Proton MRI of the Lung: How to Tame Scarce Protons and Fast Signal Decay

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Pulmonary proton MRI techniques offer the unique possibility of assessing lung function and structure without the requirement for hyperpolarization or dedicated hardware, which is mandatory for multinuclear acquisition. Five popular approaches are presented and discussed in this review: 1) oxygen enhanced (OE)-MRI; 2) arterial spin labeling (ASL); 3) Fourier decomposition (FD) MRI and other related methods including self-gated noncontrast-enhanced functional lung (SENCEFUL) MR and phase-resolved functional lung (PREFUL) imaging; 4) dynamic contrast-enhanced (DCE) MRI; and 5) ultrashort TE (UTE) MRI. While DCE MRI is the most established and well-studied perfusion measurement, FD MRI offers a free-breathing test without any contrast agent and is predestined for application in patients with renal failure or with low compliance. Additionally, FD MRI and related methods like PREFUL and SENCEFUL can act as an ionizing radiation-free V/Q scan, since ventilation and perfusion information is acquired simultaneously during one scan. For OE-MRI, different concentrations of oxygen are applied via a facemask to assess the regional change in T1, which is caused by the paramagnetic property of oxygen. Since this change is governed by a combination of ventilation, diffusion, and perfusion, a compound functional measurement can be achieved with OE-MRI. The known problem of fast T2* decay of the lung parenchyma leading to a low signal-to-noise ratio is bypassed by the UTE acquisition strategy. Computed tomography (CT)-like images allow the assessment of lung structure with high spatial resolution without ionizing radiation. Despite these different branches of proton MRI, common trends are evident among pulmonary proton MRI: 1) free-breathing acquisition with self-gating; 2) application of UTE to preserve a stronger parenchymal signal; and 3) transition from 2D to 3D acquisition. On that note, there is a visible convergence of the different methods and it is not difficult to imagine that future methods will combine different aspects of the presented methods.

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Lung diseases rank among the top 10 leading causes of death worldwide and lead to significantly reduced life quality.1 Until now, pulmonary conditions were generally classified as obstructive or restrictive lung disease. The clinical pulmonary function test (PFT) is traditionally the main tool to monitor or grade the course and stage of disease. However, PFT is a global measurement method, which is often not sensitive enough to allow for early disease detection, a precise classification of subgroups, and measurement of treatment response. Therefore, there is a growing demand for new biomarkers with higher sensitivity, which will allow faster therapy decisions to achieve better patient outcomes. In recent years the role of imaging modalities experienced a significant growth. Especially computed tomography (CT) and magnetic resonance imaging (MRI) evolved from generating static and descriptive parameters to producing dynamic, functional, and quantitative biomarkers. Since MRI can depict a wide range of contrast mechanisms without ionizing radiation, pulmonary MRI offers unique possibilities for measuring regional lung function.

Considering the low proton density in the lung and the fast signal decay due to susceptibility inhomogeneity, initial efforts concentrated mainly on using hyperpolarized noble gas MRI with helium-3 or xenon-129.2,3 Hyperpolarization, a process that increases the thermal polarization of a medium by a factor of 100,000, can compensate for the low proton density of the gaseous state and enables a sufficient signal-to-noise ratio (SNR) even at high spatial resolutions. A single inhalation of...
Ventilation and Perfusion Imaging

Pulmonary ventilation describes the process of air transport from the environment to the respiratory system. The delivery of fresh air to the alveoli is a necessary condition for gas exchange. Ventilation is altered in many pulmonary diseases such as asthma, COPD, and cystic fibrosis (CF), for example, and thus is of clinical importance. Since the amount of hydrogen in the air is negligible, a direct measurement of air delivery is not feasible with 1H MRI. Nevertheless, different approaches for indirect ventilation measurement were developed.

Besides ventilation, perfusion of the lung is the other main component required for pulmonary gas exchange. Pulmonary parenchymal perfusion is defined as pulmonary blood flow per parenchymal lung volume. Through diffusion, carbon dioxide and oxygen are exchanged between alveoli and blood. Pulmonary parenchymal perfusion is altered in many pulmonary diseases such as pulmonary embolism, CF, pulmonary hypertension, and COPD. It has been shown to be sensitive for early disease detection, diagnosis, prognosis, and treatment monitoring in patients with chronic lung diseases. Therefore, assessment of pulmonary perfusion is of clinical importance. Perfusion is usually measured with the use of gadolinium contrast agents, but other methods that utilize the effect of moving spins were developed as alternative contrast agent-free perfusion measurements.

The following subsections describe the current methods for ventilation and perfusion imaging.

