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Murine pulmonary imaging at 7T: T_2^* and T_1 with anisotropic UTE

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Abstract

Purpose—To measure the T_2^* and T_1 of mouse lung at 7T via anisotropic-resolution radial UTE with ellipsoidal k-space coverage.

Methods—Ellipsoidal field-of-view was created by expanding uniform spherical k-space coverage. The effects of T_2^* and ellipsoidal sampling on image resolution were investigated by using point-spread-function analysis and resolution phantoms. Finally, this ellipsoidal sampling approach was used to measure the lung T_2^* and T_1 of healthy C57BL/6 mice at the increasingly common preclinical field strength of 7T.

Results—Lung-parenchyma T_2^* of 17–23 week-old mice at 7T was 0.395 ± 0.033 ms. T_1 of lung and left- and right-heart ventricles was 1452.5 ± 87.0 ms, 1810.5 ± 54.6 ms, and 1602.6 ± 120.9 ms respectively. Ellipsoidal k-space sampling provides enhanced resolution for a fixed scanning time or provides equivalent (though anisotropic) spatial resolution with reduced scanning times, while simultaneously avoiding fold-in artifacts.

Conclusions—Using these techniques, the first T_2^* and T_1 measures of mouse lung at 7T are reported. UTE imaging with ellipsoidal k-space coverage significantly increases in-plane resolution without increasing scanning time, or equivalently, decreases scanning time while maintaining equivalent in-plane resolution.

Keywords

UTE MRI; T_2^* ; T_1 ; ellipsoidal k-space coverage; murine lung

INTRODUCTION

MRI provides a non-invasive, non-ionizing way to investigate the function and structure of lung in vivo, which is a complicated biological system due to its unique air-filled structure, highly dynamic perfusion and respiration (1–4). MRI parameters directly obtained by MRI that can characterize lung structure and function include MR signal intensity (5–8), and T_1 and T_2^* relaxation times. Specifically, T_1 and T_2^* relaxation times are able to provide MR

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contrast between normal and pathologic lung and provide effective approaches to quantitatively assess lung pathology (7–9). For example, shorter T_2^* in emphysema can reflect alveolar airspace enlargement, via lower tissue volume fraction and increased susceptibility effects in lung (7). The increase of macromolecule fraction in fibrosis can lead to a decrease of T_1 values of fibrotic lung (10). Since preclinical research by MRI has become more common at high fields (here 7T) (11), it is necessary to establish the T_1 and T_2^* of healthy lung, which have not yet been measured at 7T.

However, proton MR imaging of lung suffers from low signal-to-noise ratio (SNR), because of low proton density and the very short T_2^* of lung due to alveolar-air susceptibility differences. Short echo time (TE) sequences are required to minimize T_2^* -relaxation signal decay for pulmonary imaging to measure parameters such as T_1 and T_2^* more accurately. Various short-TE MR techniques, including TE-minimized gradient-recalled echo imaging (GRE) (12), Shinnar-Le Roux (SLR) pulse (13–17) with minimum phase, ultrashort echo-time imaging (UTE) (18–20), zero echo-time imaging (ZTE) (21–24), and sweep imaging with Fourier transformation (SWIFT) (25, 26) have been developed. Of these, UTE minimizes TE ($< 200 \mu\text{s}$) without the need for especially complex image reconstruction (ZTE) and specialized hardware (SWIFT), and is therefore more commonly applied for lung MRI applications.

In a typical 3D UTE sequence, data acquisition begins immediately after a radio-frequency (RF) excitation pulse while the readout gradient is ramped up for center-out k-space encoding. As selective pulses are typically avoided to minimize TE, the field-of-view (FOV) must extend outside the RF coil to avoid fold-in artifacts. For in vivo mouse lung imaging, long cylindrical birdcage coils are typically used to provide high filling factor and RF homogeneity. However, because k-space is most commonly sampled using a spherical FOV (27, 28), fold-in artifacts are avoided by selecting FOVs that are large, relative to the lung volume of interest. In these approximately cylindrical animals, this leads to sampling redundancy and unnecessarily long scanning times for a given spatial resolution.

To address this problem, Larson et al. (29) proposed a method of matching the fully sampled trajectories (often with varying angular density and constant readout gradient amplitudes) to the desired anisotropic FOV shape (both 2D and 3D), resulting in scanning time reductions and isotropic resolution without aliasing artifacts introduced. Wu et al. extended this method to provide 2D anisotropic FOV for golden-angle radial imaging (30). However, the method is not easily combined with other view orderings like the generalized golden angle for 3D FOV (31), because it is required that azimuthal angle be independent of polar angle (29). Such generalized golden-angle sampling patterns are particularly important in free-breathing preclinical applications because the nearly uniform radial spoke distribution for any acquisition period prevents motion from being confined to specific positions of k-space.

