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“Structure-Function Imaging of Lung Disease Using Ultra-Short Echo Time MRI”

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Abstract

The purpose of this review is to acquaint the reader with recent advances in ultra-short echo time (UTE) magnetic resonance imaging (MRI) of the lung and its implications for pulmonary MRI when used in conjunction with functional MRI techniques. UTE MRI has three critical advantages for lung applications: 1) high resolution, whole-lung morphological images without the use of ionizing radiation; 2) mitigation of the short transverse relaxation time constant (T2*) caused by magnetic susceptibility effects prominent at air-tissue interfaces; and 3) in conjunction with a radial acquisition and hard respiratory gating, mitigation of cardiac and respiratory motion artifacts, enabling free breathing exams. UTE MRI clearly shows the lung parenchymal changes due to idiopathic pulmonary fibrosis (IPF) and cystic fibrosis (CF). The use of UTE MRI, in conjunction with established functional lung MRI in chronic lung diseases, will serve to mitigate the need for computed tomography (CT) in children. Current limitations of UTE MRI include long scan times, poor delineation of thin walled structures (e.g. cysts and reticulation) due to limited spatial resolution, low signal to noise (SNR), and imperfect motion compensation. Despite these limitations, UTE MRI can now be considered as an alternative to multi-detector CT for the longitudinal follow up of the morphological changes from lung diseases in neonates, children and young adults, particularly as a complement to the unique functional capabilities of MRI.

Keywords

Adult; young Adult; Child; Infant; Lung; Magnetic Resonance Imaging; Perfusion; Hyperpolarized gas; xenon; Idiopathic Pulmonary Fibrosis; Cystic Fibrosis; Longitudinal Studies

Introduction

Pulmonary MRI methods are advancing rapidly, leading to increases in utility and accessibility for clinical research. One of the more exciting practical innovations is the emergence of ultra-short echo time (UTE) MRI methods optimized for pulmonary applications. The development of UTE for structural lung imaging fills a void that has typically been filled by x-ray computed tomography (CT) by providing an MRI based structural complement to the functional capabilities of pulmonary MRI. Advances in UTE MRI thus support a more comprehensive pulmonary evaluation within a single modality. The purpose of this work is to present the emerging role of structure-function associations as a means to improve interpretation of lung disease processes using an MRI-only exam.

In the first section, we describe the current capabilities of structural imaging using state-of-the-art UTE MRI. In the second section, we describe contemporary MRI techniques for measuring various functional parameters in the lungs. In sections three and four, we present some of the clinical research capabilities of structure-function MRI approaches through specific examples drawn from applications in restrictive and obstructive diseases such as idiopathic pulmonary fibrosis (IPF) and cystic fibrosis (CF). Lastly, we discuss the outlook for longitudinal pulmonary imaging methods that exploit structure-function associations in pulmonary disease. We will also discuss the principal limitations of UTE methods and highlight potential avenues for improvement. All results and methods used to generate the images in this review were approved by our institutional IRB. Hyperpolarized xenon MRI results were performed under a United States Food and Drug Administration investigational new drug approval (IND#118077).

Imaging Lung Structures with UTE MRI

Pulmonary MRI presents significant challenges compared to traditional MRI applications. In the presence of a strong magnetic field, the many air-tissue interfaces in the lung parenchyma experience induced local magnetic field variations proportional to the field strength. The magnetic susceptibility differences between tissue and air in the alveolar structures is approximately 8 parts per million (ppm) (1), causing high local field inhomogeneity (2, 3). This leads to rapid spin dephasing, resulting in very short transverse magnetization decay times ($T2^*$) of approximately 2 ms and 0.5 ms at 1.5T and 3T, respectively (4).

