Lung MRI in Parenchymal Disease

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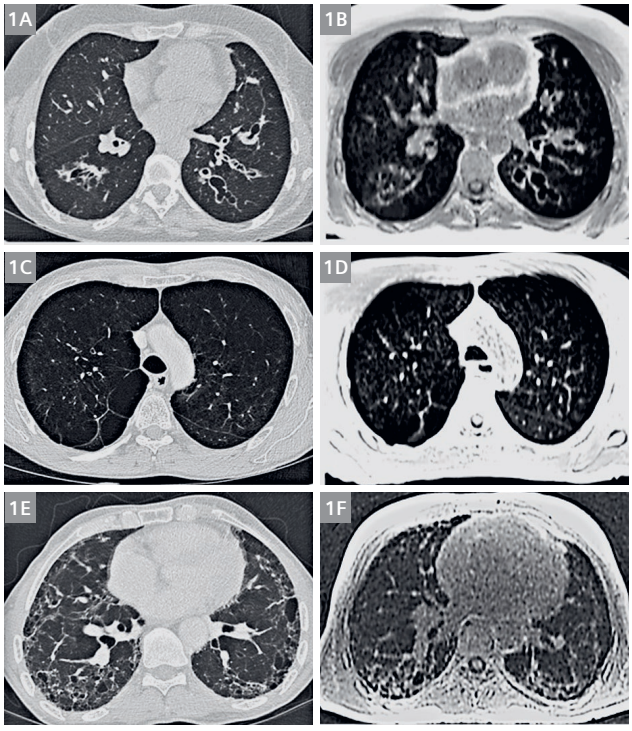
Introduction

Lung MRI has long been considered beyond the scope of MR examinations due to specific technological challenges. These include very low lung proton content, susceptibility artifacts at alveolar and parenchymal interfaces, and cardio-respiratory motions. However, recent technological solutions have emerged that could improve the clinical application of lung MRI. MRI is a radiation-free imaging modality that offers the possibility of combining both morphological and functional information, including tissue contrast characterization. This is important in an era where novel therapies have revolutionized the management of patients, which can lead to an increased need for repeat imaging to assess response to a certain treatment. In addition, artificial intelligence could allow advanced combination of data to better phenotype patients and/or predict disease outcome, since it goes beyond just morphological information. Thus, lung MRI may eventually prove a powerful tool to determine the full complexity of lung diseases that are still by no means well understood. In the following article, we summarize the most recent advances in lung MRI and give examples from our own clinical experience, with a particular focus on the potential benefit of lung MRI for routine clinical use. Images have been acquired using a 1.5T MAGNETOM Aera MRI scanner.

1. Morphological MRI

1.1 Lung MRI with ultrashort echo time

The most prominent development in morphological MRI is the advent of 3-dimensional (3D) sequences using Ultrashort Echo Time (UTE)[1] [1, 2] or even Zero Echo Time (ZTE)[1]. These sequence techniques overcome the technical difficulty of lung MRI due to the very fast decay of the lung signal, caused by the short T2* of the lung parenchyma, by shortening the TE down to a few microseconds. Conventional MR sequences use echo times in the order of magnitude of the millisecond. Imaging quality similar to that of a CT scan has been demonstrated using 3D UTE MRI in airway [3], interstitial lung disease [2] or lung nodules [4]. To date, two main sequence acquisition schemes have been developed to capture the *k*-space either with spheres or stacks of spirals. Recent evaluation has shown that a spherical mode of acquisition provides clearer detail and a higher signal than stacks of spirals. However, the 3D UTE Spiral VIBE prototype sequence[1] comprises a fully automated respiratory synchronization was possible using the stack-of-spirals sequence. This was found to be more robust to motion and therefore potentially suitable for routine applications [2].



1 **Morphological MRI**
CT **(1A, C, E)** and 3D UTE spiral VIBE sequence[1] **(1B, D, F)** acquired in a patient with cystic fibrosis (1A, B); chronic obstructive pulmonary disease (1C, D); and idiopathic fibrosis (1E, F). Images 1A and B show indications of proximal airway alteration, such as bronchiectasis, wall thickening, and mucus plugs. Images 1C and D show destruction of the lung parenchyma. This can be seen as hypoattenuating areas using CT imaging (1C) or hyposignal intensity on MRI (1D). Images 1E and F show interstitial modifications such as honeycombing, reticulation, and traction bronchiectasis. Note the good visual agreement between CT and 3D UTE MRI to depict structural alterations at high resolution.

