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Ventilation/Perfusion Imaging of the Lung Using Ultra-short Echo Time (UTE) MRI in an Animal Model of Pulmonary Embolism

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Abstract

Purpose—To test the feasibility of ultra-short echo time (UTE) MRI for assessment of regional pulmonary ventilation/perfusion in a standard 3 Tesla clinical MRI system.

Materials and Methods—MRI of the lungs was conducted with an optimized three-dimensional UTE sequence in normal rats and in a rat model of pulmonary embolism (PE) induced by a blood clot. Changes in signal intensities (SIs) due to inhalation of molecular oxygen or intravenous (i.v.) injection of Gd, which represents the distribution of ventilation and perfusion, respectively, were assessed in the lung parenchyma.

Results—The UTE MRI with a TE of 100 μ s could detect and map the changes in SI of the lung parenchyma due to the inhalation of 100% oxygen or i.v. injection of Gd in normal rats. Reduced T1 resulting from oxygen inhalation was also quantified. These changes were not observed on the images that were obtained simultaneously with a conventional range of TE (2.3 ms). Furthermore, the method could delineate the embolized lesions where the lung ventilation and perfusion were mismatched in a rat model with PE.

Conclusion—These results show the feasibility and diagnostic potential of UTE MRI for the assessment of pulmonary ventilation and perfusion which is essential for the evaluation of a variety of lung diseases.

Keywords

ultra-short echo time (UTE) MRI; pulmonary MRI; pulmonary perfusion; ventilation; ventilation–perfusion mismatch; pulmonary embolism

Gas exchange is one of the major functions of the lungs. Matched distribution of the regional pulmonary blood flow (perfusion) and ventilation is required for this process to

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occur efficiently (1). Lung ventilation and perfusion scintigraphy has been shown to demonstrate focal or diffuse abnormality in pulmonary functions. This method is essential for the diagnosis of pulmonary embolism (PE) and other pulmonary disorders. The location and extent of perfusion defects can be also assessed on single photon emission computed tomography (SPECT) (2). Although these methods have been widely available, their utility is limited by poor spatial and temporal resolution and by the use of radioactive substances (3). Currently, multidetector-row CT (MDCT) (4,5) pulmonary angiography with iodine contrast agent has been used to identify clots within pulmonary arteries with high sensitivity and specificity, and is accepted as a reference standard for diagnosis of PE (5,6). However, they have also led to increased radiation exposure. This has brought about the issue of radiation dose reduction that currently draws wide attention (7).

Over the past decade, development of fast MR imaging techniques along with more powerful hardware has overcome some of the inherent difficulties associated with properties of the lung, including low proton density, severe magnetic field susceptibility, and respiratory and cardiac motion artifacts (8). The progress being made with “short echo time (TE)” sequences appears poised to make MRI of the lung a clinically viable tool (9). Thoracic imaging by MRI has the potential to bridge anatomical and functional assessment of the lung in pulmonary disorders (10).

MRI enhanced with the use of molecular oxygen has been used to evaluate regional pulmonary ventilation and gas uptake (11). Following diffusion from the alveoli into the capillaries, molecular oxygen acts as a T1-shortening contrast agent and can be used to visualize ventilated lungs that exhibit functioning oxygen transfer (12,13). Unlike ventilation MRI using hyper-polarized noble gases such as ^{129}Xe and ^3He (14,15), oxygen-enhanced MRI can be conducted in a standard clinical system without special hardware modifications. Pulmonary perfusion can also be assessed by dynamic contrast-enhanced (DCE) perfusion imaging using a contrast enhanced T1-weighted gradient-echo sequence with short TE (~ 2 ms) before and after intravenous (i.v.) bolus injection of contrast agents such as gadolinium (Gd) complexes. Compared with nuclear medicine or CT studies, the DCE MRI offers higher temporal resolution and requires no ionizing radiation. However, the observed signal intensity (SI) does not reveal a linear relationship with respect to the concentration of contrast agent within the blood, which makes it difficult to interpret regional pulmonary perfusion parameters through the DCE MRI (16).

