Imaging of Pulmonary Pathologies
Focus on Magnetic Resonance Imaging

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Magnetic resonance imaging (MRI) of the lung has shown tremendous progress in recent years. This includes parallel imaging, new contrast agents and mechanisms, ultrafast imaging, and respiratory gating. With these improvements in speed and image quality, MRI is now ready for routine clinical use. The main advantage for MRI of the lung is its unique combination of structural and functional assessment within a single imaging examination. This comprehensive imaging assessment is an asset when compared with computed tomography, which is complemented by the fact that MRI does not carry any exposure to ionizing radiation, making it especially advantageous in children, young adults, and for follow-up examinations either in disease surveillance or therapy monitoring. Clinical indications for MRI are: pulmonary vascular disease, especially pulmonary hypertension, airway diseases, especially cystic fibrosis; neoplastic disease, including staging of lung cancer as an alternative imaging modality; all pediatric indications (e.g., congenital anomalies); as well as follow-up examinations. Under investigation is the application of MRI for chronic obstructive pulmonary disease as well as asthma. In this regard the additional benefit from MRI using hyperpolarized gases has to be determined.

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Magnetic resonance imaging (MRI) (1) of the lung is a very challenging field. Most of the healthy lung, approximately 70%, consists of air-filled spaces. As these do not contain protons, which are essential to generate a magnetic resonance (MR) image, no signal can be detected. Only 30% of the volume contains protons, either localized in the tissue or within the blood volume. However, the generation of signal from these components is hampered by two major factors. As air and tissue have very different magnetic properties, the countless interfaces between these two structures generate significant so-called susceptibility artifacts that finally result in a loss of signal of fine structures such as alveolar septae. At the same time, blood is moving with a pulsatile flow, which poses additional specific demands to the methodology of MRI. On top of these difficulties come the requirements arising from the fact that MRI of the lung has to cope with respiratory motion and cardiac contraction. Overall, the lung is probably the most difficult organ to image by MRI (2, 3).

This is the reason why the lung has long been regarded as a black hole on a whole-body MRI and seems to remain a white spot on the map of widespread MRI applications within the body. However, a series of recent developments are shedding more and more light into the black hole of MRI, and early routine clinical applications are becoming apparent.

**TECHNICAL AND PHYSIOLOGICAL ASPECTS**

Major developments in MR scanner technology have provided a broad basis for significant progress. The main driver for this development is the introduction MRI of the heart into the clinical arena but also its widespread availability for small animal studies. Three major goals have been pursued (4): (1) ultrafast imaging using parallel imaging technology, increased gradient strength with ultrashort echo-times, and improved technology for k-space sampling; (2) generation of different contrast mechanisms, such as inversion recovery, fat suppression, and diffusion-weighting (3); and (3) improved spatial resolution using three-dimensional (3D) sequences and volume interpolation (6). These developments were complemented by advances in the field of intravenous paramagnetic contrast media. These included differences in protein binding and renal excretion, higher relaxation rates, and the potential for specific targeting (7, 8).

All these developments are also helpful for MRI of the lung, although they require dedicated modifications. The early focus of the application of such techniques was to cope with respiratory and cardiac motion and to allow for the acquisition of images covering the whole lung within a single breath-hold with maximized spatial resolution. The first application was the introduction of MR angiography of the pulmonary vasculature (e.g., in pulmonary embolism or pulmonary hypertension) (9, 10). However, it soon became clear that these techniques can also be used for so-called functional imaging. Breath-hold high spatial resolution MR angiography can now be modified to a multiphasic acquisition tracking a contrast bolus from the vena cava through the right heart into the pulmonary arteries, through the capillary bed into the pulmonary veins, the left heart and the systemic circulation (11). Such data sets allow for the analysis of different vascular territories as well as anomalies and shunts (e.g., pulmonary sequestration). With a few modifications, multiphasic MR angiography can be turned into MR perfusion imaging (12, 13). This is achieved by shifting the focus from visualization of the larger vessels, so-called macrocirculation (i.e., main pulmonary arteries) down to the subsegmental branches, to detecting the effect of the contrast agent during its passage through the arterioles and the capillary bed, so-called microcirculation. MR perfusion imaging of the lung is now available on all up-to-date MR scanners. MR perfusion has been validated against the current clinical gold standard (i.e., perfusion scintigraphy using Tc-labeled albumin macro-aggregates).