Oxygen-Enhanced MRI

Oxygen-enhanced (OE-MRI) proton MRI is a method for ventilation imaging based on the weak paramagnetic property of oxygen, which, dissolved in water, contributes to longitudinal relaxation proportional to its concentration. Therefore, a change in $T_1$ can act as a surrogate for ventilation, but unlike hyperpolarization MRI, the observed signal changes reflect a combination of ventilation, perfusion, and diffusion capacity of the lung parenchyma. The basic imaging strategy encompasses $T_1$-weighted acquisition during normoxic and pure oxygen conditions to measure the relative difference either in $T_1$-weighted parenchymal signal or quantified $T_1$ time (see Fig. 1).

For dynamic OE-MRI, additional measurements during washin and washout are carried out to assess the rate of change of the $T_1$ relaxation time. Particularly, $T_1$- weighted, single-shot, half-Fourier, turbo spin echo (TSE) acquisition over several minutes prior, during, and after administration of oxygen are performed. This allows for the calculation of dynamic ventilation images and washin and washout rates. The latter are determined by exponential fitting of the $T_1$-weighted signal–time curves. Furthermore,
dynamic OE-MRI can be quantified via specific ventilation,\(^\text{14}\) which was shown to exhibit a gravitational vertical gradient in healthy volunteers and agrees with global multiple-breath nitrogen washout measurements.\(^\text{15}\)

For a better understanding of pulmonary OE measurements, the relaxation rate \(R_1\) in the absence and presence of oxygen can be described with a two-compartment model consisting of free water and water bound to macromolecules:\(^\text{16}\)

\[
\frac{1}{T_1(0)} = \frac{P_f}{T_{1f}} + \frac{P_b}{T_{1b}}
\]

where \(T_1(0)\) is the weighted average of the free water \(T_{1f}\) and \(T_{1b}\) relaxation constants according to their fractions \(P_f\) and \(P_b\). Pulmonary disease can be associated with an increase in collagen (eg, fibrosis) and hence increased water bound fraction, which leads to a decreased \(T_1(0)\) due to \(T_{1b} < T_{1f}\). The effect of oxygen on relaxation can be described as follows:

\[
\frac{1}{T_1(C_{\text{gas}})} = \frac{1}{T_1(0)} + \text{OTF} \cdot C_{\text{gas}}
\]

where \(C_{\text{gas}}\) denotes the percent concentration of oxygen in the breathing gas and the oxygen transfer function (OTF), which is a compound parameter describing the gas transfer ability of the lung by summarizing properties like the ventilation–perfusion ratio and the diffusing capacity.\(^\text{16}\)

Using a rapid \(T_1\) mapping approach with a snapshot fast low angle shot (FLASH) sequence, the OTF was calculated by acquisition of \(T_1\) maps at different oxygen concentrations and linear fitting.\(^\text{17}\) As supported by theory, the examined CF patients exhibited a lower OTF and \(T_1\) in diseased regions of the lung in comparison with inconspicuous regions.

Using a snapshot FLASH sequence, the feasibility of quantitative dynamic OE-MRI was demonstrated.\(^\text{18}\) Furthermore, it was shown that the relative signal enhancement ratio is dependent on the \(T_1\) relaxation rate during room air, which is not accounted for in \(T_1\)-weighted measurements. Considering fundamentally different \(T_1\) changes in patients with emphysema and lung fibrosis and a natural variation of \(T_1\) as a function of respiratory state,\(^\text{19,20}\) the use of \(T_1\) instead of \(T_2\)-weighted imaging is assumed to be more reliable. Nevertheless, the \(T_1\)-weighted acquisition offers the advantage of a faster acquisition, which can be even performed in free breathing and higher spatial resolution. Therefore, a sophisticated pseudo \(T_1\) map calculation, which scales the \(T_1\)-weighted images by an initial \(T_1\) map, after ensuring the same cardiac and respiratory phase with electrocardiogram (ECG) gating and a post-processing diaphragm navigator was proposed.\(^\text{21}\)

But even quantified \(T_1\) maps require further care, as demonstrated by a recent study, where the results clearly indicate that \(T_1\) is a function of echo time (TE).\(^\text{22}\) These results can be explained by extending the total lung water model to extravascular and intravascular lung water (blood)\(^\text{23}\) with different \(T_1\) and \(T_2^*\) relaxation times.\(^\text{[Correction added on March 18, 2020, after first online publication: The missing reference number was added in the preceding sentence.]}\)

Most studies with high patient numbers used the relative enhancement approach with \(T_1\)-weighted measurements. Ohno et al tested dynamic and nondynamic OE-MRI in large-scale (multicenter) studies in COPD patients and found comparable results to quantitative CT\(^\text{25-26}\) for staging and pulmonary functional loss assessment. Morgan et al were able to detect the effect of pharmacological treatment with OE-MRI in COPD patients in a multicenter study.\(^\text{27}\) In patients with lung volume reduction surgery, OE-MRI showed more accurate evaluation of postoperative clinical outcome than single photon emission computed tomography (SPECT)/CT and was at least as reliable as thin-section multidetector CT.\(^\text{28}\) Dynamic OE-MRI was sensitive to disease severity in asthma patients and reproducible measurements were made one month apart.\(^\text{29}\)