The utility of ultra-short TE (UTE) MRI in conjunction with projection acquisition of the free induction decay (FID) allows us to reduce TE to less than 100 μs to minimize signal decay caused by short transverse relaxation time (T_2^*). Several investigators have applied the method with an UTE (c.a. ~500 μs) to image the lung, and have demonstrated that the method can produce endogenous MR signal from the lung parenchyma which is usually unobservable by the conventional proton MRI methods, and depict finer pulmonary structures in the lung in animals (17,18) or human (19). Using an UTE sequence in a standard 3 Tesla (T) clinical MRI system, we have demonstrated in normal and a transgenic murine model that the emphysematous lung exhibits reduced SI and T_2^* that closely relate to lung tissue density (20) and the method could discriminate emphysematous mice from normal mice (21).

We hypothesize that the ability of the UTE MRI to acquire endogenous MR signal of the lung parenchyma will allow us to assess changes in SI due to inhalation of molecular oxygen or i.v. injection of Gd, which represent the distribution of ventilation or perfusion, respectively. The present study tested the feasibility of an optimized UTE MRI for assessment of regional pulmonary ventilation/perfusion in normal rats and in a rat model of PE in a standard 3T clinical MRI system.

MATERIALS AND METHODS

All MRI studies were conducted in a 3T whole-body human scanner (Achieva™, Philips Medical Systems, Best, Netherlands) with a small animal solenoid radiofrequency (RF) coil (63 mm in diameter and 100 mm in length; Philips Research Europe, Hamburg, Germany).

Animal Preparation

Animal protocol in this study was approved by the Institutional Animal Care and Use Committee. Eleven male rats (Sprague-Dawley, 8 weeks old, 200–300 g body weight, Charles River Laboratories, Inc., Wilmington, MA) were used for the experiments. These rats were divided into two groups: the normal control group ($n = 5$), and the PE model group ($n = 6$). The animal model of PE was generated by injection of allogeneic blood clots through jugular vein as described in the literature (22–24). Briefly, thrombi were made by collecting blood (5 mL) from a rat in a sterilized bottle. The blood clots were stabilized at room temperature for at least 24 h. After the animals were anesthetized with 1–2% isoflurane (AERRANE, Baxter Healthcare Corporation, IL) mixed in 100% oxygen, the right jugular vein was exposed and isolated, and an indwelling catheter (PE 190, 1.19 mm I.D. Becton, Dickinson and Company, NJ) was inserted in the jugular vein. The blood clots (0.12 g/kg) were injected through the catheter. The animals were subjected to the MR session approximately 1 h after the injection of the clots.

Imaging Protocol

Under anesthesia with 1.5–2% isoflurane mixed in medical grade air through a home-made mask, all animals were placed supine with the thorax centered with respect to the center of the RF coil. A phantom containing 25 mM Gd (Magnevist™, Bayer Schering Pharma, Berlin, Germany) was located next to the animal as a reference. A volume of interest (VOI) was positioned to encompass the entire lung. On the selected VOI, a nongated three-dimensional (3D) radial UTE sequence (25) was performed repeatedly with the receiver gain fixed. A simultaneous dual-acquisition sequence with $TE_1 = 0.1$ ms and $TE_2 = 2.3$ ms was acquired using a single excitation and a reversal of the readout gradient for the second acquisition. To form an echo, two center-out dual-acquisition radials were combined (25,26). Total number of radial views was 14112 with the profiles distributed isotropically over a sphere (“Koosh ball”). For reconstruction, before Fourier transformation, the acquired data were resampled to a Cartesian grid using a k -space trajectory that accounts for gradient eddy current effects (27). The UTE images were reconstructed using the standard manufacturer software, without the need of any additional customization. The other parameters were: repetition time (TR) = 10 ms, flip angle (FA) = 30°, acquisition-window duration = 1.27 ms, the used gradient strength = 31 mT/m, spectral bandwidth = 62.8 KHz