This study seeks to overcome the obstacles listed above by revisiting the use of radial UTE MRI with ellipsoidal k-space coverage which was originally implemented by Johnson et al. in the context of maximizing image resolution (32). In this approach, ellipsoidal k-space coverage is generated by expanding fully sampled spherical k-space coverage in one or more dimensions, resulting in varying spoke length and angular density for the same number of

projections. As a result the FOV can be better fit to the imaged object, significantly enhancing image resolution. Alternatively, the approach could be used to maintain equivalent (although anisotropic) voxel volume, relative to spherical k-space sampling, while decreasing total scanning time.

In this work, we confirm the expected resolution enhancement obtained using ellipsoidal k-space coverage and examine the impact of T_2^* blurring effects, using phantom experiments and point-spread-function analysis. Moreover, we make use of the improved temporal resolution provided by ellipsoidal coverage to accelerate interleaved, multi-TE measurements of T_2^* and limited-flip angle (LFA) (9, 33, 34) measurements of T_1 in the mouse heart and lung. By more rapidly acquiring these measurements, we were able to minimize the possible impact of dynamic physiological changes (i.e., anesthesia-induced atelectasis) and obtain accurate estimates of lung parenchymal density.

METHODS

All experiments were performed on a Bruker 7T scanner (Bruker BioSpec, Billerica, MA) with magnet bore inner diameter = 30 cm, and gradient coil inner diameter = 20 cm. A home-built quadrature birdcage transmitter/receiver coil with diameter of 35 mm and length of 50 mm was employed for both phantom and in-vivo imaging. The maximum gradient amplitude and slew rate of the scanner are 400 mT/m and 3400 T/m/s respectively. The minimum allowable constant gradient ramp time is 0.12 ms and was used in this study.

Pulse sequence

Supporting Figure S1 shows the pulse sequence of the radial center-out k-space acquisition used for 3D steady-state UTE imaging. After RF excitation with a hard pulse of length of 4.3 μ s, the radial readout gradient was ramped up to the predetermined direction and amplitude and remained constant until the end of data acquisition. Data acquisition began after the RF pulse with echo time TE and continued for readout duration T_{acq} . RF spoiling and gradient spoiling (35, 36) were applied in UTE sequence. After data acquisition, an opposite-polarity readout gradient was used to negate the readout gradient, and subsequently a large constant spoiler gradient was applied along the z axis for every repetition. Each RF pulse with a linear phase increment of $n \cdot 117^\circ$ (n is RF pulse number) was combined with the large spoiler gradient to spoil residual transverse magnetization and maintain incoherent steady-state magnetization (35, 36).

3D UTE with ellipsoidal k-space coverage

Golden mean sampling—A k-space sampling pattern for 3D radial UTE defines the location of the endpoints of individual spokes, roughly equidistant on a unit sphere for an isotropic FOV. The sampling scheme used in this study adopts generalized golden means (calculated by modified Fibonacci sequence and expressed by $\eta_1 = 0.46557123$, $\eta_2 = 0.68232780$ with only limited digits listed here) to generate well distributed points on a unit square (31) using the decimal fraction of $m\eta_1$ and $m\eta_2$ with $m = 1, 2, 3, \dots$. The unit square is mapped onto the surface of a unit sphere to obtain a uniform distribution of samples on the unit sphere with the polar angle and azimuthal angle calculated from $m\eta_1$ and $m\eta_2$.

respectively. With an 8-digit precision used for the golden means, as many as 10^8 different points on the unit sphere can be generated, which is necessary for high resolution imaging. The mapping relations between the unit square and unit sphere are described by the following equations,

$$\begin{cases} \theta = 2\pi\{m\eta_2\} \\ k_z = 2\{m\eta_1\} - 1 \\ k_x = \cos \theta \sqrt{1 - k_z^2}, \\ k_y = \sin \theta \sqrt{1 - k_z^2} \end{cases}$$

where $\{m\eta_1\}$ and $\{m\eta_2\}$ are the decimal fraction of $m\eta_1$ and $m\eta_2$, respectively. Additionally, $m = 1, 2, 3, \dots, N$ with N being the number of spokes fulfilling Nyquist criterion; θ is the azimuthal angle of the endpoints; and (k_x, k_y, k_z) is the coordinate of the endpoints in a Cartesian coordinate system.

