with CF, it was found that MRI-perfusion defects correlated with the degree of tissue destruction (Fig. 10.3) (Eichinger et al. 2006). It is plausible that reversibility of perfusion defects after a therapeutic intervention might serve as an indicator for response to therapy and might differentiate between regions with reversible and irreversible disease.

10.3.2 Pulmonary Flow Measurements

Parenchymal destruction can lead to dilatation and flow augmentation of bronchial arteries. As bronchial

arteries are part of the systemic circulation, they do not contribute to blood oxygenation. Thus, a higher flow in the bronchial arteries leads to a shunt-volume, which can be assessed by MRI-based flow measurements. Decreased peak blood flow velocities in the right and left pulmonary arteries were found in 10 CF-patients as compared with 15 healthy volunteers, and this may might represent early development of pulmonary hypertension in this patient group (Ley et al. 2005). However, the clinical significance of the systemic arterial shunt volume is not yet known.

10.3.3 Oxygen-enhanced MRI

Gaseous molecular oxygen is weakly paramagnetic and serves, if inhaled in high concentrations, as a contrast medium inducing a dose-dependent T1-signal increase which can be used to assess lung ventilation (Edelman et al. 1996). In a recent study of five CF patients and five healthy volunteers, the lungs of the CF patients had an inhomogeneous appearance following the inhalation of high oxygen concentrations suggesting inhomogeneous lung ventilation, presumably due to inhomogeneous lung ventilation (Jakob et al. 2004). Since oxygen is soluble in blood, the oxygen-enhanced MR images depict a combination of ventilation and perfusion (Keilholz et al. 2008). One of the difficulties with this method is that there is a relatively low difference in signal from the lung parenchyma with 21% vs 100% inspired oxygen concentration. This results in a relatively low signal to noise level in the resulting MR oxygen-enhanced images.

10.3.4 Hyperpolarized Gas MRI

Hyperpolarized helium-3 is a gaseous MRI contrast agent that, when inhaled, provides a very high MR signal from the airspaces of the lung. Hyperpolarized helium-3 MRI can be used to obtain information about lung function using static spin density imaging (de Lange et al. 1999; Kauczor et al. 1996; Woodhouse et al. 2005), dynamic spin density imaging (Gast et al. 2002; Salerno et al. 2001) or oxygen-sensitive imaging (Eberle et al. 1999; Lehmann et al. 2004). In addition, lung structure at the alveolar and distal airway level can be assessed using diffusion-weighted imaging (Morbach et al. 2005; Salerno et al. 2002). The majority of studies investigating the use of hyperpolarized helium-3 MRI in CF have used static spin density imaging. Static spin density imaging, often referred to as ventilation imaging, is performed during a breath hold following the inhalation of the hyperpolarized helium-3 gas (Altes et al. 2004). Well ventilated areas of the lung receive more helium gas and thus appear brighter than poorly ventilated areas of the lung on the MR images. Typically, the entire lung volume can be imaged in a 4–20-s breath hold, but the in plane spatial resolution is typically in the order of 3 mm and thus lower than with CT. Since children have smaller lungs than adults, the breath hold duration is shorter for children, and hyperpolarized helium MRI has been successfully performed in children as young as 4 years old without sedation (Altes et al. 2008).

The first report of hyperpolarized helium-3 MRI in CF found extensive abnormalities of ventilation on static spin density images in four subjects with moderate to severe pulmonary CF and abnormal FEV1 % predicted (Donnelly et al. 1999).

Also, using static spin density imaging, a study of 31 subjects (16 healthy volunteers and 15 patients with CF) found the CF patients had a significantly higher number of ventilation defects on helium MRI than the normal subjects (Mentore et al. 2005). Even the four CF subjects with a normal FEV1 % predicted had significantly higher ventilation defect score than the normal subjects, suggesting hyperpolarized gas MRI may be more sensitive to ventilation abnormalities than spirometry. Moderate correlations between the ventilation defect score and spirometry were found (Fig. 10.4). In this study, eight of the CF patients underwent a therapeutic intervention first with nebulized albuterol followed by DNase and chest physical therapy. Repeated helium-3 MRI after therapy showed changes in the ventilation defect score. Thus, this study demonstrated the feasibility of using hyperpolarized helium-3 MRI as an outcome measure in the evaluation of airway clearance techniques.