[1] *WIP, the product is currently under development and is not for sale in the U.S. and in other countries. Its future availability cannot be ensured.*

1.2 Qualitative and quantitative imaging of airways

Imaging of airways is one the most challenging areas of lung MRI. Indeed, imaging of the central bronchi requires high spatial resolution to achieve clear distinction between the airway wall and airway lumen. Conversely, small airway disease requires high contrast resolution to allow identification of parenchymal intensities lower than that of the normal lung, as a surrogate of small airway disease alterations. Radiation-free evaluation of patients with chronic airway diseases such as cystic fibrosis or asthma, has been used to create an MR scores of disease severity.

3D UTE could be used not only to visualize structural abnormalities qualitatively (Fig. 1) but also to quantify the extent of disease (Fig. 2). In this context, quantification of central airway remodeling has recently been reported in 3D [5], as well as volumetric quantification of emphysema in patients with COPD [6]. These quantitative measurements may be beneficial to improve the reproducibility and the reliability of structural evaluation, as compared with visual analysis.

1.3 Interstitial lung disease

3D UTE allows visualization of visual parenchymal alterations such as honeycombing, reticulation, traction bronchiectasis, cysts or ground glass opacities, with similar reproducibility to that of gold standard CT imaging (Fig. 2). Imaging plays a pivotal role in the management of patients with interstitial lung disease (ILD), and MRI may also play a role in improved phenotyping of patients.

1.4 Evolution of respiratory synchronization.

Image acquisition with 3D UTE with high isotropic resolution still takes several minutes and therefore respiratory motion compensation is needed. Early respiratory synchronization has been proposed using external devices such as a belt. These devices were shown to be inefficient at suppressing motion adequately in certain cases such as obese patients or patients with irregular breathing [2]. More recently, respiratory synchronization using fully automated sequences makes this potentially suitable for routine applications [7]. Novel applications using 4D MRI with dynamic lung MR imaging have also been reported [8]. A further recent approach has shown that MRI could be applied *in vivo* using pulsatile flow ventilation with breath-hold for 10 minutes or longer [9].

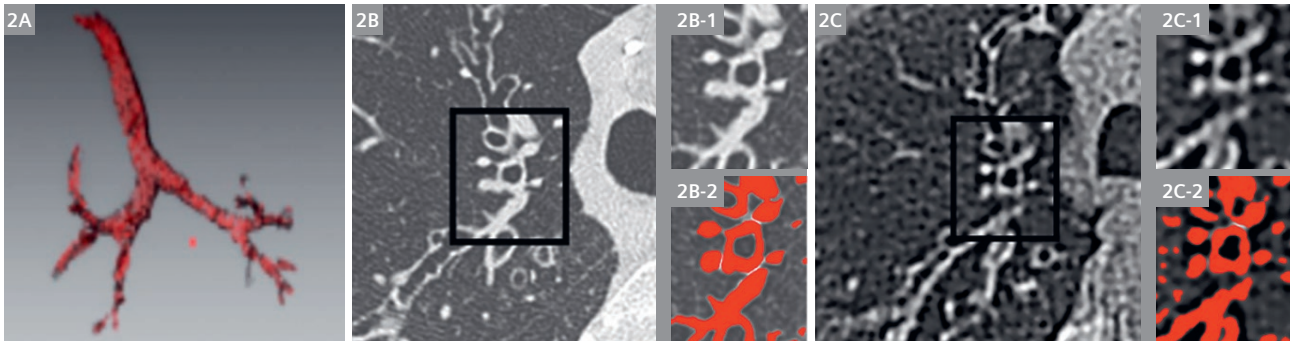
2. Contrast MRI

2.1 T1- and T2-weighted MR sequences

The true benefit of MRI is the ability to add tissue contrast characterization to purely morphological information. Critical phenomena related to inflammation or remodeling processes can be seen, which can allow clinicians to adapt or follow-up treatment.