k-Space expansion—Uniform, 3D spherical k-space coverage can be deformed by expanding or compressing a Nyquist-sampled sphere in arbitrary directions to generate FOVs that can be shaped to more fully cover the object of interest. In this study, ellipsoidal k-space coverage was achieved by expanding k_i by α_i , where $k_{i,ellipse} = \alpha_i k_{i,sphere}$ and α_i is the ratio of expansion with $i = x, y, z$. For $\alpha_x, \alpha_y > 1, \alpha_x = \alpha_y$, spherical k-space coverage is reshaped into a tri-axial (scalene) ellipsoid, resulting in an FOV shape that is an altered tri-axial ellipsoid as well. Because spherical k-space coverage was isotropically expanded in the k_x - k_y plane ($\alpha_x = \alpha_y > 1$), spherical k-space coverage was reshaped into an oblate ellipsoid of revolution with short axis parallel to the k_z axis, resulting in a FOV shape that was a prolate ellipsoid of revolution with long axis parallel to the z axis, with care taken to ensure full coverage of the object by the ellipsoidal FOV. The FOV in the x - y plane decreased by a ratio of α_x accordingly, and the resolution in the x - y plane was enhanced correspondingly by the same ratio. A k_z - k_x view of the sampling patterns in Figure 1 (a) shows the evolution of spherical to ellipsoidal k-space coverage when $\alpha_x = \alpha_y = 2$.

PSF analysis—Point spread function (PSF) of k-space sampling patterns was used to analyze the FOV and resolution in image space (29). PSFs were calculated by gridding data of all ones in MATLAB (MathWorks, Inc., Natick, MA). 32 points were sampled on each of 12868 projections and 4 pairs of expansion factors ($\alpha_x = \alpha_y = 1, 2, 4; \alpha_x = 2, \alpha_y = 4$) were used to investigate the influence of k-space expansion on FOV and resolution. All 4 k-space sampling patterns were rescaled by the same factor before gridding in order to obtain the same voxel size in image space and a grid oversampling ratio of 8 was used to show the full aliasing lobes.

PSFs (with $\alpha_x = \alpha_y = 2$ and 64 points sampled on each of 51480 projections) under influence of T_2^* decay were also calculated to investigate the dependence of single-voxel SNR and blurring on T_2^* decay (28, 37). The dependence of single-voxel SNR on T_{acq} and T_2^* is obtained from the PSF amplitude weighted by the square root of the readout duration (37), i.e., $SNR \propto \sqrt{T_{acq}} \cdot PSF(\theta)$. Resolution is characterized by the full width at half maximum (FWHM) of PSF.

Phantom imaging

To verify the PSF analysis of blurring caused by T_2^* decay, a 2-mm-thick rolled rubber was imaged at one short readout duration ($T_{\text{acq}} = 0.26$ ms) and one long readout duration ($T_{\text{acq}} = 1.18$ ms) respectively by changing receiver bandwidth (500 kHz vs 90 kHz) and readout-gradient strength. 100 points were sampled on each of 125664 projections with $\text{TR}/\text{TE} = 10/0.075$ ms, $\text{FA} = 20^\circ$, and $\text{FOV} = 30 \text{ mm} \times 30 \text{ mm} \times 60 \text{ mm}$ ($\alpha_x = \alpha_y = 2$). Images of the rolled rubber were acquired by UTE with multiple TEs to measure T_2^* before carrying out the varied readout-duration imaging.

To demonstrate the resolution enhancement by ellipsoidal k-space coverage, a commercial resolution phantom (High Precision Devices, Inc., Boulder, CO) filled with deionized water was imaged. 64 points were sampled on each of 51480 projections with $\text{TR}/\text{TE} = 10/0.075$ ms, $\text{FA} = 5^\circ$, receiver bandwidth = 100 kHz, $\text{FOV} = 20 \text{ mm} \times 20 \text{ mm} \times 60 \text{ mm}$ for $\alpha_x = \alpha_y = 3$, and $60 \text{ mm} \times 60 \text{ mm} \times 60 \text{ mm}$ for $\alpha_x = \alpha_y = 1$. The pore size ranges from 0.4 mm to 0.8 mm, while the inter-pore spacing ranges from 0.8 mm to 1.6 mm.

In vivo experiments

All animal studies were approved by the Institutional Animal Care and Use Committee in Cincinnati Children's Hospital Medical Center. Eighteen 17–23 week-old healthy C57BL/6 mice were used. Animals were anesthetized by 1.5–2% isoflurane for free breathing and placed supine with lung in the center of coil during imaging. A small-animal monitoring system (SA Instruments, Inc., Stony Brook, NY) was used to monitor respiratory rate and body temperature and provided a TTL signal for respiratory gating at end expiration.