A recent study of 18 children with CF (age 5 to 17 years) confirmed that hyperpolarized helium-3 MRI can be performed by children with CF and found moderate to weak correlations between static spin density hyperpolarized helium-3 MRI and spirometry or chest X-ray (Van Beek et al. 2007). It was the opinion of the authors that the weak correlations were the result of a greater sensitivity of hyperpolarized helium-3 MRI to ventilatory abnormalities than spirometry or chest X-ray. Another recent study compared static spin density helium-3 MRI with CT in eight adults with CF and found a strong correlation between the MRI percent ventilation and the Bhalla score (Bhalla et al. 1991) from CT (McMahon et al. 2006). Further, the correlations between hyperpolarized helium-3 MRI and

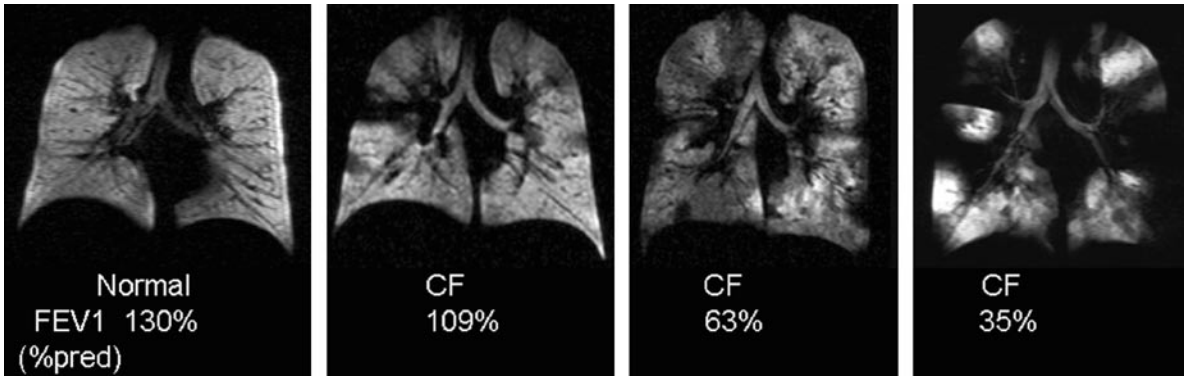

Fig. 10.4. Coronal hyperpolarized helium MR ventilation images from a normal subject and three different patients with CF. The CF patients have more ventilation defects than the normal subject, and the number of defects increases with worsening FEV1 (% predicted). (Reprint with permisson. Altes TA, Eichinger M, Puderbach M (2007) Magnetic Resonance Imaging of the Lung in Cystic Fibrosis. Proceedings of the American Thoracic Society 4:322–325)

spirometry were stronger than those between CT and spirometry. Thus, this study suggests that hyperpolarized helium-3 MRI may represent a safe alternative to CT for the evaluation of CF lung disease.

To date, little work has been done in CF evaluating the other mechanisms of contrast possible with hyperpolarized helium-3 MRI including dynamic ventilation (Koumellis et al. 2005), diffusion weighted, or oxygen sensitive imaging. Further, the special equipment required to perform hyperpolarized helium-3 MRI is both expensive and not yet widely available, and hyperpolarized helium-3 as a MRI contrast agent has not yet been approved by the Food and Drug Administration, so use of this technique is currently limited to a few academic medical centers.

10.4 Future Directions for MRI in CF

MRI of the lung is a promising but relatively new field. Thus, the majority of studies exploring lung MRI in CF have involved small numbers of subjects and have been observational, simply describing the imaging findings of CF. One of the issues related to using imaging as an endpoint is that the images themselves are not an endpoint. Typically information about the disease in question has to be extracted from the images. For example, nodal size is an imaging-based endpoint used in assessing metastatic disease. With chest CT, a variety of scoring systems for CF have been proposed to do just this, reduce a large set of images to a single number or small set of numbers that characterize the disease severity/activity. The development of imaging-based endpoints or scores for lung MRI in CF is in its infancy. First the salient imaging features must be determined and a method, based on either human scoring or computer based image analysis, devised for quantifying these features. For proton MRI, methods based on the CT scoring schemes could be developed. For the functional lung MRI techniques, new analysis methods will need to be developed and specifically validated in CF. It has been proposed that to validate an endpoint or outcome surrogate, it must be shown to be accurate, reproducible, feasible over time, biologically plausible, reflect the severity of disease, improve rapidly with effective treatment, and correlated with true clinical outcomes (Brody 2004; Smith et al. 2003). Of these characteristics, lung MRI is biologically plausible and likely feasible over time. Clinical trials are required to determine whether endpoints derived from any of the lung MRI methods discussed above posses the remainder of these characteristics.