However, there is a major difference: MRI is a first- and single-pass three-dimensional (3D) investigation over time (4D) that primarily relies on evaluation of the time point of peak enhancement, whereas perfusion scintigraphy is a steady-state 2D or 3D evaluation based on temporary occlusion of a small number of arterioles that allows for regional and quantitative assessment of the pulmonary perfusion defects. Novel developments in post-processing of MRI of the lung take benefit from the temporal information obtained by 4D perfusion MRI. Thus, it is no longer about perfusion being present or absent, but also about the time course of perfusion, so-called capillary filling time. Delayed, presumably “collateral” or systemic perfusion...
can be identified. In addition, MRI perfusion data can be post-
processed using pharmacokinetic modeling. Such models pro-
vide quantitative data for the mean transit time, as well as the
pulmonary blood volume and flow, respectively (14). Recent
work has shown that there is a considerable physiologic
variability of these parameters, especially with breathing,
motion, and posture (15). The field of pulmonary hemody-
namics can also be approached with the techniques developed for
MRI of the heart. They allow for measurements of blood flow in
the main pulmonary artery, providing quantitative readouts
such as peak velocity or net forward volume. Not surprisingly,
these measurements exhibit systemic differences when com-
pared with echocardiography, which relies on surrogate mea-
surements within the right heart or the outflow tract. First studies
show a good agreement between estimates of pulmonary
arterial pressure or pulmonary vascular resistance derived by
MR-based blood flow measurements (16, 17). New develop-
ments enable multidirectional flow analysis (18), providing new
insights into physiologic and pathologic flow profiles. In general,
MR flow measurements are an established and proven method
for the comparison between pulmonary arterial and systemic
blood flow volume, which is essential for assessment and
quantification of shunt volumes (e.g., left-to-right shunt through
the bronchial arteries) (19). The assessment of pulmonary
hemodynamics can be complemented by an MR study of right
heart or valvular function, including endystolic and enddiastolic
volumes as well as ejection fraction, paradoxical septal
motion, and pulmonary valve stenosis or tricuspid valve insuffi-
ciency.

However, pulmonary circulation is only one aspect of gas
exchange. Ventilation is the second major component, and
there are several approaches to visualize and quantify ventila-
tion using MRI. It has to be kept in mind that direct visualiza-
tion of the airways and especially their walls is limited. Instead,
dedicated sequences are highly sensitive to fluid and mucus. As
such mucus plugging, like in cystic fibrosis, is a very attractive
target for MRI (20). In addition, 4D MRI is capable of visualizing
the breathing motion in real time and analyzing the respective lung volumes. MR-based lung volumetry has demonstrated excellent agreement and correlation with simul-
taneous spirometry (21, 22). Techniques for split lung analyses
are already in place, whereas lobar analyses of lung volumes
over the breathing cycle are still work in progress. This in-
formation can also be applied to analyze local motion using
vector graphics and might serve to simulate tissue strain and
respiratory mechanical stress in the future (23).

Even more attractive than respiratory motion is the direct
visualization of ventilation using dedicated tracer gases and MR
techniques. Hyperpolarized noble gases, such as helium-3 and
xenon-129, have received a lot of attention during the past years.
Until now helium-3 has been the favorite gas for several reasons:
high polarization rates were easier to obtain, it is easier to handle
since it is inert and not taken up by the body through the alveolo-
capillary membrane, and it provides nice images with high signal
and contrast to noise (24, 25). A four-step strategy was established
including the following. (1) A single breath-hold acquisition after
inhalation of a bolus containing hyperpolarized He-3. This allows
for determination of ventilation defects, which can be estimated as
a ventilation defect volume relative to the total lung volume
(26, 27). (2) Dynamic imaging during inhalation of the tracer gas:
alveolar filling time. This provides information on the temporal
kinetics, such as regions with delayed or even collateral ventila-
tion (28). (3) Diffusion-weighted MRI allowing for measuring
alveolar size using the apparent diffusion coefficient (ADC). Good correlations were found with quantitative CT, histopathol-
ygy, and morphometry, as well as pulmonary function tests (29,
Functional Imaging