At our institution, we use the T1 VIBE sequence, which is a gradient echo sequence using low flip angle and rapid repetition time. A spoiler removes transverse magnetization and offers strong T1 weighting. The main advantage of T1 VIBE is the rapid acquisition, enabling T1 information to be obtained within an apnea of less than 15 seconds.

To obtain T2 contrast information, the T2 BLADE sequence is one of the most commonly used sequence for lung imaging. The blade-like trajectory through *k*-space offers some unique advantages. The center of *k*-space, which contains the highest signal amplitude and contributes most to image contrast, is oversampled, meaning that the signal-to-noise and contrast-to-noise ratios are high. Oversampling in this region also leads to redundant information, meaning that the data for new each blade can be compared to the data from previous blades for consistency. If the patient moves between blades, the data for the second blade can be corrected (or even completely discarded) based on how anomalous its key information appears. Owing to the need for long TE and TR, the sequence is



2 Morphological MRI
Quantitative measurement of central airways using 3D UTE MRI. Owing to the 3D isotropic resolution of the 3D UTE sequence and the contrast difference between bronchial air and the lung parenchyma, a 3D extraction of the bronchial tree from MRI was possible **(2A)**. Images 2B and 2C represent the right superior lobe of a cystic fibrosis patient using CT imaging **(2B)** and 3D UTE MRI **(2C)**. The black rectangle indicates the area of magnification of the right apical segmental bronchus as shown on 2B-1 (CT imaging) and 2C-1 (MRI), respectively. The high spatial resolution of MRI makes automated quantification of the bronchial wall and lumen areas feasible (shown here in red on 2B-2 and 2C-2).

T2-weighted. Moreover, respiratory synchronization using a navigator positioned on the diaphragm also allows the removal of respiratory motion artifacts.

2.2 Characterization of airway inflammation

Acute inflammation of the airways causes increased water and cellular content within the airway wall and/or lumen, which results in increased signal in a T2-weighted acquisition [10, 11]. A T2 BLADE sequence enables a more sensitive detection of airway inflammation (Fig. 3). Combining T1 and T2 sequences has also been demonstrated as efficient in increasing the specificity of evaluation. In a study conducted in 110 patients with cystic fibrosis, mucus impaction with the so-called IMIS sign (Inverted Mucoid Impaction Signal) was found to be 100% specific for the diagnosis of allergic broncho-pulmonary aspergillosis (ABPA) (Fig. 4). This is particularly important in CF patients, since ABPA requires the use of corticosteroids instead of antibiotics [12]. A quantitative measurement of T1 or T2 mapping is also possible using novel sequences, combining both morphological T2 and T2 quantification [13] (Fig. 5).

2.3 Detection of inflammation in ILD

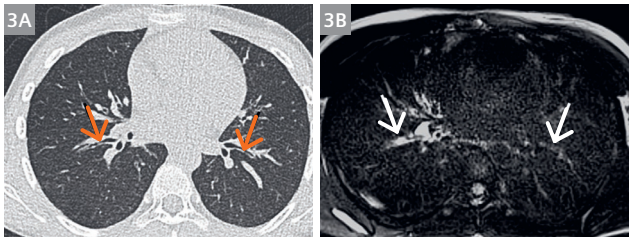
ILD may also benefit from the use of contrast characterization. Lung inflammation can be visualized accurately using T2 contrast.

Specific evaluation can also be found in some disease conditions, where an increase in iron can modify the signal from the lung parenchyma.

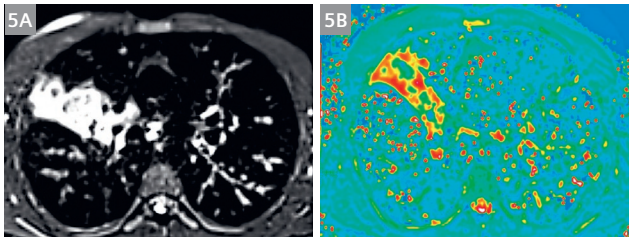
Characterization and quantification of T1 and T2 are also possible using novel MR sequences and mapping of the lung signal [13, 14]. These quantifications may open up the possibility of quantitative evaluations in ILD to assess disease extent or severity, especially in patients undergoing specific treatment (Fig. 6).