(784.4 Hz / voxel), field of view (FOV) = 50³ mm, matrix size = 84³ (595 µm isotropic resolution, reconstructed to 192³ matrix), number of excitations (NEX) = 1, and total scan time = 2 min 21 s. For ventilation imaging, a set of four UTE images was acquired for each rat first with air inhalation (baseline) and then with 100% oxygen inhalation, respectively. In addition, UTE imaging was repeated with other three different flip angles (5°, 10°, 20°) to measure T1 of the lung parenchyma under both conditions. For subsequent perfusion imaging under air inhalation, 12 postcontrast UTE images were obtained after i.v. injection of Gd at a dose of 0.2 mmol Gd/kg (Magnevist™, Bayer Schering Pharma, Berlin, Germany). The four baseline images obtained for ventilation imaging were also used as precontrast images. An approximately 5-min interval was used between the scans after switching the gasses. The study design of the imaging session is shown in Figure 1.

Image Analysis

In the control rats, we first measured the length of the long axis of each right and left lung on the obtained 3D image, then selected an axial image at 50% location between the apex and the caudal end for the following SI measure as demonstrated in our previous work (20). On the selected image, SI of the lung parenchyma in each animal was measured in four different regions of interest (ROIs, two for each right and left lung, 32 pixels and 2.5 mm² in each ROI) which were selected, taking care to avoid main pulmonary vessels as described previously (20). SI was also analyzed in air to provide an estimate of noise in each image and all measured SIs were corrected by the noise (28). Percent change in SI after administration of oxygen or Gd was then calculated using the following equation:

$$\% \text{ change in SI} = (SI_{\text{post}} - SI_{\text{pre}}) / SI_{\text{pre}} \times 100(\%),$$

where SI_{post} and SI_{pre} is SI measured before and after the administration of oxygen or Gd. SI and % change in SI in each animal were determined as an average within four ROIs. T1 map was generated from the image series obtained at different FAs (5, 10, 20, 30°) under both air and oxygen inhalation. T1 values were measured on the T1 map in the same four ROIs and averaged in each animal.

In the PE model rats, the SIs and % changes in SI were measured and analyzed using the same procedure in both normal and abnormal tissues, which were determined visually on the first image after the injection of Gd and were further confirmed in histopathological examinations. All image processing was conducted using an imaging processing software (ImageJ, version 1.40g). To generate volume rendering (VR) image, we used a free image processing software (Insight Toolkit SNAP) (29).

Histology

Histopathological evaluations were performed on the PE model group. Following euthanasia by overdose of the anesthesia, the trachea was exposed and cannulated. The lungs were inflated in the closed chest condition at 20 cmH₂O by tracheal instillation of 10% formalin and the tracheal cannula was clamped to maintain fluid pressure. After fixation in situ, the lungs were removed and immersed in 10% formalin overnight. The lung tissue was embedded in optimal cutting temperature compound and flash frozen. The tissue was

sectioned on a Leica 3050S cryostat at 8 μm . Pathologic slices were obtained in an axial plane and stained for hematoxylineosin for microscopic examination to verify the presence and location of embolism in pulmonary arteries.

Statistical Analysis

All values were expressed as mean $\pm$ standard deviation (SD). In the control group, % change in SI or T1s of the lung parenchyma were compared between under air and 100% oxygen conditions by paired t-test. The % change in SI of the lung after the injection of Gd (12 points were collected with time after injection up to 30 min) was compared with the baseline (average of 4 points) using an analysis of variance (ANOVA) followed by paired Dunnett multiple-comparison test. In the PE model group, the % change in SI by oxygen inhalation was compared between the normal and embolized tissues by Student t-test. The % change in SI by Gd injection was compared between normal and embolized tissue by Student t-test at each time point. All statistical analyses were performed by using a commercial software (Prism 5.0TM, GraphPad Software, Inc., San Diego, CA), and $P < 0.05$ was considered to indicate statistically significant difference.