Renne et al were able to show significant \(T_1\) and OTF differences in 69 out of 76 double-lung transplantation patients who could tolerate the oxygen mask for different chronic lung allograft dysfunction (CLAD) stages, proposing OTF as a potential early detection marker for CLAD.\(^\text{30}\) Quantified \(T_1\) showed highly abnormal \(T_1\) and \(\Delta T_1\) in COPD and mild changes in asthma patients.\(^\text{31,32}\)

Although most OE-MRI studies concentrate on \(T_1\) mechanisms, it was suggested to use \(T_2^*\) as a more accurate ventilation marker.\(^\text{33}\) Considering that \(T_2^*\) is governed by the geometrical properties of alveoli/tissue interfaces, ventilated areas are expected to produce lower \(T_2^*\) values while breathing oxygen in comparison with room air due to the increased susceptibility gradient.\(^\text{33}\) Thereby, \(T_2^*\) can provide a more direct ventilation measurement in comparison with \(T_1\). Both \(T_1\) and \(T_2^*\) provide approximately a relative difference of 10–15% after the administration of 100% oxygen in healthy volunteers.\(^\text{33-35}\) Motivated by the fact that \(T_1\) and \(T_2^*\) are providing complementary information, a technique with ultrashort TE (UTE) and golden-angle radial acquisition for simultaneous measurement of \(T_1\) and \(T_2^*\) was developed.\(^\text{36}\) Besides additional information, self-gating allows maps at arbitrary respiratory positions and does not require additional image registration, which was shown to be beneficial for breath-hold-based OE-MRI acquisitions.\(^\text{37}\)

State-of-the-art developments use more time-efficient acquisition strategies, which image the whole lung in 3D with isotropic resolution. The feasibility of OE-MRI with twisted projection imaging (TPI)\(^\text{38}\) and OE-MRI with radial UTE acquisition\(^\text{39,40}\) was demonstrated.

**Fourier Decomposition and Related Methods**

The first attempts to assess the ventilation in the lung parenchyma during respiration of normal room air were
undertaken on low-field MRI to minimize the fast signal decay.\cite{41,42} An important component of this approach was the combination of free-breathing acquisition with nonrigid registration for motion compensation.\cite{43} This enabled the acquisition of image data beyond typical breath-hold durations for analysis of voxelwise time series during natural breathing with sufficient SNR. The MRI signal is dependent on the local composition of air and lung parenchyma providing an indirect measurement of ventilation.\cite{44} For example, the relative signal change between inspiration and expiration can be quantified via fractional ventilation.\cite{41} Since imaging occurs in a steady-state regime, blood flow into the imaged slice leads to further variation of the signal acting as a surrogate for perfusion. This phenomenon is also well known as the time-of-flight effect in spin-echo and gradient-echo imaging. As both mentioned signal modulations are occurring at the respiratory or cardiac frequency, a Fourier decomposition (FD) can be used to assess both components individually, which is known as FD-MRI.\cite{42,45} If ventilation measurement is the main objective, more simple methods, which employ signal subtraction, can be used without further filtering, assuming that perfusion variations will cancel out with enough averaging.\cite{41,46}

The successful FD-MRI analysis relies on a sufficiently low TE (below 1 msec) to reduce signal decay and a high temporal resolution (typically three images/s) to measure frequency components according to the Nyquist sampling theorem. For application at a 1.5T human scanner, an optimized balanced steady-state free-precession (bSSFP) sequence is required.\cite{45} The bSSFP sequence is known to show a $T_2/T_1$ dependency, which intensifies fluids like blood and is therefore very suited to display the signal modulation by blood inflow during perfusion. Also, the $T_2$ signal decay is slower in comparison with $T_2^*$ of, eg, a spoiled gradient echo sequence (Spoiled-GRE). On the other hand, this sequence type is very sensitive to $B_0$ field inhomogeneities and susceptibility differences, which can result in banding artifacts. Therefore, to minimize artifacts due to susceptibility variations with a very short relaxation time (TR), further optimizations, including excitation pulses and gradient switching patterns by partial echo readouts and ramp sampling, were developed.\cite{47,48} Further improvements utilized variable flip angles to increase SNR while adhering to specific absorption rate limitations.\cite{49}

Despite these developments, it was demonstrated that Spoiled-GRE imaging can be a viable alternative as well.\cite{50}
This simple and widely accessible acquisition strategy in combination with the other advantages of FD imaging is of great interest, especially in the context of multicenter studies, when the implementation has to be performed on multiple scanner types from different vendors. Additionally, functional imaging with a Spoiled-GRE sequence was demonstrated to be applicable at 3T, which is difficult using bSSFP due to the increased field inhomogeneity in the lung parenchyma at 3T.