To demonstrate resolution enhancement for in-vivo imaging, one animal was imaged with $\alpha_x = \alpha_y = 1$ and 2 respectively, 64 points on each of 51480 projections, $\text{TR} = 10$ ms, and $\text{TE} = 0.075$ ms.

Twelve 17–23 week-old mice were imaged by UTE ($\alpha_x = \alpha_y = 2$), to measure the T_2^* of mouse lung parenchyma; 64 points were sampled on each of 51480 projections with $\text{FOV} = 30 \text{ mm} \times 30 \text{ mm} \times 60 \text{ mm}$, $\text{TR} = 10$ ms, and $\text{TE} = 0.075, 0.2, 0.4, 0.6, 0.9, 1.3$ ms. A receiver bandwidth of 300 kHz was used for the near-optimal readout duration ($T_{\text{acq}} = 0.27$ ms) for maximum single-voxel SNR based on the initial T_2^* measurement of two mice. RF pulses were applied periodically (period = TR) as shown in Figure 1 (b) to reach a steady state, but the data were only sampled inside the gating window to minimize motion artifacts. Each k-space spoke was sampled for a consecutive series of TEs (interleaved multi-TE method).

Six mice were imaged at end expiration by UTE with two different flip angles ($\text{FA} = 3^\circ, 17^\circ$) and $\text{TE} = 0.075$ ms to calculate T_1 maps (9, 33, 34), with all the other parameters the same as above. To measure the actual flip angle, UTE with readout gradient turned off was used to acquire data over a spherical deionized water phantom. The amplitude of leading 30 FIDs of deionized water, acquired with total duration $\ll T_1$ (38), was fitted to $S_n = S_0 \cdot \cos^n(\text{FA})$.

Image reconstruction and data analysis

Gridding reconstruction methods (39–42) have been well developed to process data sampled with non-Cartesian k-space trajectories. Here we use an established iterative numerical method (43, 44) to calculate the weighting function to compensate for nonuniform sampling density. Before regridding, the ellipsoidal k-space coverage is rescaled, thus k_x and k_y falling in between -0.5 and $+0.5$, and k_z $-0.5/\alpha_x$ and $+0.5/\alpha_x$. The weighted sampled points are convolved with an optimized Kaiser-Bessel window (45) with width of 5 pixels, and then resampled onto a Cartesian grid with oversampling ratio of $2\alpha_x$ (here, $\alpha_x = \alpha_y$). The entire reconstruction process was performed in MATLAB (MathWorks, Inc., Natick, MA).

A commercial graphic processing software package (Amira, FEI Company, Hillsboro, OR) was used to semi-manually segment out regions of interest (ROI) for lung parenchyma from other soft tissues with particular care taken to exclude large blood vessels and major bronchi. For T_2^* measurement, average signal intensity (SI) in lung parenchyma ROIs was corrected for noise, estimated by the average SI in background in each image (46). T_2^* was calculated by performing exponential fitting to the noise-corrected lung parenchyma SI versus TEs with custom software in MATLAB. T_2^* maps were also generated by performing exponential fitting to the magnitude images versus TEs pixel by pixel. T_1 maps were calculated by LFA method developed by Wang et al. (9, 33, 34) on a pixel-by-pixel basis from images acquired at two different flip angles. T_1 values for heart and lung parenchyma were measured by segmenting out ROIs in the left ventricle and right ventricle of heart and lung parenchyma respectively in T_1 map.

MR signal averaged over an ROI in the left ventricle of heart was used as a reference for estimating lung parenchymal density. The ratio of lung parenchymal signal to heart signal is weighted by the T_2^* and T_1 of heart and lung. Because the T_2^* of heart is much longer than the T_2^* of lung (47), the weighting of heart T_2^* with TE = 0.075 ms can be considered negligible. Assuming the heart density is 1.07 g/cc (8, 48), lung parenchymal density was estimated from the ratio of lung parenchymal signal to heart signal at TE = 0.075 ms by applying T_1 correction to heart and lung (49) and applying T_2^* correction to lung.

Mean and standard deviation (SD) of each quantity were calculated.

RESULTS

PSF analysis

The cross sections of the PSF of sampling pattern at $z = 0$, $y = 0$, and $x = 0$ shown in Figure 2 demonstrate the influence of k-space expansion on FOV. The separation between the main peak (bright spots in the center) and the aliasing peak (indicated by white arrows) along x or y axis is FOV_z and $\text{FOV}_z/2$ for k-space expansion factors $\alpha_x = \alpha_y = 1, 2$, respectively, as shown in Figure 2 (a) and (b). Similarly, the separations between main peak and aliasing peak are $\text{FOV}_z/2$ and $\text{FOV}_z/4$ along the x and y axes, respectively, for $\alpha_x = 2$, $\alpha_y = 4$, as shown in Figure 2 (c).