Equation 1 describes the signal evolution of a spoiled gradient recalled echo (SPGR) sequence (5) as a function of repetition time (TR), flip angle (θ), and echo time (TE).

$$S = \frac{M_0 \sin \theta (1 - e^{-TR/T1})}{1 - \cos \theta e^{-TR/T1}} e^{-TE/T2^*} \quad (1)$$

UTE MRI mitigates the rapid signal loss from short $T2^*$ by reducing the TE to the scale of 0-200 microseconds (μ s) to sample the free induction decay (FID) as early as possible after radio frequency (RF) excitation. Rapid sampling after RF excitation mitigates the impact of the exponential signal decay on image signal to noise ratio (SNR) and spatial resolution. Even when using UTE, the low tissue density of the lung parenchyma ($\sim 0.2 \text{ g/cm}^3$) makes signal averaging a necessity to improve SNR for high resolution imaging of normal lung structures with MRI. Conversely, pathology in the lungs is easier to image using UTE as there is less ventilation of the air spaces and more protons available for image formation.

Bergin et al. pioneered UTE in the lungs using 3D radial methods in 1991 (6). Later, the implementation of advanced encoding techniques improved 3D radial techniques and introduced slice selective 2D imaging using half-pulse excitation techniques (7–10). Both 2D and 3D methods depend on non-Cartesian trajectories which most commonly use pseudo-random view ordering such as Golden Angle (11) or “bit reversal” (12) ordering. In specialized applications interleaved acquisition of multiple echoes can be acquired during gradient flyback or with RF excitation of different chemical species. Radial and other non-Cartesian trajectories such as spiral (13) and cones (9, 14) typically use regridded interpolation (15) in the spatial frequency domain prior to application of the inverse 2D or 3D discrete Fourier transform to reconstruct the 2D or 3D images, respectively.

Current TE times for 3D radial methods at the time of this publication range from 0–200 μ s depending on RF excitation pulse design and application. This suggests a reasonable threshold for defining “ultrashort” TE in the lungs as less than 200 μ s. There are significant design differences between 2D and 3D UTE sequences. Modifications to traditional 2D MRI slice selection by using two sequential half pulse excitations (10) followed immediately by acquisition enables extremely short echo times of approximately 8 μ s, while a simple approach for attaining UTE in 3D is to use a hard pulse followed by rapid acquisition with a center-out trajectory.

Several other factors beyond TE should be considered to optimize for pulmonary imaging, including: 1) limiting the FOV to the lung region, 2) controlling for respiratory motion, and 3) variable density readout strategies to minimize blurring along the readout direction due to the short $T2^*$ and consequently rapidly decaying FID. Among the limitations of non-Cartesian acquisitions is the lack of a bandlimited field of view (FOV); for certain views, signal from outside the bandwidth encoded by the readout can create aliasing artifacts. These artifacts typically manifest as streaks in radial acquisitions (16) and blurring and ringing in spiral trajectories (17). Such artifacts have been mitigated in two ways: using RF coils with sensitivities limited to the desired FOV, and through locally selective RF pulses at the cost of increased TE. For example, in lung imaging it is often worthwhile to trade off a short TE against a longer, slab selective RF pulse to mitigate streak and motion artifacts from outside the FOV (18).

Pulmonary UTE acquisitions are most often performed with respiratory-gating (either prospective or retrospective) during free breathing. Free breathing imaging allows for the acquisition of many more radial projections than would be feasible during a breath hold, improving SNR through additional signal averaging with application in both adult and

pediatric patients (3, 19–21). This is crucial to provide sufficient SNR in patients with chronic respiratory diseases and dyspnea where breath hold methods are infeasible. These free breathing acquisitions commonly use pseudo-random view ordering, such as Golden Angle (11) or “bit reversal” (12), to mitigate image artifacts due to motion. Over-gridding and non-uniform sampling during the readout may also be used to further limit spiral or streak artifacts (18, 22). Recent 3D radial and spiral UTE sequences are optimized for applications in lung imaging to provide coverage of the chest region analogous to the typical coverage of chest CT with isotropic resolution of 1.0-1.5 mm (13).