A related approach uses a nonphase-encoded direct current (DC) measurement in addition to a Spoiled-GRE acquisition to obtain highly resolved perfusion-weighted and ventilation-weighted images by sorting the quasirandomly acquired phase encoded lines according to their respiratory and cardiac phase.53

Transferring this idea to the individual acquired Spoiled-GRE images, phase sorting according to cardiac and ventilation phase was demonstrated to generate phase-resolved functional lung (PREFUL) perfusion and ventilation cycles with increased temporal resolution.54 Using PREFUL MRI signal-derived regional flow-volume loops, significant differences in patients after double lung transplantation with different CLAD stages were found.55 In contrast, the conventional flow volume (FV) parameter did not show significant differences between healthy lung transplants and early-stage CLAD, suggesting increased sensitivity of PREFUL-derived flow volume loops for early disease.56 A similar approach including phase sorting for ventilation with a respiratory below signal was applied to create pseudo-3D ventilation maps from multiple 2D slices.57

Although respiratory and cardiac frequencies are not stationary and can lead to low repeatability or SNR, different methods were developed to achieve a more robust post-processing algorithm, including: 1) wavelet decomposition58,59 and nonuniform Fourier decomposition,60 which can account for temporal changes in frequency; 2) adapted filter design and/or gated amplitude calculation51,61; 3) an optimized registration to account for large deformation steps51; 4) matrix pencil decomposition for more accurate amplitude calculation.62

Nevertheless, all previously mentioned methods suffer from 2D limitations, including slow and ineffective acquisition of the whole lung and through-plane motion. Therefore, different attempts were undertaken to image the whole lung volume and generate 3D ventilation maps. An often-employed idea is to use k-space sampling with self-gating to retrospectively reconstruct images at different lung volumes. Alternatively, multiple acquisitions are performed in breath-hold at least at two different respiration states. Successful acquisitions were performed with stack-of-stars63,64 (see Fig. 2) and koosh ball trajectory.65

FIGURE 3: Coronal and sagittal fractional ventilation and perfusion-weighted maps of a patient with COPD obtained with a free-breathing, contrast agent-free method (PREFUL) pre- and post-14 days of inhaler treatment. Please note the visible improvements (arrowheads) in perfusion and ventilation after treatment and the possibility for a pixelwise ventilation-perfusion assessment.
Interestingly, the registration process offers the possibility to calculate the local expansion and inflation of the lung. In this approach, the ventilation is derived from the Jacobian determinant and not from the MR signal. Using this approach in combination with two 3D UTE breath-hold acquisitions, this concept was successfully applied in healthy volunteers and patients with fibrosis. Similarly, a regional 3D flow-volume loop measurement was demonstrated with a self-gated 3D radial UTE sequence acquisition. A straightforward approach using signal subtraction of multivolume breath-hold acquired measurements with a spoiled gradient echo sequence showed promising results in comparison with He-3 in patients with asthma or emphysema. Recently, a study with similar methodology was performed with 3D bSSFP acquisition using a more elaborate signal model. Despite encouraging results, all 3D methods are at an early evidence stage and require reproducibility assessment with higher sample size and further validation with gold standard methods like hyperpolarized gas MRI.

However, 2D free-breathing MRI was validated with different techniques in many patient cohorts in recent years. Comparisons with dynamic contrast-enhanced (DCE) MRI showed good agreement in 34 CF patients, in 15 patients with nonsmall-cell lung cancer, in 65 patients with suspected chronic pulmonary embolism, and 47 COPD patients. Nevertheless, contrast agent-free MRI is generally inferior with regard to image quality and perfusion and is typically evaluated as perfusion-weighted information without quantification. A quantification method, borrowed from arterial spin labeling (ASL) imaging, was introduced, but further validation is pending. A recent study demonstrated a good correlation to single photon emission computed tomography (SPECT) in addition to DCE in CTEPH patients. [Correction added on March 18, 2020, after first online publication: The missing reference number was added in the preceding sentence.]

Ventilation was validated in 12 patients with COPD and 14 patients with bronchiectasis with He-3 MRI, CT, and PFT, in 16 patients with asthma with He-3 and PFT, in 27 COPD patients with F-19, and in 20 CF patients and 20 healthy volunteers with PFT. Free-breathing MRI ventilation markers were found to correlate with PFT and ventilation defects agree with hyperpolarized MRI and F-19. Also, PREFUL ventilation MRI was sensitive to detect significant regional ventilation changes in a double-blind, randomized, crossover drug trial testing the effect of inhaled indacaterol/glycopyrronium in hyperinflated patients with COPD (see Figs. 3 and 4). This shows that free-breathing MRI ventilation markers are ready to be used as outcome parameters in clinical trials. Overall, there is good agreement with hyperpolarized noble gas MRI, considering the quite different acquisition (breath-hold vs. free-breathing). Furthermore, FD and related methods are much easier to acquire with lower barriers to entry compared to hyperpolarized noble gas MRI and are ready for clinical translation.