The benefits of functional imaging are important for clinical management, and this information cannot be obtained from CT alone or requires a sequence of different imaging modalities (e.g., CT and nuclear medicine). This holds true for image-based assessment of at least four diseases.

COPD. Proton and hyperpolarized gas MRI have been widely studied in patients with COPD. As the structural changes, especially in the emphysema phenotype of COPD, primarily lead to a loss of tissue, emphysema is very difficult to image using MRI (Figure 1). Thus, it is not surprising that MRI performance was inferior to that of CT with regard to detection and phenotyping of COPD (37). However, one of the hallmarks of COPD is the existence of ventilation defects, which are easily detected by applying a tracer gas such as in hyperpolarized gas MRI. Several investigators have successfully attempted to grade and characterize COPD based on the amount, size, shape, and distribution of the ventilation defects using He-3 MRI. Extensive wedge-shaped and lobar ventilation defects are typical findings in advanced COPD. The assessment of the ventilation defects can be complemented by alveolar size imaging using the measurement of the apparent diffusion coefficient (ADC) and alveolar filling time using dynamic imaging of the distribution kinetics of ventilation. We presume that two major phenotypes can be differentiated as follows: the emphysema phenotype will exhibit high ADC values together with a low amount of ventilation defects, whereas the airway phenotype will show extensive ventilation defects and almost normal ADC values (27). Unfortunately, there is not enough experience with Xe-129 MRI in COPD, yet.

It is well known also from nuclear medicine studies that ventilation defects in COPD will induce matching defects of pulmonary perfusion due to the Euler-Liljestrand reflex of hypoxic vasoconstriction. This principle can be adopted for perfusion MRI, which shows widespread perfusion defects in patients with COPD (Figure 1) that also correlate with disease severity (41). Surprisingly, not all perfusion defects do match areas of emphysematous destruction visible on CT. Thus, about 20% of emphysematous areas on CT will have preserved perfusion, which might turn them into attractive targets for endoscopic or surgical therapies. At the same time, a perfusion defect in an area without emphysematous destruction might represent a reversible manifestation of COPD that resolves after application of a bronchial dilator. Dynamic MRI during tidal and forced breathing provides details about static and dynamic lung volumes as well as the respiratory mechanics. Hyperinflation, air trapping, and pendelluft can be observed. Together with the results of perfusion MRI, targeting of regional therapy of COPD seems feasible.

Asthma. At this time there are several highly encouraging reports on the application of He-3 MRI in asthma; however, there is not experience with Xe-129 or proton MRI. He-3 MRI has elucidated some issues around asthma. Ventilation defects are already present in individuals with asthma with normal lung function. The ventilation defect volume seems to correlate with the decline in FEV1. After bronchodilation ventilation defects partially disappear as FEV1 improves. Ventilation defects predominantly reappear in the same locations where they existed before (42, 43).

CF. MRI is widely used for disease surveillance in CF, although there are not many reports in the literature. Recent work has shown that MRI is very capable of demonstrating the typical bronchiectatic changes of CF as well as mucus plugging (Figure 2), and MRI has the same diagnostic value as CT in grading the severity of the disease according to the Bhalla/ Helbich score (44). Perfusion MRI helps to enhance the sensitivity of proton MRI (Figure 2) as bronchial obstruction and subsequent perfusion defects will normally precede structural changes such as fibrosis or bronchiectatic destruction. Perfusion defects in areas with minor or moderate structural changes might also indicate potentially reversible disease. Blood flow measurements are helpful in the detection of occult...
Pulmonary hypertension, which develops slowly with age and disease progression (19). Comparative blood flow measurements in the pulmonary arteries and the aorta detect substantial left-to-right shunt volumes representing the blood supply through the bronchial arteries to the destroyed lung areas. This shunt volume poses a significant volume burden to the left heart in patients with CF.