The PSF main peaks (measure of true resolution) along x , y or z directions are shown in Figure 3. The full widths at half maximum (FWHM) of the PSFs along the z axis are almost

equal for different expansion factors (6.4 pixels, 6.4 pixels, 6.9 pixels and 6.6 pixels for $a_x = a_y = 1, 2, 4$; $a_x = 2$, $a_y = 4$ respectively). FWHMs of PSFs along x and y axes are 6.2, 3.3, and 1.8 pixels, for $a_x = a_y = 1, 2, 4$ respectively, while the FWHMs of PSF for $a_x = 2$, $a_y = 4$ are 3.5 pixels and 1.7 pixels along x and y axes, respectively, demonstrating the expected linear relationship between resolution enhancement and k-space expansion.

PSF under influence of T_2^* relaxation was calculated for the generalized golden means radial sampling with 64 points on each of 51480 projections when the expansion factors a_x and a_y were 2. The normalized SNR as a function of sampling duration T_{acq} is given in Supporting Figure S2 (a). By numerical calculation, we obtain the SNR maximum at $T_{acq} = 0.68 T_2^*$, close to the result of spherical coverage ($0.69 T_2^*$) by Rahmer et al. (37). The FWHM as a function of sampling duration T_{acq} is shown in Supporting Figure S2 (b), and increases with T_{acq} due to T_2^* blurring. FWHM along the z axis (solid line) is twice the value along the x or y axis (dashed line) at all T_{acq} , consistent with $a_x = a_y = 2$, and $a_z = 1$.

Phantom imaging

The T_2^* of rolled rubber was measured to be ~ 0.6 ms. Images were acquired by UTE at two different readout durations ($T_{acq} = 0.43 T_2^*$, $1.96 T_2^*$) with $a_x = a_y = 2$, $a_z = 1$, and are shown in Figure 4. Blurring was observed in Figure 4 (b) acquired at long readout-duration, which was caused by T_2^* decay, but no obvious blurring was observed in the image acquired at short readout duration in Figure 4 (a).

Resolution phantom images by UTE with expansion factors $a_x = a_y = 1$ and $a_x = a_y = 3$ are shown in Figure 5; dashed lines depict FOV. There is obvious blurring in the x and y directions in Figure 5 (a) left and middle columns without k-space expansion, relative to the counterparts with k-space expansion in Figure 5 (b). In addition to the blurring around the small structures in the expansion plane (x - y plane) in Figure 5 (a), weak blurring was also seen in the non-expansion direction (z axis), because the structure blocks were not exactly parallel to the x axis. Signal intensity at both ends of the phantom is lower than in the middle because of RF excitation inhomogeneity. SNR in the bright region is 320.6 and 38.8 for $a_x = a_y = 1$ and $a_x = a_y = 3$ respectively, consistent with the ratio of voxel volume.

In vivo mouse imaging

Representative images of mouse lung acquired by UTE with k-space expansion factors $a_x = a_y = 1$ and $a_x = a_y = 2$ are shown in Figure 6. SNR in lung parenchyma is 33.0 and 123.6 for $a_x = a_y = 2$ and $a_x = a_y = 1$ respectively, consistent with the ratio of voxel volume. With the same acquisition time and number of projections of 51480, UTE with $a_x = a_y = 2$ provides higher resolution as is demonstrated by the sharper lung boundary (indicated by the black arrows in the axial and sagittal slices in Figure 6) and clearer blood vessels (indicated by the black arrows in the coronal slices in Figure 6).

Representative T_1 map of one mouse and the corresponding proton images at $FA = 3^\circ$ and 17° are shown in Figure 7 (d), (a) and (b) respectively. ROIs indicated by the blue mask in Figure 7 (c) were selected in lung parenchyma, with particular care taken to exclude blood vessels, to measure T_1 of lung parenchyma. ROIs indicated by the green and red masks in

Figure 7 (c) were also selected to measure the T_1 of heart, separately for the left and right ventricles.

T_1 values of heart and lung at 7T for individual mice are listed in Table 1. Lung parenchyma T_1 is measured to be 1452.5 ± 87.0 ms at 7T, smaller than the heart T_1 (1810.5 ± 54.6 ms in left ventricle and 1602.6 ± 120.9 ms in right ventricle).