RESULTS

Ventilation/Perfusion Imaging in the Control Group

Figure 2b demonstrates a representative % change in SI map after inhalation of 100% oxygen on a UTE image in a normal rat. SI in the lung parenchyma increased by $15 \pm 4\%$ ($P = 0.001$, Fig. 2c) due to inhalation of 100% oxygen in which the enhancement was higher than that in the surrounding tissues, e.g., skeletal and cardiac muscles. At the same time, the T1 of the lung parenchyma decreased by 23% (air: 1370 ± 159 ms vs 100% oxygen: 1049 ± 93 ms, $P < 0.01$, Fig. 2d). Figure 3 shows representative UTE images (a–b) and a % change in SI map immediately after injection of Gd (c), demonstrating strong enhancement over the entire lung parenchyma. Time course of % change in SI of the lung parenchyma before and after (up to 30 min) in the control group is shown in Figure 3e. The % change in SI was the highest ($480 \pm 172\%$) on the first image obtained immediately after Gd injection, then it decreased gradually over time and leveled off ($229 \pm 132\%$) up to 30 min after injection.

Ventilation/Perfusion Imaging in the PE Group

On the UTE images obtained immediately after Gd injection (Fig. 4a), the animals with PE exhibited 1 to 6 spotted regions (22 total) of reduced enhancement in the lung which corresponded to the abnormal regions in gross histopathological specimens (Fig. 4c). The mean size of the reduced enhancement area was 5.7 ± 1.5 mm (range, 2.9–8.4 mm), and all of the regions were located in the peripheral areas of the lungs. Clot forms were further confirmed in all those regions whereas no such a lesion was found in the surrounding tissues in the histopathological examination. Figure 4d shows a representative micrograph of a blood clot which is present in the proximal pulmonary artery in the embolized tissue. Time course of % change in SI of the normal and embolized tissue in the lungs before and after Gd injection (up to 30 min) is shown in Figure 5a. In the normal tissue, SI increased by $403 \pm 130\%$ immediately after Gd injection, and then gradually decreased over time, still retaining $111 \pm 103\%$ up to 30 min. This trend was very similar to the trend seen in the

control group demonstrated in Figure 3e. In the embolized tissue, the increase in SI was significantly lower ($183 \pm 129\%$; $P < 0.05$) on the image immediately after Gd injection than that in the normal parenchyma ($403 \pm 130\%$), and the enhancement was still remaining $111 \pm 118\%$ up to 30 min after the injection indicating the delayed washout.

By contrast, these embolized tissues revealed almost identical changes in SI with the surrounding normal parenchyma in response to oxygen inhalation (normal tissue: $17 \pm 5\%$ vs embolized tissue: $17 \pm 5\%$, not significant, Fig. 5b), which indicates the presence of areas of ventilation–perfusion mismatch. Figure 6 shows a representative case of the ventilation–perfusion mismatch where the oxygen-enhanced image shows relatively homogenous enhancement over the entire lung while Gd-enhanced image shows multiple peripheral areas with reduced enhancement in both lungs.

DISCUSSION

Previous work to develop pulmonary MRI clearly revealed that the potential to evaluate the lung tissues increases as TE becomes shorter (30,31), although it is still challenging to detect MR signal from the lung parenchyma. The 3D radial UTE sequence we used could achieve TE of 100 μ s and provided endogenous MR signal from the pulmonary parenchyma as observed in the previous reports in small rodents (20,21). The signal is acquired using a center-out sampling scheme, which corresponds to sampling the FID. The readout starts immediately after the RF system is switched from transmit to receive. Thus, the coil-dependent switching time defines the minimal TE. To increase T1 sensitivity, we increased FA than that used previously (20,21) (30° versus 10°), although the ability to acquire the parenchymal MR signal was reduced. However, the sequence allowed direct assessment of the change in MR signal of the pulmonary parenchyma to visualize the distribution of ventilation and perfusion.