The emergence of robust UTE MRI has played an important role in several lung imaging applications. Both 2D and 3D UTE MRI techniques produce CT-like contrast in the lung parenchyma. While x-ray CT unquestionably depicts lung structures with greater reliability and spatial resolution, UTE MRI can provide the same diagnostic information without the use of ionizing radiation and within the same exam as functional lung MRI (23). The 2D half-pulse excitation methods can image a slice within a breath-hold and have shown promise for characterizing COPD in congruence with CT density markers (24). Ma and colleagues also found a significant correlation ($r = -0.71$; $P = 0.005$) between whole lung proton signal-intensity on pulmonary UTE MRI and CT lung density as measured using the lung area less than -950 Hounsfield units (HU) at full inspiration (24). More recently, free-breathing 3D UTE-MRI techniques were used to quantify pulmonary parenchymal density of neonatal lung diseases, including congenital diaphragmatic hernia and bronchopulmonary dysplasia, demonstrating regional correlation between proton signal intensity and CT HU values for a subset of clinically indicated cases (25, 26).

The unity of these various strategies enables the visualization of many structures that would not be visible at conventional echo times of ~ 1 -2 ms. These effects can be seen in figures 1 and 2. Figure 1 illustrates an optimized UTE pulse sequence diagram that was used to image scleroderma. This pulse sequence uses a slab selective pulse with a variable density readout and oversampling by a factor of two to provide clear images of lung structures and relatively hyperintense regions of fibrosis not readily visualized with conventional echo times (18). Figure 2 demonstrates the comparable diagnostic value between a high-resolution CT (HRCT) image and a UTE image. Both modalities visualize the bronchiectasis and mucus plugging associated with CF very well. When further applied to severe asthma, UTE shows similar lung density information as HRCT, advocating the use of UTE to detect air trapping (Figure 3). Later in this review, we will elaborate on the clinical research implications of these recent improvements in structure-function MRI.

Imaging Lung Function with Hyperpolarized ^{129}Xe , DCE Perfusion, and OE MRI

While UTE can provide high quality anatomical information about the lungs, one of the advantages of MRI is that it also provides unique functional imaging capabilities that can be used in the clinical interpretation of lung diseases. UTE MRI addresses similar challenges of short $T2^*$ and low tissue density for not only anatomical imaging but also for several emerging functional methods using gas agents such as hyperpolarized ^{129}Xe MRI and oxygen-enhanced MRI, especially since both techniques depend on rapidly decaying signal from the dissolved phases of these gases. The coupling of both structural and multiple

functional imaging techniques can be used to obtain a more comprehensive assessment of the regional function of the lungs. Specifically, using functional techniques we aim to measure the status of three metrics of lung function that could be useful in tracking diseases: regional ventilation, gas exchange, and perfusion.

Hyperpolarized gas MRI techniques using inhaled ^{129}Xe contrast agents have enabled measurements of ventilation, and recently, new measures of lung disease related to gas transfer (27, 28). Upon inhalation, ^{129}Xe dissolves into the parenchymal tissues and bloodstream. As seen in Figure 4, these dissolved-phase components experience chemical shifts relative to the gas-phase: ^{129}Xe dissolved in the parenchymal tissues and blood plasma (collectively referred to as the barrier compartment) is shifted 197 ppm, while ^{129}Xe in the red blood cells (RBC) is shifted 215 ppm at 1.5T. These spectral shifts enable imaging of the ^{129}Xe distributions in each compartment, generating separate regional images of gas dissolved in the barrier tissues and RBCs of the lung.