He-3 MRI has also been successfully applied in CF. As in COPD, the amount of ventilation defects is clearly associated with the decline in FEV₁ (45, 46). Further details on a He-3 MRI-based characterization of CF have not been published, yet.

Pulmonary hypertension. MRI offers a comprehensive assessment of pulmonary hypertension by the following steps: MR angiography and MR perfusion imaging to differentiate between thromboembolic etiology and other disease entities (Figure 3) (47, 48). Furthermore, MR angiography allows for an in-depth evaluation of the localization of the chronic thromboembolic material and performs equally to digital subtraction angiography (DSA) and CTA for surgical planning (49, 50). MR perfusion can be quantitatively evaluated and allows for an assessment of small vessel disease severity. The deduction in perfusion correlates with disease severity, and first results are promising that perfusion is a sensitive surrogate for disease monitoring (51). Structural imaging of the lung will allow exclusion of parenchymal diseases. Measurements of blood flow and right heart provide estimates for pulmonary arterial pressure as well as cardiac strain and concomitant valvular disease.

Monitoring and Follow-up Imaging

All studies in patients in whom the radiation dose exposure is really an issue are first line indications for MRI. Although novel CT techniques will allow for a substantial decrease in radiation dose, the accumulation of radiation dose with regular imaging follow-up of the lungs over time, particularly in children, adolescents, and young adults (especially women), is substantial, and has to be avoided. Thus, therapy monitoring and annual follow-up of CF should be performed by MRI. Also, MRI should be used as the first line imaging modality in children with congenital or acquired pulmonary, and associated cardiac and vascular, abnormalities (52).

Contrast Agents

All imaging in patients in whom there are contraindications to iodinated contrast in CT, which would normally serve as the first-line modality. Contraindications include known allergy, thyroid disease, renal insufficiency, and sometimes pregnancy. In these situations, MRI can be used for the diagnosis of acute pulmonary embolism, including functional assessment of right heart strain as well as pulmonary tumors, nodules, and interstitial lung disease.

FUTURE PERSPECTIVES

With its rapid development during recent years, MRI of the lung is now really at the threshold of broad clinical application. Airway and vascular diseases, as well as nodules and lung cancer, will be a major focus. A standard protocol has been established for MRI of the lung. It is straightforward to use and also well suited to study airway diseases.

In cystic fibrosis, proton MRI will continue to gain ground as the first-line imaging modality especially for annual follow-up studies. The combination of structural imaging, MR perfusion, and blood flow measurements holds great promise, as it provides much more information about disease extent and the subsequent functional compromise than chest radiography, which is insensitive, or CT with its higher dose. In this context, we presume that MRI will be capable of providing quantitative and semiquantitative read-outs, “scores,” and will also be applied for therapy monitoring studies on a short-term basis.

In COPD, MRI is highly attractive because of its unique combination of structural and functional assessment. We are confident that MRI and an associated software evaluation platform can be implemented as a first-line imaging modality in COPD within the next 6 years. During this time, MRI and a dedicated protocol will have to prove that they are reproducible and reliable, and the quantitative read-outs will have to be validated. In addition, the role of MRI in phenotyping COPD still has to be determined. At the moment, it is unclear whether...
and non-infectious) still has to be determined. In asthma, the clinical availability of hyperpolarized gas MRI is urgently awaited. MRI should also be used as a comprehensive first-line imaging modality in the assessment of pulmonary hypertension, lung cancer, and all pediatric lung diseases and cardiopulmonary anomalies.

The role of MRI in inflammatory lung diseases (infectious and non-infectious) still has to be determined.

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