The performance of oxygen-enhanced MRI heavily relies on the ability to obtain signal from the lung parenchyma and on the sensitivity of the imaging sequence to the change in parenchymal T1 value (32). In most of previous studies in human, investigators have used a half-Fourier single-shot turbo spin-echo (HASTE) or single-shot fast spin-echo with minimum TE (e.g., 4 ms) because spin-echo type sequences can reduce susceptibility effect and the combination with an inversion-recovery pulse can increase T1 sensitivity. Although these studies demonstrate the clinical utility of the method for the evaluation of ventilation, use of these conventional MR sequences has limitations in the achievable TE and the observed signal enhancement ratio varies by the selection of inversion recovery time. In addition, modulation of T1 values seen in parenchymal lesions may complicate the variation. For example, it was reported that the T1 values of the lung were shorter in pulmonary emphysema (33) and fibrosis (34) than in normal lungs. Moreover, inversion-recovery HASTE is time consuming, and difficult to assess oxygen-enhancement within whole lung. By contrast, the use of UTE sequence produces sufficient MR signal from the parenchyma to assess its change without inversion recovery pulse. The parenchymal signal increased by $15 \pm 4\%$ in the normal rat with accompanying reduction of the mean tissue T1 relaxation time (1370 ± 159 ms to 1049 ± 93 ms; 23%) when the inhalation gas was switch from air to 100% oxygen. Watt et al (32) reported in mice using an inversion recovery fast

spin-echo sequence that the SI increased $16 \pm 9\%$ and $11 \pm 7\%$ in the right and left lobes, respectively. Although we did not see such a difference between the right and left lungs in rats (right: $15 \pm 5\%$, left: $15 \pm 6\%$), our result of % change ($15 \pm 4\%$) in the normal parenchyma by the UTE MRI appeared consistent with their results while the coefficient variation of our values were much smaller. The T1 shortening effect was similar in both studies (23% versus 20%) (32). Pracht et al reported in human that the T2* in the lung parenchyma reduced by 10% by inhalation of oxygen (35); however, this effect is trivial at TE of 100 μ s.

Oxygen-enhanced MR imaging is particularly sensitive to motion artifact/position mismatch because the regional ventilation is assessed on the subtraction image between the images acquired with 100% oxygen and air inhalation. Therefore, it is critical to avoid misregistration between the images. Hence, acquisition methods in conjunction with the elaborated respiratory and cardiac synchronization (12) or implementing navigator echoes (36) have been discussed. In our study, it is important to note that none of obtained images were degraded by obvious motion artifact although neither cardiac nor respiratory gating was implemented. This was because of the radial trajectory through *k*-space in which the FID is sampled from the center of the *k*-space, and thus the center of *k*-space is heavily oversampled to eliminate motion artifact. Indeed, the T2* values measured with and without respiratory gating were similar (1.00 ± 0.13 ms versus 1.16 ± 0.15 ms) in the same system (21). This motion insensitivity offers a definite advantage in generation of the calculated images (e.g., ventilation/ perfusion maps) and assessment of regional parenchymal function. Nevertheless, we should pay close attention to control respiratory rate under inhalation of air and 100% oxygen because the parenchymal SI must be averaged out over the entire respiratory cycle.

First-pass DCE perfusion MRI of the lung can provide regional blood volume/flow and mean transit time to detect focal functional defects (3,16,37); however, the accuracy of these numbers remains debatable. With optimization of injection volume and Gd concentration to avoid saturation effects of enhancement by means of high concentration in the first-pass bolus, the method could yield equivalent results compared with multidetector row CT (MDCT) in quantifying the extent and predict the outcome of PE (38). However, there are still remaining concerns regarding limited spatial resolution, use of high rate bolus injection of contrast agent and requirement of sophisticated image processing method to analyze the first pass of the agent. By contrast, UTE MRI can provide isotropic 3D data with potentially higher spatial resolution although it is not as time-resolved. Observed enhancement at each time point after Gd injection is an average value over the duration of image acquisition (c.a. 2.5 min). However, the areas depicted as “signal void” relative to the surrounding normal parenchyma correspond well to anatomical PE lesions (Fig. 4). Unlike DCE perfusion MRI, the UTE MRI method does not quantify vascular perfusion directly but maps the effect of perfusion changes on the parenchyma analogous to that of perfusion scintigraphy. Weak residual enhancement in the PE lesions could have been caused by partial vascular obstruction, local inflammation and increased capillary permeability that allowed Gd to enter the interstitial space, and/or collateral perfusion arising from the bronchial circulation. Indeed, the first image after injection of Gd was the best to delineate the PE lesions and the

contrast between the normal and embolized tissues decreased at later time points (Fig. 5a). Further studies are necessary to evaluate the sensitivity and specificity of the UTE MRI method in detecting different degrees of embolism and reperfusion, and whether the observed enhancement correlate with hemodynamic changes.