**Dynamic Contrast-Enhanced MRI**

DCE-MRI is a well-established and routine method of perfusion imaging in various areas of the human body (see Fig. 5). The basic principle of DCE-MRI is the time-resolved data acquisition after intravenous bolus administration of a paramagnetic contrast agent. The increase in the local contrast agent concentration leads to a shortening of the $T_1$ relaxation time, and thus to a signal increase in the $T_1$-weighted image. $T_1$-weighted sequences with a 3D acquisition technique allow the visualization of signal enhancement by the contrast agent throughout the lung as a function of time. The data are evaluated visually, semiquantitatively by descriptive parameters or quantitatively, based on mathematical models of contrast agent kinetics.

Simplified semiquantitative parameters for analyzing DCE-MRI data are the slope of the initial signal rise, the maximum signal increase, the time-to-peak, and the time of arrival of the bolus. Also, using mathematical modeling, quantitative assessment of pulmonary blood volume, pulmonary blood flow (see Fig. 6), and mean transit time is well established. Several approaches for quantification of regional pulmonary perfusion by MRI have been proposed. They are based on the indicator dilution theory. A linear relationship between the contrast concentration in the blood pool and

![FIGURE 4: Besides fractional ventilation (first column) and perfusion-weighted maps, techniques like SENCEFUL or PREFUL (shown here) can be used to assess the ventilation and perfusion dynamics of the full respiration and cardiac cycles. Here the ventilation cycle was used to calculate a flow-volume loop correlation metric (FVL-CM) (second column), which is a similarity measurement of regional MR signal-derived flow-volume curves (third column) to a healthy reference curve.](image-url)
and the MRI signal intensity is essential for the accurate quantification of pulmonary perfusion. Nikolaou et al demonstrated that this linear relationship is maintained up to a contrast dose of 0.05 mmol/kg bodyweight gadodiamide, while others suggest lower contrast doses <0.036 mmol/kg bodyweight at 1.5T.

DCE-MRI has been extensively validated against the standard methods of scintigraphy and SPECT. For the acquisition of DCE-MRI data, fast 3D gradient echo sequences are used, which offer very good spatial and temporal resolution using view sharing such as time-resolved imaging of contrast kinetics (TRICKS) or time-resolved angiography with interleaved stochastic trajectories (TWIST), in combination with parallel imaging. Temporal resolution has less influence than the contrast-to-noise ratio (CNR) on the quantification of pulmonary blood flow. On the other hand, pulmonary blood volume is more influenced by temporal resolution than by CNR. Thus, sequence optimization should aim for a suitable balance of sufficient CNR on the one hand, and sufficient temporal resolution on the other hand. Recently, fully automated end-to-end pipelines to extract pulmonary parenchymal perfusion measures on a lobar level have been developed using deep learning for lung segmentation. This reduces markedly the labor-intensive postprocessing time and is a vital step for translation of this technique into the clinic and large multicenter trials.

DCE MRI has been used in many clinical studies and is shown to be sensitive for early disease detection, diagnosis, prognostication, and treatment monitoring: In COPD patients, perfusion MRI could detect a reduction in pulmonary microvascular blood flow even in mild COPD and an improvement after 2-week long-acting beta agonist (LABA)/LABA combination inhaler therapy. In young children with CF, perfusion MRI has been shown to detect early disease and is able to monitor treatment response with added value to clinical lung function testing. Patients with chronic thromboembolic pulmonary hypertension (CTEPH), perfusion MRI is feasible to quantify perfusion changes after pulmonary endarterectomy and pulmonary balloon angioplasty and predict postoperative outcome. In a retrospective single-center registry study, lung perfusion MRI had high sensitivity, equivalent to perfusion scintigraphy and SPECT in diagnosing CTEPH. The MRI parameters derived from dynamic perfusion imaging integrated MR-PET scans have been shown to be useful for predicting treatment response in 30 nonsmall-cell lung cancer patients treated with radiation- and chemotherapy; furthermore, these parameters were correlated with clinical and survival outcomes including tumor progression and death.

Arterial Spin Labeling

ASL, also known as arterial spin tagging (AST), is a method to measure perfusion using the water molecules of blood as indigenous tracers (see Fig. 6). Therefore, no injection of exogenous contrast material (eg, gadolinium) is required. Despite the relatively low proton density of lung parenchyma, its very high tissue-specific perfusion and a large blood volume compartment makes it a suitable candidate for ASL imaging.