2.4. Diffusion MRI

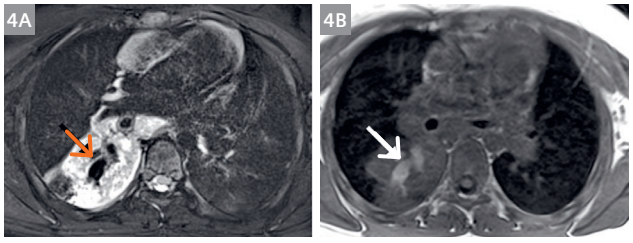
Diffusion MRI can be used to differentiate between those areas of inflammation associated with increased cellular content and those related to increased vasogenic edema, i.e. free water content (Fig. 7). Combining the extent of T2-weighted diffusion MRI visually has been shown to discriminate CF patients with respiratory exacerbation



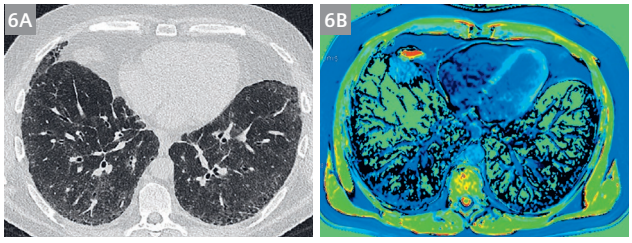
3 **Contrast MRI**
CT scan **(3A)** and T2 BLADE MRI **(3B)** of a 9-year-old female with cystic fibrosis during respiratory exacerbation. On the CT image, orange arrows indicate segmental bronchi that do not appear morphologically different. On the MR image, there is a marked hyperintense T2 signal from the right-sided bronchi compared with the left bronchi (white arrows) indicating an acute inflammatory state of the right lung.



5 T2 radial TSE **(5A)** and corresponding T2 mapping reconstruction **(5B)** in a male with cystic fibrosis and respiratory exacerbation. Both morphological information (5A) and signal intensity information (5B) are available to assess the disease severity and follow-up treatment, both qualitatively (5A) and quantitatively (5B).



4 T2-weighted **(4A)** and T1-weighted **(4B)** MRI of a young female with cystic fibrosis. There is acute lung consolidation of the right lower lobe shown by hyper T2 and hypo T1 contrasts. Conversely, there is a large bronchocele within the lung infiltrate with complete reversal of contrast. This is indicated by the hypo T2 (orange arrow) and hyper T1 (white arrow) contrasts. The inverted mucus impaction signal (IMIS) is specific to the diagnosis of allergic bronchopulmonary aspergillosis, which requires corticosteroid treatment.



6 CT scan **(6A)** and postcontrast-enhaned T1 mapping **(6B)** in a young male with severe sarcoidosis. There is diffuse ground glass opacity on image 6A. On image 6B, the postcontrast reduction of T1 values is predominantly located within the peribronchovascular and subpleural regions. This indicates the lymphatic dominance of lesions, which is in agreement with the physiopathology of the disease. Note that the degree of T1 reduction can be quantified on image 6B.

[15]. However, the spatial resolution of Diffusion MRI does not allow the assessment of fine structures such as bronchial wall and mucus plugs, whereas the signal visible on Diffusion MRI relates to both a T2-shinethrough effect and a diffusion effect [16].

3. Functional MRI

3.1 Contrast-enhanced MRI of perfusion

One of the most widely documented applications of functional MRI is MRI perfusion in chronic airway disease. In cystic fibrosis, it has been proposed that this evaluation technique could be part of the disease scoring of severity. Variations in treatment and applicability to children as young as 2 or 3 years old have been consistently demonstrated [17, 18]. Nevertheless, developing non-contrast-enhanced MR would increase the clinical applicability [16].