Another possible benefit to leverage UTE MRI is that we can implement both ventilation and perfusion imaging with an identical spatial resolution, which would lead to more accurate evaluation of ventilation–perfusion mismatch. The UTE MRI is directly translatable to clinical use as shown by the use in the present study of a 3T clinical MRI system. Further studies will test the clinical utility of the method for ventilation/ perfusion imaging of the lung in human subjects.

In conclusion, ventilation/perfusion imaging of the lung by UTE MRI in a 3T clinical MRI system is feasible. The method provides sufficient MR signal from the lung parenchyma to detect changes due to inhalation of 100% oxygen or i.v. injection of Gd and delineates spatial ventilation–perfusion mismatch in PE lesions. This direct assessment of the change in MR signal of the pulmonary parenchyma supports the diagnostic potential of UTE MRI for the evaluation of regional ventilation and perfusion without incurring the risks of radiation exposure.

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Figure 1.

Summary of study protocol. Each column represents an 3D UTE imaging ($FA = 30^\circ$, $NEX = 1$, c.a. 2.5 min). For ventilation imaging, a set of four UTE images are acquired under air inhalation (baseline) which were followed by 100% oxygen inhalation. Additionally, UTE images with a series of FA (5° , 10° , 20°) are obtained for T1 measurement of the lung parenchyma under both conditions in the control group. For subsequent perfusion imaging under air inhalation, 12 postcontrast UTE images are obtained after intravenous (i.v.) injection of Gd.

Figure 2.

Representative transverse UTE image of the lung (a) and map of % change in SI after inhalation of 100% oxygen (b) in a control rat. Note that the enhancement is higher than that in the surrounding tissues, e.g., skeletal and cardiac muscles. % change in SI (c) and change in T1 (d) in the lung parenchyma due to inhalation of 100% oxygen in the control group (n = 5). Data are expressed as changes relative to baseline. ** $P < 0.01$, *** $P < 0.001$ by paired t-test. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 3.

Representative transverse UTE images of the lung before (a) and immediately after (b) Gd injection and map of % change in SI (c) in a control rat. Note that the enhancement in the lung parenchyma is not visible in the image at TE of 2.3ms (d). Time course of % change in SI of the lung parenchyma (e) before and after Gd injection in the control group (n = 5). Data are expressed as changes relative to baseline. # $P < 0.05$ by an analysis of variance (ANOVA) followed by paired Dunnett multiple-comparison test. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 4.

Representative transverse UTE images of the lung at TE of 100 μ s (**a**) in a rat with PE, showing focal reduced enhancement in the right lung (arrows) obtained immediately after Gd injection. Note that the contrast is not visible on the UTE image at TE of 2.3 ms (**b**). The gross histology of the lung in the same rat (**c**) shows that the corresponding lung regions in the right lung appear abnormal (arrows). Typical micrograph (**d**, HE staining, $\times 12.5$) of a clot form (arrow) in the proximal pulmonary artery found in the corresponding embolized tissue. Bar = 1 mm. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 5.

a: Time course of % change in SI of the normal and embolized tissues in the lungs before and after Gd injection in the PE group (n = 6). **b:** The % change in SI of the embolized and surrounding normal tissues due to oxygen inhalation. **c:** The % change in SI of the embolized and normal tissues in the first image after Gd injection. Note that the embolized tissues yield mostly identical changes in SI in response to oxygen inhalation but much less change in response to Gd injection relative to the surrounding normal parenchyma, suggesting ventilation–perfusion mismatch. * $P < 0.05$ by Student t-test.

Figure 6.

Typical maps of % change in SI due to oxygen inhalation (a) or Gd injection (b) at a same coronal slab and volume rendering image (c) in a rat lung with PE, showing the areas of ventilation-perfusion mismatch (arrows). Gross histology (d) identifies the embolized tissues in the corresponding areas in the right lung (arrows).