Depending on the specific method, a module of preparation pulses ("Labeling") is used to create a pair of flow-sensitive and flow-insensitive images. The two images differ only in the way that tagging radiofrequency (RF) pulses change the signal of blood flowing into the imaged section, while keeping the signal from the stationary structures unchanged between images. Subtraction of the two images creates an image in which the signal in a voxel is proportional to the amount of pulmonary arterial blood delivered during the previous heart cycle. Typically, two ECG-gated images of a selected slice, which are taken 5–8 seconds apart during a single breath-hold, are acquired with SSFP or a half-Fourier single shot turbo spin-echo (HASTE) readout.

One important aspect of ASL imaging is the off-resonance excitation of the bound water pool leading to unwanted magnetization transfer (MT) effects, which can substantially affect the perfusion-weighted difference image. One way of MT compensation is the signal targeting with alternating RF (STAR). The basic idea is to use symmetrically placed labeling pulses in relation to the readout region.

![FIGURE 5: DCE MRI of a patient with CTEPH illustrated by coronal PBF maps at three different slice positions. Please note the pronounced parenchymal regions with no or very low PBF values indicating perfusion defects.](image-url)
Assuming that MT effects are symmetric, these effects will cancel out in the final image. Nevertheless, this labeling strategy limits the artifact-free application in the lung to the sagittal plane and results in a relatively long transit time of labeled blood. A more popular way of MT compensation in the lung is the flow-sensitive alternating inversion recovery (FAIR) or the modified FAIRER acquisition scheme. In short, a global inversion pulse is applied for labeling and a selective inversion pulse for readout. The centered application of inversion pulses results in an effective MT compensation.

The first ASL application in the human lung was reported by Edelman et al, who used a HASTE readout with STAR MT compensation. After successful pulmonary application of FAIR and FAIRER, this approach was further investigated to detect perfusion deficits in an animal model of pulmonary embolism and perfusion heterogeneity induced by gravity and lung inflation. Furthermore, this ASL method soon became a popular addition to OE-MRI for ionizing radiation-free V/Q measurement. Further studies investigated feasibility and possible pitfalls of accurate quantification of regional pulmonary blood flow due to pulsatile blood flow and tracer saturation effects. These results suggest especially a careful interpretation of coronal slices, which contain parts of the left and/or right pulmonary arteries. Using the more reliable sagittal plane, FAIR ASL was applied in 33 CF patients, showing significantly lowered perfusion in upper lobes in comparison with five healthy volunteers and a strong correlation with forced expiratory volume in 1 second (FEV1).

Since most ASL, including FAIR, techniques require two separate acquisitions, misregistration between two breathhold acquisitions due to different respiratory levels can occur. This can lead to ghosting of the blood vessels and major artifacts near the diaphragm.

For this reason, single-shot techniques including double inversion recovery (DIR) and SEEPAGE have been proposed for pulmonary imaging. Both methods rely on a complete suppression of stationary tissue. Alternatively, a FAIR acquisition with UTE, as demonstrated with small-animal imaging at 7T, can provide the benefits of reduced motion artifacts, self-gating, and increased SNR. Considering a series of long breathhold acquisitions, required for a complete coverage of the lung, this is a promising development for clinical application.

**Structural Imaging**

In general, loss of lung function leads to structural alterations in most chronic lung diseases. Thus, depiction of lung structure is of clinical importance. Due to superior spatial resolution, image quality and short acquisition time compared to proton MRI imaging of lung structure is still the domain of CT in clinical routine. However, in recent years novel UTE proton MRI techniques have emerged, which are able to...
produce “CT like” image quality as they overcome the very short $T_2^*$ relaxation times of normal lung tissue (see Fig. 7).\textsuperscript{116,117}

UTE sequences are gradient echo sequences with a very short TE. The definition of “ultrashort” is not precisely defined and is generally thought to be a TE less than 100 $\mu$s. For structural lung MRI the purpose of the short TE is to preserve the proton signal in the lung parenchyma, which is very quickly destroyed by exponential decay, with a short $T_2^*$ of about 1–2 msec at 1.5T due to different magnetic susceptibilities at the numerous boundaries between air, alveolar wall, and blood in the lung parenchyma.\textsuperscript{118} Considering that the initial proton signal is already reduced due to the relatively low proton density of normal lung tissue, which is only about 30% relative to chest wall muscle,\textsuperscript{119} a significant increase in SNR can be achieved by sampling the k-space as quickly as possible. The gained SNR allows better depiction of lung structure and can be partially traded for a higher spatial resolution to approach the image resolutions of CT.