Pulmonary MR spectroscopic imaging (MRSI) techniques to visualize regional distributions of different ^{129}Xe compartments have previously been explored using 2D and 3D techniques such as one-point Dixon (29, 30) and Iterative Decomposition of Water and Fat with Echo Asymmetry and Least-Squares Estimation (IDEAL) (31). Dixon and IDEAL are employed in this setting because they can provide volumetric, whole lung coverage within a single breath hold. While conventional chemical shift imaging techniques are feasible (32), they are typically time-inefficient and result in limited coverage and spatial resolution over the duration of a breath-hold. These limitations favor the use of either a one-point Dixon method that must assume a common global phase relationship between the barrier and RBC compartments (33), or a more constrained model-based approach with multi-echo radial trajectories (4 echo times necessary to isolate the 3 compartments) (31, 34). From these separated compartments, regional maps are calculated of the ratios of ^{129}Xe in the barrier tissue to the airspaces (barrier:gas), RBCs to airspaces (RBC:gas) and RBCs to barrier tissues (RBC:barrier), providing information on gas transfer in the lung. Since the $T2^*$ of dissolved ^{129}Xe is approximately 2 ms (29, 35), it is worth noting that both approaches depend on minimizing echo time to efficiently acquire the hyperpolarized gas signal before the signal decays substantially. In the methods discussed in this publication, a 3D UTE radial acquisition is implemented to achieve the short echo times required to mitigate this loss of signal.

Dynamic Contrast Enhanced (DCE) perfusion imaging techniques using gadolinium-based contrast agents (GBCAs) have shown promise for more than a decade. Recently, translational advances have enabled the investigation of diseases such as pulmonary embolism(36, 37), pulmonary hypertension (24–26), and CF in pediatric and young adult populations (38–40). In pulmonary DCE MRI contrast is injected and dynamic images are acquired prior and during the passage of the contrast bolus. Quantitative hemodynamic parameters can be estimated by taking advantage of the temporal data. Because of the rapid passage of the contrast bolus, quantification is only possible when the temporal resolution of the acquisition exceeds 1–2 seconds/frame (41). This is typically accomplished by using a spoiled gradient echo sequence with parallel imaging as well as undersampling each image and reconstructing using view sharing techniques (42, 43).

Quantification is then performed by applying the well-known indicator dilution model to the contrast kinetic curves on a voxel-wise basis (44). More specifically, quantification is achieved by first correcting the measured signal intensity for the known non-linear response to contrast agent concentration (45). Second, an arterial input function (manually picked) is deconvolved from each voxel kinetic curve using truncated singular value decomposition. This produces an estimated transfer function for each voxel (46) from which quantitative values can be obtained in human subjects with healthy lungs (Figure 5) and chronic lung disease (Figure 6) within a short 15-20s breath-hold. Three quantitative parameters can be derived from first pass DCE MRI, pulmonary blood flow (PBF), pulmonary blood volume (PBV), and mean transit time (MTT). These parameters could be used to shed light on how physiological changes relate to structural changes that can be seen with UTE. It should be noted that quantitative DCE perfusion imaging was recently demonstrated to be feasible within a breath hold in humans using a highly undersampled UTE sequence with compressed sensing reconstruction (47). This technical advance could serve to mitigate the need to perform registration on the structural/anatomical datasets, which can result in alignment errors.

Oxygen-Enhanced (OE) MRI has also seen recent advances due to improved UTE techniques. OE MRI in tissues and blood is an older method (48) that has experienced steady development (49–52) due to its practicality—low cost, widespread availability, and use of conventional proton, rather than broadband multi-nuclear MRI clinical platforms (28). Typically, OE MRI works by acquiring two sets of T1-weighted images, one during normoxic breathing and the other during hyperoxic breathing. Increased oxygen concentrations cause T1 shortening in tissue and blood due to the paramagnetic effects of molecular oxygen, thus image subtraction of the two acquisitions produces signal enhancement maps that highlight areas of increased oxygenation (8, 9). These methods have typically used 2D inversion-recovery (IR) and fast spin echo (FSE, also known as rapid refocusing with relaxation enhancement – or RARE) methods to achieve T1-weighted contrast in the lungs where the T1 recovery time depends on oxygen partial pressure (PO_2). Therefore, the T1 change between normoxic and hyperoxic free-breathing can be used to visualize regional changes in PO_2 in the lung tissue and blood that correspond to regional ventilation and blood volume (Figure 7). Important limitations to the conventional 2D IR and FSE approaches to OE MRI include limited thoracic coverage and long scan times. The combination of 3D radial UTE acquisition with OE MRI works to mitigate these limitations by improving SNR efficiency (e.g. no IR is needed), while providing whole lung coverage and reduced cardiac motion sensitivity (53).