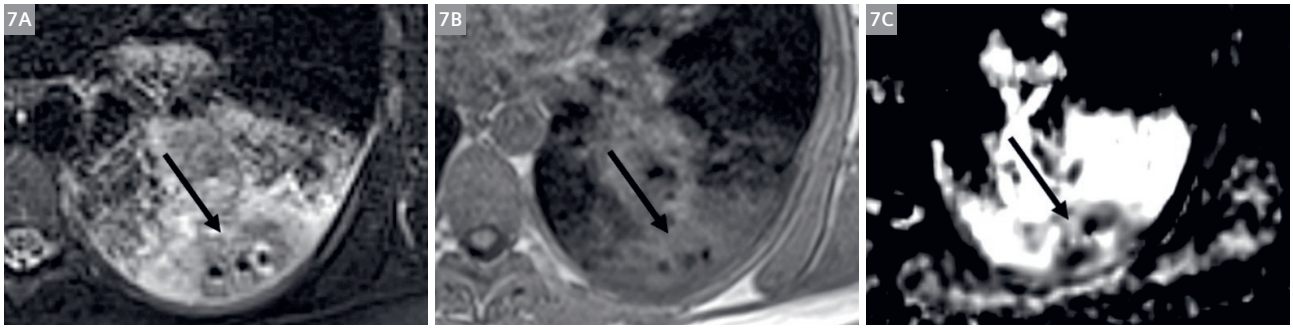
3.2 Contrast-enhanced MRI of ventilation

MRI of ventilation using noble gases has been a major breakthrough in the study of small airway disease impairment providing an exquisite level of details [20, 21]. Fusion between ventilation maps and morphological UTE volumes has been proposed to assess disease severity [22]. However, specialist MR scans are needed and the examination is cost-intensive.

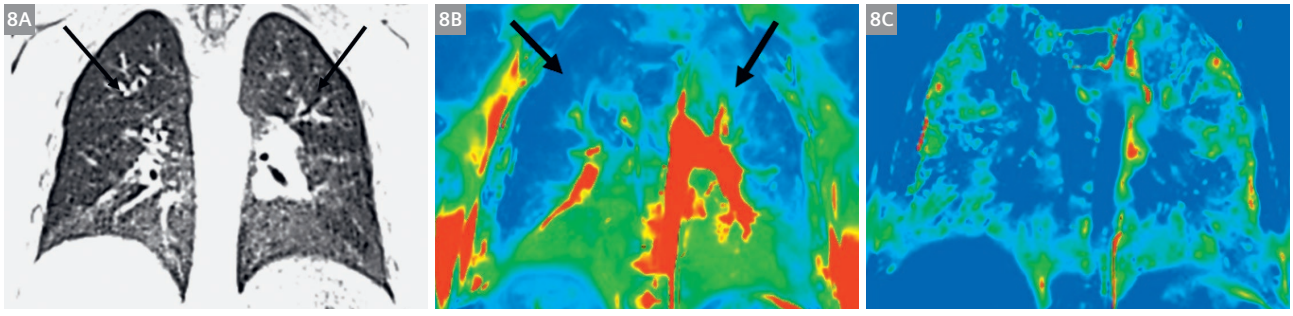
Ventilation MRI using oxygen has also shown potential in cases of lung allograft rejection [23] or cystic fibrosis [24]. However, oxygen is non-specific between ventilation and perfusion.

3.3 Non contrast-enhanced MRI of ventilation and perfusion

A promising development in functional MRI is the Fourier decomposition MRI [25]. This technique has been shown to generate ventilation-weighted and perfusion-weighted maps, without any contrast product injection or ventilation (Fig. 8). The technique has been validated against hyperpolarized ^{3}He and dynamic contrast-enhanced MRI [26]. Another variant is SENCEFUL MRI [27]. However, this technique is 2D only and may require a very long acquisition time to cover an entire lung. Evaluation in patients with lung disease could be helpful by adding deeper insights into small airway disease in patients with asthma, COPD, or cystic fibrosis.



7 **Contrast MRI**
T2 BLADE **(7A)**, T1 VIBE **(7B)** and Diffusion **(7C)** MR sequences in a female with cystic fibrosis and respiratory exacerbation. There is an area of intra-parenchymal air within a lung consolidation of the left lower lobe (black arrow). The diffusion coefficient map in C confirms a restricted area within a water-filled consolidation. This is compatible with an abscess that requires intensive antibiotic therapy.