References

Abolmaali N, Schmidt H, Anjorin A, Posselt H-G, Vogl TJ (2002) Chrispin-Norman-score and Bhalla-score of patients with cystic fibrosis: Comparative study of chest radiographs and MR-Imaging. Presented at European Congress of Radiology 2002

Altes TA, Rehm PK, Harrell F, Salerno M, Daniel TM, de Lange EE (2004) Ventilation imaging of the lung: comparison of hyperpolarized helium-3 MR imaging with Xe-133 scintigraphy. Acad Radiol 11:729–734

Altes T, Mata J, Froh D, Paget-Brown AO, de Lange EE, Mugler JP (2008) Abnormalities of lung structure in children with bronchopulmonary dysplasia as assessed by diffusion hyperpolarized helium-3 MRI. Presented at International Society of Magnetic Resonance in Medicine 2008

Beall R J (2005) Executive Vice President for Medical Affairs of the Cystic Fibrosis Foundation (2005) Statement at NACFC 2005

Bhalla M, Turcios N, Aponte V, Jenkins M, Leitman BS, McCauley DI, Naidich DP (1991) Cystic fibrosis: scoring system with thin-section CT. Radiology 179:783–788

Brenner DJ (2002) Estimating cancer risks from pediatric CT: going from the qualitative to the quantitative. Pediatr Radiol 32:228–231

Brenner DJ (2004) Radiation risks potentially associated with low-dose CT screening of adult smokers for lung cancer. Radiology 231:440–445

Brody AS (2004) Scoring systems for CT in cystic fibrosis: who cares? Radiology 231:296–298

Brody AS, Molina PL, Klein JS, Rothman BS, Ramagopal M, Swartz DR (1999) High-resolution computed tomography of the chest in children with cystic fibrosis: support for use as an outcome surrogate. Pediatr Radiol 29:731–735

Brody AS, Tiddens HA, Castile RG, Coxson HO, de Jong PA, Goldin J, Huda W, Long FR, McNitt-Gray M, Rock M, Robinson TE, Sagel SD (2005) Computed tomography in the evaluation of cystic fibrosis lung disease. Am J Respir Crit Care Med 172:1246–1252

Carr DH, Oades P, Trotman-Dickenson B, Mohiaddin R, Wells AU, Bush A (1995) Magnetic resonance scanning in cystic fibrosis: comparison with computed tomography. Clin Radiol 50:84–89

Chrispin AR, Norman AP (1974) The systematic evaluation of the chest radiograph in cystic fibrosis. Pediatr Radiol 2:101–106

de Lange EE, Mugler JP III, Brookeman JR, Knight-Scott J, Truwit JD, Teates CD, Daniel TM, Bogorad PL, Cates GD (1999) Lung air spaces: MR imaging evaluation with hyperpolarized 3He gas. Radiology 210:851–857

Donnelly LF, MacFall JR, McAdams HP, Majure JM, Smith J, Frush DP, Bogorad P, Charles HC, Ravin CE (1999) Cystic fibrosis: combined hyperpolarized 3He-enhanced and conventional proton MR imaging in the lung--preliminary observations. Radiology 212:885–889

Eberle B, Weiler N, Markstaller K, Kauczor HU, Deninger A, Ebert M, Grossmann T, Heil W, Lauer LO, Roberts TPL, Schreiber WG, Surkau R, Dick WF, Otten EW, Thelen M (1999) Analysis of intrapulmonary O-2 concentration by NIR imaging of inhaled hyperpolarized helium-3. J Appl Physiol 87:2043–2052

Edelman RR, Hatabu H, Tadamura E, Li W, Prasad PV (1996) Noninvasive assessment of regional ventilation in the human lung using oxygen-enhanced magnetic resonance imaging. Nat Med 2:1236–1239