Lung parenchymal signal decreases dramatically with TE, highlighting the importance of short echo times in imaging lung at 7T. Representative axial images of mouse lung acquired at different TEs (0.075 ms, 0.6 ms, 1.3 ms) are shown in Figure 8 (a), while the resulting T_2^* map is shown in Figure 8 (c). The blue mask in Figure 8 (b) shows how lung parenchyma was segmented from other soft tissues for T_2^* measurement. Heart ROIs in the left ventricle with homogeneous intensity were also segmented out as indicated by the red masks in Figure 8 (b) to estimate lung parenchymal density.

T_2^* results of lung parenchyma measured from the UTE images are listed in Table 2. T_2^* and density of lung parenchyma in 17–23 week old mice at 7T are 0.395 ± 0.033 ms and 0.66 ± 0.06 g/cc, respectively.

DISCUSSION

Imaging the mouse lung at 7T

High and ultra-high field MRI is becoming more common due to non-lung applications (50–53). However, pulmonary imaging by MRI at 7T is challenging due to low SNR caused by the low proton density and ultra-short T_2^* , making lung parenchyma have particularly low SNR on conventional Cartesian MR images (5). In this study, an ultra-short echo-time (UTE) sequence with ellipsoidal k-space coverage was applied to optimize lung tissue signal for T_1 and T_2^* measurements, which may be useful biomarkers for various lung abnormalities like alveolar simplification (developmental emphysema) or perfusion deficits.

Preventing fold-in artifacts

PSF analysis shows that ellipsoidal k-space coverage can achieve reduced transverse FOV and increased in-plane resolution for the same number of projections in k-space, which was verified by phantom and mouse imaging (Figure 5 & Figure 6). The reduced FOV avoided the use of slab selection when imaging regions within a long object, with the advantage of reducing TE. Although a SLR pulse with minimum phase can be used to achieve slab selection while minimizing TE, the resulting TE is still longer than that of a UTE sequence because a refocusing gradient is required (54). A particularly short coil covering only the region of interest provides another method for decreasing FOV and reducing aliasing, but at the expense of decreased B_1 homogeneity. We also showed that the dependence of single-voxel SNR and resolution on readout duration is similar to that for spherical k-space coverage (37) and was verified by imaging of rubber with short T_2^* . Therefore a near-optimal readout duration ($\sim 0.69 T_2^*$) was chosen for mouse lung imaging to increase SNR.

Achieving incoherent steady state

RF spoiling and gradient spoiling, which were developed for GRE imaging (35, 36), were added to UTE sequence in this study. Even though oversampling near the k-space center has the effect of averaging to make UTE images less sensitive to motion artifacts, respiratory gating was used to minimize the effects of respiratory motion. A UTE sequence with RF spoiling and gradient spoiling but without data acquisition was applied even outside the gating window to retain steady-state longitudinal magnetization.

T₁ measurements at 7T

Due to the ultra-short T₂^{*}, it can be challenging to precisely measure the T₁ of lung by conventional saturation recovery or inversion recovery methods with long TE. The limited flip angle method (LFA) combined with UTE not only gives high SNR in lung parenchyma, but also provides 3D T₁ mapping with less scanning time than that required for conventional saturation recovery or inversion recovery methods. However, LFA is sensitive to incomplete spoiling when TR is very short, which is why we applied RF spoiling and gradient spoiling for UTE. LFA is also sensitive to inaccurate FA estimation especially for long T₁ tissue, so flip angles were measured during imaging experiments. An FA combination (= 3°, 17°) was adopted based on previous work (9, 33) to optimize the precision in T₁ estimation.

No previous data for T₁ of mouse heart and lung have been reported at the field strength of 7T. Stanisz et al. reported in vitro heart T₁ of 1471 ± 31 ms at 3T and 1030 ± 34 ms at 1.5T by inversion recovery (IR) pulse sequence (47), smaller than the in vivo heart T₁ of both ventricles in this study at 7T (1810.5 ± 54.6 ms and 1602.6 ± 120.9 ms in the left and right ventricles respectively) (55). Mouse lung T₁ in this study was found to be 1452.5 ± 87.0 ms, larger than that (1255 ± 63 ms) reported by Alamidi at 4.7T (9), also using the LFA method. However, Zurek et al. reported a longer lung T₁ of 1850 ± 32 ms at 4.7T using a longer TE of 0.4 ms (56). With longer TE, the signal contribution from blood in capillaries with longer T₂^{*} and T₁ dominates lung parenchyma with shorter T₂^{*} and T₁ (57).

T₁ relaxation in blood was found to linearly increase with deoxygenation level (58, 59). The degree of deoxygenation is 1–2% in arterial blood and 30–40% in venous blood in heart under physiologic conditions (58), leading to longer T₁ in arterial blood. The left ventricle of heart contains arterial blood while the right ventricle contains venous blood, which explains why the left-ventricular T₁ is longer than the right-ventricular T₁ in Figure 7 (d) and Table 1.