Applications to Idiopathic Pulmonary Fibrosis

The capabilities of UTE MRI to provide parenchymal contrast both for anatomic and dissolved phase components of hyperpolarized ^{129}Xe MRI promises to more fully characterize the regional disease process in fibrotic lung diseases that interfere with regional gas exchange. Measures of regional gas exchange derived from hyperpolarized ^{129}Xe magnetic resonance spectroscopic imaging may be uniquely suited to the study of gas exchange, especially in difficult to diagnose and treat interstitial lung diseases (ILDs) such as idiopathic pulmonary fibrosis (IPF). Global lung averages of the barrier:gas and RBC:gas

ratios of the hyperpolarized ^{129}Xe dissolved phase spectra are highly correlated to measures that are proportional to surface area for gas exchange, such as diffusion capacity of the lung for carbon monoxide (DLCO), which measures the partial pressure difference between inspired and expired carbon monoxide (54, 55).

IPF is defined as a chronic, progressive, fibrosing ILD of unknown cause. As is common for ILD, IPF is a restrictive disease associated with eventual parenchymal scarring, reduced mechanical compliance, and impaired function that culminates in reduced gas exchange due to barrier thickening encompassing the septal walls of the lung acini. Diagnosis of IPF relies upon best judgement of a multi-disciplinary team rather than being solely based on direct observation of specific features (56) and most often depends on a combination of CT and/or biopsy findings of usual interstitial pneumonia (UIP) in the presence of characteristic patient demographics and risks (e.g. Age>50, male predilection, smoking) and in the absence of alternative etiologies for ILD (connective tissue disease, drug or environmental exposures). The typical UIP pattern on chest CT in IPF is basal and subpleural predominant honeycombing and reticulation with sparse or absent ground glass opacity (Figure 6). IPF is one of the most difficult to manage forms of fibrotic ILD due to the lack of a modifiable etiology for the disorder, the progressive nature of the disease, and the heterogeneity in individual prognosis. Unfortunately, while chest CT in IPF can characterize the pattern and extent of disease in the lungs for diagnosis, these patterns have thus far shown limited value in predicting survival and response to therapy and especially in distinguishing regions of active vs. stable disease (57).

Global pulmonary function testing is the most common method for longitudinal evaluation in IPF as both percent predicted functional vital capacity (FVC%p) and DLCO (DLCO%p) tests have been shown to correlate with survival (57). Typically, a >10% drop in FVC%p between visits is indicative of progression initiating a clinical decision-making process concerning possible drug therapies, and intensive monitoring. Clinically, the DLCO%p is used primarily for staging rather than progression (58). While useful, global pulmonary function testing does not provide regional information about IPF, which is known to manifest in the basal and peripheral portions of the lungs, thus highlighting an opportunity for pulmonary MRI.

For a typical UIP pattern with honeycombing and reticulation in the lung bases (Figure 8), regional increase in the barrier:gas ratio along with reduced RBC:gas ratio is often observed in these highly fibrotic regions suggestive of gas diffusion-block. This is in contrast to the homogeneous distribution of both barrier:gas and RBC:gas ratios for the normal subject in Figure 9. Complementary regional measures within an MRI-only exam may distinguish such regions of diffusion block from areas of active inflammation (e.g. increased barrier signal in the absence of reduced RBC) that may point to the onset of disease progression and could therefore offer a tool to guide more aggressive therapy approaches before functional decline manifests globally.

DCE MRI of pulmonary perfusion is potentially a complementary method to the MRSI-based measures of regional gas exchange described above. Figure 6 shows the structure-function association between hyperintense regions on UTE and pulmonary blood flow

measured with DCE MRI in a subject with IPF. In contrast to an age-matched healthy normal volunteer (Figure 5), the spatial juxtaposition makes it clear that there is a reduction in blood flow in areas spatially corresponding to fibrosis, particularly in the posterior basal lung regions, as is common in IPF. However, we can also see focal areas of hyperintense structural signal that lack corresponding perfusion defects. One possible explanation is that these areas reflect active inflammation without capillary destruction as opposed to late stage fibrosis where severe capillary destruction has already occurred.