Eibel R, Herzog P, Dietrich O, Rieger CT, Ostermann H, Reiser MF, Schoenberg SO (2006) Pulmonary abnormalities in immunocompromised patients: comparative detection with parallel acquisition MR imaging and thin-section helical CT. Radiology 241:880–891

Eichinger M, Puderbach M, Fink C, Gahr J, Ley S, Plathow C, Tuengerthal S, Zuna I, Muller FM, Kauczor HU (2006) Contrast-enhanced 3D MRI of lung perfusion in children with cystic fibrosis-initial results. Eur Radiol 16:2147–2152

Fiel SB, Friedman AC, Caroline DF, Radecki PD, Faerber E, Grumbach K (1987) Magnetic resonance imaging in young adults with cystic fibrosis. Chest 91:181–184

Frush DP, Donnelly LF, Rosen NS (2003) Computed tomography and radiation risks: what pediatric health care providers should know. Pediatrics 112:951–957

Gast KK, Puderbach MU, Rodriguez I, Eberle B, Markstaller K, Hanke AT, Schmiedeskamp J, Weiler N, Lill J, Schreiber WG, Thelen M, Kauczor HU (2002) Dynamic ventilation (3)He-magnetic resonance imaging with lung motion correction: gas flow distribution analysis. Invest Radiol 37:126–134

Gibson RL, Burns JL, Ramsey BW (2003) Pathophysiology and management of pulmonary infections in cystic fibrosis. Am J Respir Crit Care Med 168:918–951

Hatabu H, Gaa J, Kim D, Li W, Prasad PV, Edelman RR (1996) Pulmonary perfusion: qualitative assessment with dynamic contrast-enhanced MRI using ultra-short TE and inversion recovery turbo FLASH. Magn Reson Med 36:503–508

Hebestreit A, Schultz G, Trusen A, Hebestreit H (2004) Follow-up of acute pulmonary complications in cystic fibrosis by magnetic resonance imaging: a pilot study. Acta Paediatr 93:414–416

Helbich TH, Heinz-Peer G, Eichler I, Wunderbaldinger P, Gotz M, Wojnarowski C, Brasch RC, Herold CJ (1999) Cystic fibrosis: CT assessment of lung involvement in children and adults. Radiology 213:537–544

Huda W, Vance A (2007) Patient radiation doses from adult and pediatric CT. AJR Am J Roentgenol 188:540–546

Jakob PM, Wang T, Schultz G, Hebestreit H, Hebestreit A, Hahn D (2004) Assessment of human pulmonary function using oxygen-enhanced T1 imaging in patients with cystic fibrosis. Magn Reson Med 51:1009–1016

Kauczor HU, Hofmann D, Kreitner KF, Nilgens H, Surkau R, Heil W, Potthast A, Knopp MV, Otten EW, Thelen M (1996) Normal and abnormal pulmonary ventilation: visualization at hyperpolarized He-3 MR imaging. Radiology 201:564–568

Keilholz S, Knight-Scott J, Mata J, Fujiwara N, Altes T, Berr S, Hagspiel K (2008) The contributions of ventilation and perfusion in O2-enhanced MRI. Presented at International Society of Magnetic Resonance in Medicine 2008

Kerem E, Reisman J, Corey M, Canny GJ, Levison H (1992) Prediction of mortality in patients with cystic fibrosis. N Engl J Med 326:1187–1191

Koumellis P, van Beek EJ, Woodhouse N, Fichele S, Swift AJ, Paley MN, Hill C, Taylor CJ, Wild JM (2005) Quantitative analysis of regional airways obstruction using dynamic hyperpolarized 3He MRI-preliminary results in children with cystic fibrosis. J Magn Reson Imaging 22:420–426

Lehmann F, Eberle B, Markstaller K, Gast KK, Schmiedeskamp J, Blumler P, Kauczor HU, Schreiber WG (2004) A software program for quantitative analysis of alveolar oxygen partial pressure (p(A)O(2)) with oxygen-sensitive (3)He-MRI. Rofo 176:1390–1398

Levin DL, Hatabu H (2004) MR evaluation of pulmonary blood flow. J Thorac Imaging 19:241–249