8 **Functional MRI**
3D UTE **(8A)** and Fourier transform reconstruction of lung perfusion **(8B)** and ventilation **(8C)** in a young female with cystic fibrosis and respiratory exacerbation in a coronal view. Black arrows show areas of reduced perfusion on image B, with a regional distribution resembling the areas of hypointensities on image 8A. However, there are multiple ventilation defects on image 8C that do not perfectly match the perfusion defects, reflecting the two different types of information.

3.4. Contrast-enhanced MRI in ILD

A few reports exist on the use of contrast agents in ILD in humans. However, better characterization of tissue components related to fibrosis (Fig. 9), inflammation or vascular disease could be expected from MRI [28].

4. Proposed lung MR protocol

Physicians can, of course, always adapt their protocol according to the clinical context. For routine application, the main constraints are imaging quality, acquisition time, and the tolerability of the patient, especially those with breathing difficulties.

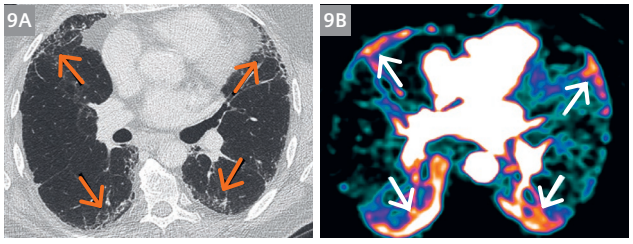
Therefore, the prototype 3D UTE Spiral VIBE[1] pulse sequence has a strong argument for consideration as the core of any MR protocol dedicated to lung imaging. Indeed, 3D UTE delivers morphological information similar to that from a CT scan. Isotropic voxel dimension enables 3D reformations in all directions, preventing the need for repeated 2D acquisitions. The lack of repetition of MR sequences leads to a dramatic reduction in acquisition time. This makes the procedure more tolerable for the patient, especially when repetition of 2D sequences may require repeated breath-holding maneuvers. In addition to the information provided on central airways, UTE MRI also visualizes variations in the signal of the lung parenchyma as a surrogate for distal airway remodeling.

Moreover, simple tissue contrast characterization is possible using MR sequences such as T1 VIBE and T2 BLADE. The former lasts 15 seconds within a single breath-hold and the latter usually 3 to 4 minutes in free breathing.

Vascular assessment is often beneficial for follow-up of patients with chronic lung disease, owing to the need for catheter placement that may potentially lead to complications due to thrombus. A quick overview of the vascular trunks and bed can be provided, for example using the TrueFISP sequence.

Finally, functional MRI with or without contrast product injection or inhalation may be used either in a specific disease condition or to answer research questions.

Table 1 summarizes the proposed standardized lung MR protocol including 3D UTE MRI, T1 VIBE, T2 BLADE, and TrueFISP sequences as a core, in 8 to 10 minutes, and without contrast media exposure, and then with additional functional sequences adapted to the clinical context.



9 CT image **(9A)** and first-pass perfusion MRI **(9B)** in an older male with idiopathic pulmonary fibrosis. Orange arrows on the CT image indicate areas of honeycombing. There is marked increased velocity in first-pass perfusion in the areas of honeycombing on image 9B (white arrows).

Conclusion

Lung MRI is a powerful tool to assess and follow-up lung diseases without the use of ionizing radiation. Recent technological innovations allow the robust evaluation of both morphological and functional information with direct implications for clinical routine use.

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Core protocol	Sequence	Acquisition time	Expected information	Typical clinical use
Morphology	3D UTE Spiral VIBE[1]	6 minutes	Isotropic high resolution with 3D reformations	Any
Contrast	T1 VIBE	15 seconds	T1 contrast	Any
	T2 BLADE	2–4 minutes	T2 contrast	Any
	TrueFISP	20 seconds	Vascular contrast	Any
Clinically oriented sequences				
Perfusion	Contrast-enhanced or non-contrast-enhanced sequence			Airway diseases
Ventilation	Contrast-enhanced or non-contrast-enhanced sequence			Airway diseases
Diffusion	DWI-MRI			Inflammation, cancer

Table 1: Proposed standardized lung MRI protocol for routine use

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