T₂^{*} measurements at 7T

The interleaved multi-TE method for T₂^{*} measurements involved a number of discrete TEs for each breath, so prospective gating was much more convenient. This method, acquiring data as a series of TEs per spoke, minimized the displacement between images at different TEs caused by the body motion of animals, thus generating accurate T₂^{*} maps with noise correction. Henkelman et al. (60) developed a numerical method to correct noise in magnitude images assuming noise is gaussian, and Miller et al. (46) used the average squared values of background and a region of interest to calculate actual average squared value of magnitude over that region of interest. We used Miller et al.'s method for its simplicity and accuracy.

Ellipsoidal UTE generated higher-resolution images for the same scanning time as required for spherical UTE, making blood vessels more visible to be excluded from lung parenchyma for accurate measurement of T_2^* . In addition, ellipsoidal UTE reduced scanning time for the same high-resolution images as acquired by spherical UTE, measuring T_2^* within lung parenchyma more accurately by avoiding the potential confounder of atelectasis, which increases with the time of anaesthesia (61). This is of particular utility with high-value transgenic mice or for scanner with high time demands.

No data for mouse lung T_2^* were previously reported at 7T. Olsson et al. found a T_2^* of 0.46 ± 0.05 ms in lung of 8-week-old C57BL/6 mice at 4.7T (8), and Togao et al. reported a T_2^* of 0.91 ± 0.10 ms in 8-week-old mice at 3T (6). Takahashi et al. also reported a T_2^* of 1.00 ± 0.13 ms in 5–6 week-old mice at 3T (7). The shorter T_2^* of 0.395 ± 0.033 ms in lung of 17–23 week-old mice in this study (Table 2), is due to the higher field inhomogeneity near the air-tissue interfaces inside the lung induced by stronger field and air-tissue susceptibility difference. The lung density of 17–23 week-old mice measured by MRI is 0.66 ± 0.06 g/cc, similar to lung density of 0.57 g/cc measured by μ CT previously (8).

CONCLUSION

T_2^* and T_1 of lung parenchyma were measured for the first time at 7T, using an optimized UTE with ellipsoidal k-space coverage which avoided the confounder of atelectasis by minimizing scanning time for high-resolution images. An interleaved multi-TE method for UTE MRI was developed to measure T_2^* , while a limited-flip-angle method was used to measure T_1 of mouse lung. Point-spread function analysis demonstrates in-plane resolution enhancement and FOV reduction by ellipsoidal k-space coverage as well as the influence of T_2^* relaxation on single-voxel SNR and resolution, which were all verified by phantom and mouse imaging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(a) The k_z - k_x view of a spherical k-space coverage (left) which is isotropically expanded by a factor of 2 in the k_x - k_y plane into an ellipsoidal k-space coverage (right). (b) Interleaved multi-TE acquisition by UTE. Data were sampled on each spoke in k-space at 6 consecutive TEs at end expiration by gating. The RF pulse and gradient pulse were also applied outside the gating window so that longitudinal magnetization remained at steady state at all scanning times.

Figure 2.

PSF (point-spread function) cross sections at $z=0$ (Axial), $y=0$ (Coronal), and $x=0$ (Sagittal) for expansion factors (a) $\alpha_x = \alpha_y = \alpha_z = 1$, (b) $\alpha_x = \alpha_y = 2$, $\alpha_z = 1$, and (c) $\alpha_x = 2$, $\alpha_y = 4$, $\alpha_z = 1$ respectively. Separation between the aliasing peaks (pointed by the white arrows) and the main peaks (bright regions in the center) equals the FOV. The separation between the main peak and aliasing peak along the z axis equals the FOV_z for all expansion factors (with $\alpha_z = 1$), while the separation equals FOV_z/α_x and FOV_z/α_y along the x and y axes respectively.

Figure 3.

Normalized PSFs along (a) z axis, (b) x axis and (c) y axis. FWHMs along the z axis are almost equal: 6.4, 6.4, 6.9, and 6.6 pixels for $(\alpha_x, \alpha_y) = (1, 1)$, $(2, 2)$, $(4, 4)$, and $(2, 4)$ respectively, with $\alpha_z = 1$ in all cases. FWHMs along the x and y axes are 6.2, 3.3 and 1.8 pixels for $(\alpha_x, \alpha_y) = (1, 1)$, $(2, 2)$, and $(4, 4)$ respectively, while FWHMs are 3.5 and 1.7 pixels along the x and y axes respectively for $(\alpha_x, \alpha_y) = (2, 4)$.

$$T_{\text{acq}} = 0.43T_2^*$$

(a)

$$T_{\text{acq}} = 1.96T_2^*$$

(b)

Figure 4.