Ley S, Puderbach M, Fink C, Eichinger M, Plathow C, Teiner S, Wiebel M, Muller FM, Kauczor HU (2005) Assessment of hemodynamic changes in the systemic and pulmonary arterial circulation in patients with cystic fibrosis using phase-contrast MRI. Eur Radiol 15:1575–1580

Mai VM, Berr SS (1999) MR perfusion imaging of pulmonary parenchyma using pulsed arterial spin labeling techniques: FAIRER and FAIR. J Magn Reson Imaging 9:483–487

McMahon CJ, Dodd JD, Hill C, Woodhouse N, Wild JM, Fichele S, Gallagher CG, Skehan SJ, van Beek EJR, Masterson JB (2006) Hyperpolarized (3)helium magnetic resonance ventilation imaging of the lung in cystic fibrosis: comparison with high resolution CT and spirometry. Eur Radiol 16:2483–2490

Mentore K, Froh DK, de Lange EE, Brookeman JR, Paget-Brown AO, Altes TA (2005) Hyperpolarized HHe 3 MRI of the lung in cystic fibrosis: assessment at baseline and after bronchodilator and airway clearance treatment. Acad Radiol 12:1423–1429

Morbach AE, Gast KK, Schmiedeskamp J, Dahmen A, Herweling A, Heussel CP, Kauczor HU, Schreiber WG (2005) Diffusion-weighted BM of the lung with hyperpolarized helium-3: a study of reproducibility. J Magn Reson Imaging 21:765–774

Puderbach M, Eichinger M, Gahr J, Ley S, Tuengerthal S, Schmahl A, Fink C, Plathow C, Wiebel M, Muller FM, Kauczor HU (2007a) Proton MRI appearance of cystic fibrosis: comparison to CT. Eur Radiol 17:716–724

Puderbach M, Eichinger M, Haeselbarth J, Ley S, Kopp-Schneider A, Tuengerthal S, Schmaehl A, Fink C, Plathow C, Wiebel M, Demirakca S, Muller FM, Kauczor HU (2007b) Assessment of morphological MRI for pulmonary changes in cystic fibrosis (CF) patients – comparison to thin-section CT and chest X-ray. Invest Radiol 42:715–725

Robinson TE (2004) High-resolution CT scanning: potential outcome measure. Curr Opin Pulm Med 10:537–541

Rupprecht T, Bowing B, Kuth R, Deimling M, Rascher W, Wagner M (2002) Steady-state free precession projection MRI as a potential alternative to the conventional chest X-ray in pediatric patients with suspected pneumonia. Eur Radiol 12:2752–2756

Salerno M, Altes TA, Brookeman JR, de Lange EE, Mugler JP (2001) Dynamic spiral MRI of pulmonary gas flow using hyperpolarized He-3: Preliminary studies in healthy and diseased lungs. Magn Reson Med 46:667–677

Salerno M, de Lange EE, Altes TA, Truwit JD, Brookeman JR, Mugler JP (2002) Emphysema: hyperpolarized helium 3 diffusion MR imaging of the lungs compared with spirometric indexes – initial experience. Radiology 222:252–260

Smith JJ, Sorensen AG, Thrall JH (2003) Biomarkers in imaging: realizing radiology's future. Radiology 227:633–638

Stadler A, Jakob PM, Griswold M, Barth M, Bankier AA (2005) T1 mapping of the entire lung parenchyma: influence of the respiratory phase in healthy individuals. J Magn Reson Imaging 21:759–764

Stern M, Wiedemann B, Wenzlaff P (2008) From registry to quality management: the German Cystic Fibrosis Quality Assessment project 1995-2006. Eur Respir J 31:29–35

Van Beek EJR, Hill C, Woodhouse N, Fichele S, Fleming S, Howe B, Bott S, Wild JM, Taylor CJ (2007) Assessment of lung disease in children with cystic fibrosis using hyperpolarized 3-Helium MRI: comparison with Shwachman score, Chrispin-Norman score and spirometry. Eur Radiol 17:1018–1024

Woodhouse N, Wild JM, Paley MNJ, Fichele S, Said Z, Swift AJ, van Beek EJR (2005) Combined helium-3/proton magnetic resonance imaging measurement of ventilated lung volumes in smokers compared to never-smokers. J Magn Reson Imaging 21:365–369