The comparison of regions of diffusion block, as seen with hyperpolarized ^{129}Xe , to areas that are not yet matched by perfusion defects represents one way to further explore this hypothesis. A similar concept has been applied to pulmonary hypertension using an MRI-based measure of regional ventilation perfusion mismatch (59). Such ventilation-perfusion mismatch may point to regions of salvageable lung, enabling highly targeted anti-fibrotic therapies (60). In general, regional measures are likely to be more sensitive than either FVC %p or DLCO%p and provide a more physiologic basis for assessing regional disease progression in IPF (61). If fully realized, this concept of a combined structure-function imaging biomarker could provide a regionally specific and safe method for longitudinal clinical monitoring of drug therapy response.

Applications to Cystic Fibrosis

OE-MRI provides a potential alternative to hyperpolarized xenon MRI to assess regional obstruction in diseases such as CF (62). The complementarity of structure and function afforded by OE MRI with UTE can provide a framework for interpreting the functional severity of structural abnormalities in CF. CF is an obstructive lung disease caused by infection, chronic inflammation, and mucus plugging due to the mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene leading to impaired mucus clearance from the central airways. The genetic origin of this disease has an even more prominent pediatric component that leads to progressive loss of function due to chronic infection, inflammation, and airway mucus plugging (63, 64). The consequence of these mechanisms of airway injury is highlighted in surveillance of subjects with CF in which areas of bronchiectasis and mucus plugging often correspond to perfusion defects that, unfortunately, become more prominent during and after exacerbation (63). Multiple small molecule “gain of function” drug therapies have been introduced in the past 5 years leading to promising improvements in some patients (65) and the prospect of mitigating exacerbation events to stabilize function. These therapies are increasingly being delivered in younger patients where imaging methods would have value in establishing regional response (66), especially in patients with less common CFTR mutations where benefit from the drugs targeting more common mutations may be assumed to have more marginal effect. Besides its prominent role in CF, mucus plugging has also been implicated in central airway obstruction in asthma and could be another target for regional therapies guided by imaging (67). OE MRI with UTE can also potentially overcome concerns about CT dose in pediatric patients and may provide a useful adjunct for more frequent longitudinal assessment in patients with instability who may need more intense monitoring and follow-up.

One of the advantages of OE MRI using UTE is the inherent spatial alignment of the ventilation-weighted measures to structural UTE MRI (Figure 10). This provides a means to gauge structure-function associations without interpolation errors associated with registration of parametric maps. For example, the juxtaposition of patterns of bronchiectasis and air trapping visualized on UTE with semi-quantitative measures of regional ventilation defects from PSE maps depicts ventilation and perfusion defects local to areas of structural abnormality. This is seen in Figure 11, which exemplifies the ability to visualize the morphological and corresponding physiological abnormalities, such as ventilation defects comparable to those observed on hyperpolarized gas MRI (62), in a severe CF patient.

Outlook/Limitations

Recent advances in UTE MRI methods in combination with the unique functional lung imaging capabilities of MRI – including hyperpolarized gas, perfusion, and oxygen-enhanced contrast – show promise for applications in restrictive and obstructive lung diseases. Quantitative functional measures in the context of lung structures on UTE MRI, especially with inherently co-registered images, can help to interpret the functional consequence of fibrosis, bronchiectasis, mucus plugging and air trapping with potential consequences for improved diagnosis and measurement of treatment response in IPF and CF.

More generally, therapies to slow the progression of regionally heterogeneous chronic lung diseases will benefit from safe, longitudinal, regional biomarkers of lung function to guide and monitor treatment response (60, 66, 68). One of the core benefits to using MRI techniques in general is the lack of ionizing radiation. The previously described structural and functional techniques, applied cooperatively, provide a comprehensive evaluation of pulmonary structure and function without the risk of accumulating radiation dose that is typical of longitudinal evaluation with chest CT. This ability to evaluate disease progression with MRI in populations where multiple low dose multi-detector CT (MDCT) scans would still have unacceptable cancer risk (69, 70) is potentially a powerful tool for assessing therapy response.