UTE-MRI of the lung is often performed with a 3D-radial (“koosh-ball”) trajectory. For a nonselective excitation of the whole lung volume, a very short, hard RF pulse is played out. After a hardware-dependent dead time (40–100 $\mu$s),\textsuperscript{119} a center-out k-space encoding with ramp-sampling is performed to avoid further delay. The acquisition of data during gradient ramping is necessary, but can lead to image distortions caused by eddy currents and gradient delays.\textsuperscript{117} This problem is a well-known issue of non-Cartesian imaging and can require additional measurements.\textsuperscript{120,121} Zero TE (ZTE) sequences avoid the problem of ramp-sampling by switching gradients prior to excitation,\textsuperscript{122} but therefore miss acquiring data near the k-space center. This missing data can be filled up by algebraic reconstruction\textsuperscript{123} or additional measurements like pointwise encoding time reduction with radial acquisition (PETRA).\textsuperscript{119,124} As a downside, ZTE sequences miss the opportunity for self-gating, which is an essential prerequisite to obtain high-quality images without motion blurring.\textsuperscript{125}

There are multiple other variants of UTE sequence variations, including UTE with variable readout gradients for improved uniformity of sampling density,\textsuperscript{126} UTE with radial stack of stars trajectory,\textsuperscript{127} and spiral UTE for better sampling efficiency.\textsuperscript{128}

UTE and ZTE sequences have entered the clinical arena and have been used for lung nodule detection, for detecting neonatal lung disease, for monitoring of patients with CF, and quantifying emphysema in COPD patients, for example, with similar resolution compared to chest CT. A free-breathing UTE sequence has been shown to have high sensitivity for the detection of small pulmonary nodules (4–8 mm) and outperformed a 3D dual-echo GRE technique for the detection of small, non-fluorodeoxyglucose-avid nodules.\textsuperscript{129} In another study including 52 patients, pulmonary thin-section MRI with UTE was useful in nodule detection and evaluation of nodule type, and it is considered at least as efficacious as standard- or reduced-dose thin-section CT.\textsuperscript{130}

In a recent study in 42 neonates, UTE MRI has been shown to assess structural abnormalities of bronchopulmonary dysplasia, to describe disease severity, and to predict short-term outcomes more accurately than any individual standard clinical measure.\textsuperscript{131} UTE also assess “minus pathologies” such as emphysema and bullae in good agreement with CT ($\kappa = 0.75–0.78$) in a study with 85 patients.\textsuperscript{132} Certainly the strength of UTE MRI is the depiction of these “minus pathologies”; however, a good test performance with conventional 3D gradient echo sequences has been shown in a lung cancer screening trial using MRI.\textsuperscript{133,134} That study with 224 participants with clinically relevant Lung-RADS findings with a score of 3 and higher were never missed by MRI.\textsuperscript{134} A recent study demonstrates the advantages of low field strength (0.55T) MR with high-performance hardware in comparison with a 1.5T scanner with regard to better field homogeneity, which results in significantly better image quality for assessment of pulmonary “minus pathologies”.\textsuperscript{135}

For imaging “plus pathologies,” especially with increased water (edema, pneumonia, effusion, mucus) or cell content (tumor) fast spin echo $T_2$-weighted sequences, short tau inversion recovery (STIR) sequences, steady-state free precession sequences, and diffusion-weighted imaging have been proposed in addition to 2D and 3D $T_2$-weighted sequences and were described extensively in recent reviews.\textsuperscript{136,137} They are frequently used in clinical routine, especially in vulnerable patients such as children and pregnant women, where CT is avoided due to ionizing radiation.\textsuperscript{138,139} Also, they are useful to depict subtle chest wall invasion of lung cancer due to superior soft-tissue contrast compared to CT, as well as due to the capability of capturing tumor motion with respiratory dynamic cine images.\textsuperscript{140}

**FIGURE 7:** Coronal CT (left) and UTE MRI (right) acquisition. Using a spiral trajectory, the center of k-space is acquired prior to the fast $T_2^*$ decay of the lung parenchyma to obtain a sufficient SNR for lung structure imaging with MRI. Although the spatial resolution is still inferior to CT, UTE MRI can be used to perform nodule or emphysema detection on “CT like” images as in this COPD patient with significant emphysema and an 8 mm lung nodule in the right lung (arrow).
Outlook and Conclusion

This review focused on five different methods of pulmonary proton MRI for ventilation, perfusion, and structure assessment: 1) OE-MRI, 2) ASL, 3) FD MRI and related methods, 4) DCE MRI, and 5) UTE MRI. While DCE perfusion MRI is clinically well established, recent concerns about the safety of gadolinium-based contrast agents with regard to deposition in the brain were raised. Considering this debated area of research and known contraindication of patients with renal failure, there is a growing demand for contrast agent-free measurement alternatives like ASL or FD MRI. In combination with free-breathing acquisition strategies, ASL and FD MRI offer a patient-friendly perfusion test. Thus, such methods can be very useful for short-term monitoring or treatment response measurement and warrant further development.