Axial slices of a rolled rubber imaged by golden means based UTE at (a) $T_{\text{acq}} = 0.43 T_2^*$ and (b) $T_{\text{acq}} = 1.96 T_2^*$ with slice thickness = 0.3 mm and in-plane resolution = 0.15 mm $\times$ 0.15 mm. No blurring was observed in images acquired at $T_{\text{acq}} = 0.43 T_2^*$, but severe blurring was observed in images acquired at $T_{\text{acq}} = 1.96 T_2^*$.

Figure 5.

Representative axial ($z = 0$), coronal ($y = 0$) and sagittal ($x = 0$) slices of resolution phantom (filled with deionized water; pore diameter = 0.8–0.4 mm and inter-pore spacing = 1.6–0.8 mm from top to bottom) imaged by UTE with k-space expansion factors (a) $\alpha_x = \alpha_y = \alpha_z = 1$, and (b) $\alpha_x = \alpha_y = 3$, $\alpha_z = 1$. Imaging parameters are TR = 10 ms, TE = 0.21 ms, FA = 5°, FOV = 20 mm × 20 mm × 60 mm (in x , y , and z directions) in (b), and matrix = 128 × 128 × 128. The dashed lines depict the FOV in (b), while the FOV = 60 mm × 60 mm × 60 mm is larger in each image in (a). Severe blurring appears in (a) rather than (b).

Figure 6.

Axial, coronal and sagittal images acquired by UTE with (a) spherical k-space coverage, voxel size = $0.47 \times 0.47 \times 0.47 \text{ mm}^3$ and (b) ellipsoidal k-space coverage, voxel size = $0.23 \times 0.23 \times 0.47 \text{ mm}^3$, for the same number of projections (51480). The higher resolution of ellipsoidal UTE in the axial plane is evident to the eye, as indicated by the black arrows.

Figure 7.

Representative axial slices of proton images acquired at two different flip angles (a) $FA = 3^\circ$, (b) $FA = 17^\circ$, and the (c) segmenting mask based on proton image applied to the resulting (d) T_1 map for T_1 measurement. Voxel = $0.23 \text{ mm} \times 0.23 \text{ mm} \times 0.47 \text{ mm}$, expansion factors $a_x = a_y = 2$, $a_z = 1$, and number of projections = 51480. In (c), the green and red masks indicate ROIs in the right and left ventricles of heart, respectively, and the blue mask indicates the lung parenchyma. In this case, T_1 of the heart = $1736.3 \pm 187.2 \text{ ms}$ and $1438.1 \pm 139.0 \text{ ms}$ respectively in the left and right ventricles. T_1 of lung parenchyma = $1381.2 \pm 226.7 \text{ ms}$.

Figure 8.

(a) Representative axial images of mouse lung at 3 of the 6 TEs acquired with ellipsoidal k-space coverage, (b) segmenting mask for lung parenchyma and heart, and (c) resulting T_2^* map generated by exponentially fitting the magnitude images versus TEs pixel by pixel.

Table 1Heart and lung T_1 of six 22-week-old mice at 7T.

Mouse #	Mass (g)	T_1 (ms) of heart (left ventricle)	T_1 (ms) of heart (right ventricle)	T_1 of lung (ms)
1	33.8	1736.3	1438.1	1381.2
2	26.8	1825.0	1586.2	1412.0
3	23.8	1868.3	1647.7	1576.4
4	20.6	1749.9	1524.5	1394.5
5	25.2	1830.9	1624.0	1550.7
6	32.7	1852.7	1809.0	1400.3
Mean $\pm$ SD	27.1 $\pm$ 5.2	1810.5 $\pm$ 54.6	1602.6 $\pm$ 120.9	1452.5 $\pm$ 87.0

Table 2T₂* and density of mouse lung parenchyma at 7T.

Mouse #	Age (weeks)	Mass (g)	T ₂ * of lung (ms)	Lung parenchymal density (g/cc)
1	23	33.8	0.425	0.61
3	22	23.8	0.399	0.67
4	22	20.6	0.393	0.69
5	22	25.2	0.372	0.75
6	22	32.7	0.443	0.58
12	23	30.3	0.330	0.68
13	23	27.5	0.354	0.78
14	23	28.2	0.438	0.61
15	17	26.4	0.409	0.58
16	17	27.2	0.385	0.62
17	17	26.1	0.401	0.69
18	17	27.1	0.390	0.64
Mean ± SD	20.7 ± 2.7	27.4 ± 3.6	0.395 ± 0.033	0.66 ± 0.06