The current limitations of lung UTE stem primarily from low SNR of lung tissues due to high induced local magnetic susceptibility, low proton density, and motion. The use of UTE reclaims some parenchymal signal, but the reality remains that most techniques depend on extended acquisition times of several minutes to as long as 20 minutes in some applications. Consequently, the method remains sensitive to respiratory motion despite the use of hard gating. Inconsistency of respiratory motion is common in lung disease and residual image blurring, especially near the diaphragm is still apparent in many subjects. Additionally, expiratory and inspiratory lung volumes near the physiological residual volume and total lung capacity that would best reflect air trapping and emphysema as on CT are not yet feasible at high resolution using 3D UTE methods. Thus, while 3D UTE MRI methods show tremendous promise in the clinical research domain, further technical advances are needed to make these methods more robust for routine clinical application. Recently, techniques such as soft-gating of the respiratory signal (71), the use of a temporally resolved low-resolution 3D navigator and compressed sensing (72), as well as technical improvements on the UTE pulse sequence (73) have shown promise for addressing some of these challenges.

Conclusion

Ultrashort echo time methods have bridged a previously existing gap which mandated the use of computed tomography for the imaging of lung structure. The imaging physician, scientists and pulmonologists can now use UTE to study the lung parenchyma, DCE magnetic resonance for angiography and lung perfusion. Both hyperpolarized xenon and oxygen-enhanced MRI can further exploit UTE methods to improve data acquisition efficiency to quantify regional gas exchange and ventilation in the context of lung anatomic structures in fibrotic and obstructive lung disease. Thus, MRI can now be considered as a competitive choice for the integrated investigation of many pulmonary pathologies, especially for the safe assessment of the longitudinal effects of new therapies on regional lung function without the use of ionizing radiation.

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Key point:

Ultra short echo time magnetic resonance imaging is an important advance for the quantification of lung structural changes secondary to pulmonary disease. The added safety of using a non-ionizing imaging method as a complement to functional imaging offers an alternative to computed tomography with an improved safety profile for diagnosing and monitoring chronic lung disease, especially in children.

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Figure 1:

Ultra-short echo time (UTE) MRI in scleroderma. The pulse sequence timing showing first and second echo times (TE's) at 0.08 ms (center-out) and 2.1 ms (radial-in), respectively (left). Corresponding 3D radial images acquired at the UTE of 0.08 ms (a) and conventional TE of 2.1 ms (b) demonstrated much improved visualization of fibrosis on UTE. In the 3D isotropic resolution UTE images, full chest coverage affords visualization of lung structures such as fissures (c) normally not seen on lung MRI. Not only the fibrosis, but also the dilated, fluid and debris-filled esophagus is visualized. Adapted from (16).

Figure 2:
UTE MRI in Cystic Fibrosis (CF). High-resolution computed tomography (HRCT) images (a) acquired 14 months prior to UTE MRI (b) in a 17 year-old with CF. Arrow indicates a region of bronchiectasis and mucus plugging well visualized on both HRCT and UTE MRI. Images were acquired using 3D radial UTE as in (16).

Figure 3:

Parenchymal density measures in obstructive lung disease comparing HRCT (a) and UTE (b) scans of a 63-year-old woman with severe asthma. Histogram analysis is commonly used in HRCT for detection of air trapping (-856 HU threshold) at expiratory lung volume. A similar histogram analysis of signal values normalized to a reference tissue (e.g. left ventricular blood pool) may be useful with UTE MRI for detecting regions of air trapping (arrows). Images were acquired using 3D radial UTE as in (16).

Figure 4:

The global dissolved phase hyperpolarized ^{129}Xe gas spectrum in the lungs after gas inhalation and breath-hold. The chemical shift at approximately 215 ppm for the red blood cells (RBC) and 197 ppm for the barrier (tissue + blood plasma) relative to ^{129}Xe gas phase resonance frequency. Adapted from (25).