OE-MRI offers a promising approach to assess the regional pulmonary functional gas exchange using oxygen as an abundant contrast agent. Since an oxygen supply is available in most MR units and OE-MRI is feasible at clinical proton MR scanners, the experimental and technological burden is much lower in comparison with hyperpolarized MRI. A multitude of different quantitative and semiquantitative parameters can be derived, which were demonstrated to be sensitive in COPD, CF, and asthma patients. Nevertheless, several investigators point out the importance of $T_1$ quantification for adequate interpretation. Also, most acquisition approaches typically involve a series of multiple breath-holds and rather long acquisition times due to the washin and washout process, which can make the acquisition of the whole lung a challenge in clinical routine. The more sophisticated sequences with 3D acquisition and self-gating are an elegant solution for this problem, but require further evidence. The fact that OE-MRI provides a compound measurement of ventilation, perfusion, and diffusion can be an advantage or disadvantage depending on the respective clinical question. In this regard, the possibility of using $T_2$*-based OE-MRI as a supplementary measurement is very attractive, but requires further investigation.

FD and related free-breathing methods offer a completely noninvasive simultaneous V/Q assessment in free breathing. In comparison with all other described methods, FD has possibly the lowest technological burden. After a successful setup of a postprocessing pipeline, acquisition can be performed with widely available sequences. The perfect match of ventilation and perfusion information is a unique property of this method and might replace the current scintigraphy and SPECT-based V/Q scans in the future. To achieve this goal, existing approaches for improved reproducibility and image quality need further refinement and evaluation in multicenter studies.

Considering the recent developments of pulmonary MRI there are some remarkable common features: 1) the use of free-breathing acquisition with self-gating; 2) application of UTE to preserve a stronger parenchymal signal; and 3) transition from 2D to 3D acquisition. On that note, there is a visible convergence of the different methods and it is not difficult to imagine that future methods will combine different aspects of the presented methods. There are already good examples for such developments, for example: a FAIR acquisition with UTE (ASL) or free-breathing DCE-MRI with self-gating. Furthermore, substantial work is needed to adapt the methods to the clinical routine, especially with regard to fast reconstruction/calculation, visual representation, and selection of the most robust and useful biomarkers, which clearly need to provide added clinical value. There is also a need for more studies, which demonstrate the direct applications of pulmonary MRI methods, eg, as a response measurement to antiinflammatory asthma treatment or as a free-breathing UTE imaging for depiction of lung structure during radiotherapy.

For clinical routine it is important to implement tailored lung MRI protocols to focus on the specific clinical question:

While CT is still the main clinical tool to visualize lung structure in COPD patients, $T_2$-weighted sequences for inflammation and mucus plugging, UTE for emphysema detection, DCE for regional perfusion assessment (for example, for preoperative lung resection surgery planning) and PREFUL/FD-related techniques for V and Q and VQ match/mismatch assessment for treatment monitoring can be used.

As CF is routinely diagnosed in newborns, MRI is more and more frequently used in toddlers and adolescents to monitor disease and treatment response due to the lack of ionizing radiation. In general, this is the reason why lung MRI has become more popular in children in recent years. [Correction added on March 18, 2020, after first online publication: There was a duplicate reference in the References list. This has been removed and the citation corrected here to Ref. 138. The remaining references have been renumbered.] $T_2$*-weighted sequences for inflammation and mucus plugging and free-breathing PREFUL/FD-related techniques for V and Q and VQ match/mismatch assessment should be used. Also, DCE MRI can be helpful for measuring regional perfusion; however, gadolinium-based contrast agents may not be used in newborns and babies, as they are not approved for clinical use in this age group.

For lung fibrosis, CT is still the main clinical tool to depict and monitor disease. However, 129Xe MRI can measure pulmonary gas-exchange impairment and has the potential in idiopathic pulmonary fibrosis for diagnosis, prognosis, and assessment of therapeutic response in clinical trials. Preliminary work using proton-based MRI techniques such as late-enhancement MRI is still limited to pilot studies.

For diagnosis and monitoring treatment response in CTEPH patients, cardiopulmonary MRI is used in specialized
clinical centers using DCE MRI for measuring regional pulmonary perfusion. Early work for CTEPH diagnosis using Fourier decomposition-derived V/Q maps is also promising.

A recent work has shown that PREFUL MRI is sensitive to detect early chronic lung allograft dysfunction; however, further longitudinal studies are needed to confirm the superiority to the clinical lung function test in this clinical setting.

In conclusion, proton MRI offers a range of powerful and creative methods to deal with the challenges of pulmonary MRI. Most important, these methods share a relatively low technological burden and could be easily implemented on a large scale.

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