Figure 5:

Structure-function associations in a 64-year-old healthy volunteer. Note the dependent portion of the lungs exhibits increased perfusion as expected. Larger vessels can be seen as hyperintense regions on UTE images and as regions with increased blood flow on perfusion images (red arrows). UTE images were acquired with an optimized 3D radial UTE sequence (16). Perfusion images were acquired using an interleaved variable density SPGR sequence (38).

Figure 6:

Structure-function associations in IPF lung disease. A 63 year old female with IPF with regions of apparent hyperintense signal on UTE consistent with fibrotic injury (upper row) and bilateral basal perfusion defects at the same locations (white arrows, middle row). Corresponding CT scans reveal honeycombing and reticulation in the same regions (black arrows, bottom row). The white arrows point to hyperintense regions in the UTE images that are spatially associated with perfusion deficits while the red arrows point to hyperintense regions that do not show perfusion deficits, demonstrating the potential of structure-function imaging to distinguish disease characteristics that may not be gleaned from anatomic images alone. UTE images were acquired with an optimized 3D radial UTE sequence (16). Perfusion images were acquired using an interleaved variable density SPGR sequence (38).

Figure 7:

Oxygen-enhanced (OE) UTE showing percent signal enhancement (PSE) for the 0.08 ms (A) and 2.1 ms (B) echo times, respectively. Signal contrast for OE UTE is primarily T1 weighted (C) such that the paramagnetic effects of hyperoxic (100% O₂) vs. normoxic (21% O₂) breathing makes it possible to visualize oxygen dissolved in the tissues and blood of the lungs. Adapted from (48).

Figure 8:

Structure-function association between hyperpolarized ^{129}Xe MR spectroscopic imaging of the dissolved phases and UTE MRI in IPF lung disease. Structural UTE images (a) showing typical hyperintense fibrotic regions (arrows) in a 64 year-old male subject diagnosed with IPF that correspond to regional thickening of the barrier (b) and reduced RBC signal (c) relative to the polarized gas compartment. Note the heterogeneity of the parametric maps compared to a healthy normal subject in Figure 9. Images were acquired using the strategy detailed in Kaushik et al. (31).

Figure 9: Structure-function association between hyperpolarized ^{129}Xe MR spectroscopic imaging of the dissolved phases and UTE MRI. The chemical shift at approximately 215 ppm for the RBC and 197 ppm for the Barrier (tissue + blood plasma) relative to Xe gas phase resonance frequency (a) is leveraged using spectroscopic imaging to produce separate barrier:gas (b) and RBC:gas (c) ratio images, which can be fused to structural UTE images (b). Note the homogeneous distribution throughout the lungs for both barrier:gas and RBC:gas ratios in a healthy normal 45 year-old female subject. Images were acquired using the strategy detailed in Kaushik et al. (31).

Figure 10:

Structure-function association between oxygen-enhanced (OE) and UTE MRI in a healthy normal subject using UTE. Image volumes are acquired during normoxic and hyperoxic free-breathing and subtracted to result in the percent signal enhancement (PSE and color bar) based on T1-shortening in the presence of higher concentration of paramagnetic O_2 . Enhancement in the lungs, left ventricle, left atrium, and aorta can be readily visualized with 3D isotropic resolution. Relevant pulse sequence parameters are described in detail in Zha et al. (62, 69).

Figure 11:

The OE MRI derived using the same UTE images is spatially registered. Spatial associations between structural CF abnormalities on UTE MRI for a 37-year-old woman with cystic fibrosis (a & c) juxtaposed with (b & d) PSE defects on OE MRI simultaneously depict morphological (air trapping, pleural finding, bronchiectasis, and pleural finding - arrows) and physiological (ventilation defects – green outline) abnormalities. Color bar indicates percent signal enhancement (PSE). Relevant pulse sequence parameters are described in detail in Zha et al. (62, 69).