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Simultaneous MRI of Lung Structure and Perfusion in a Single Breath-hold

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Abstract

Purpose—To develop and demonstrate a breath-held 3D radial ultrashort echo time (UTE) acquisition to visualize co-registered lung perfusion and vascular structure.

Methods—Nine healthy dogs were scanned twice at 3T. Contrast-enhanced pulmonary perfusion scans were acquired with a temporally interleaved 3D radial UTE (TE = 0.08 ms) sequence in a breath-hold (1 sec time frames over a 33 second breath-hold). The 3D breath-held volume was reconstructed into a time-resolved perfusion datasets, and a composite vascular structure dataset. For structural comparison, a 5 min respiratory-gated 3D radial UTE scan was acquired. Data was analyzed by quantitative metrics and radiologist scoring.

Results—Appropriate time-course of contrast was seen in all subjects. Right ventricle to aorta transit times were 7.4 ± 2.0 s. Relative lung enhancement was a factor of 8.4 ± 1.5 . Radiologist scoring showed similarly excellent visualization of the pulmonary arteries to the subsegmental level in breath-held (94% of cases) and respiratory-gated (100% of cases) acquisitions ($p = 0.33$) despite the aggressive under sampling in the breath-held scan. Similar, differentiation of lung tissue and airways was achieved by both acquisition methods.

Conclusions—A time-resolved 3D radial UTE sequence for simultaneous imaging of pulmonary perfusion and co-registered vascular structure is feasible.

Keywords

3D radial UTE for lung imaging; pulmonary perfusion; vascular structure

INTRODUCTION

Lung diseases usually cause both structural and functional changes. For example, pulmonary emboli (PE) restrict flow in the pulmonary arteries leading to decreased perfusion distally. To identify the source and impact of PE on lung function, imaging of the vascular anatomy and perfusion is required in combination with structural images to rule out alternative diagnosis. Traditionally, computed tomography (CT) has been used to assess the lung vasculature and structure, while scintigraphy has been used to evaluate lung perfusion and ventilation. Over the past decade, magnetic resonance imaging (MRI) has shown growing promise as a cross-sectional modality for imaging lung structure (1–5), ventilation (6), and perfusion (7,8). Early pilot studies in different patient populations have suggested that these approaches may have clinical utility. The combination of these techniques within a single modality holds promise for co-registered and complementary functional and structural images within a single exam and without the use of ionizing radiation. However, current MRI protocols for pulmonary emboli require separate scans optimized for evaluation of vascular structure and pulmonary perfusion. Although effective, separate structure and function imaging protocols complicate workflow and diagnosis. Improved efficiency and diagnostic accuracy is likely to be achieved for an MRI technique capable of joint assessment of vascular structure and perfusion in a manner similar to that used routinely with CT.

Highly accelerated contrast-enhanced MRI has enabled the acquisition of high resolution pulmonary perfusion and angiography (MRA) (9–11). Unfortunately, the conflicting needs for high spatial resolution for MRA (~1.5mm isotropic) and high temporal resolution for perfusion (~1 sec) pose a challenge for a single imaging sequence. Conventionally, to achieve sufficient temporal resolution for perfusion, relatively low spatial resolution is used, typically 3–4 mm in each dimension (11–14). While these perfusion sequences are likely sufficient to identify clinically significant focal perfusion defects, they are inadequate to directly visualize the corresponding vascular pathology (e.g. filling defects due to pulmonary emboli). Conversely, pulmonary MRA scans are most often acquired non-dynamically, precluding their use for robust evaluation of perfusion defects (15,16). For these reasons, evaluation of both vasculature structure and perfusion typically requires two separate breath-held scans.

The precise correlation of vascular structure and perfusion abnormalities on these separate scans requires retrospective image registration. However, image registration is complicated by elastic lung deformation and differing contrasts in perfusion and angiography scans, making it difficult to integrate into routine clinical workflows. In practice, structure-function correlation is performed subjectively by a radiologist using visual side-by-side inspection of the images. A single breath-held acquisition producing intrinsically co-registered vasculature structure and perfusion images would more efficiently correlate lung structure

with function and would enable integration within a reasonable clinical workflow. Furthermore, this strategy would also reduce the number of breath-holds, contrast injections, and overall scan time in a patient population that is liable to be dyspneic and unable to tolerate long exams.

Radial sampling enables higher temporal resolution, spatial resolution and coverage compared to Cartesian sampling due to the repeated sampling of the center of k-space. In particular, 3D radial sampling has been demonstrated for full chest coverage for both dynamic MRA (17) and ultra short echo time (UTE) applications (18). When combined with center-out sampling (as in UTE) marked improvement in the visualization of structural lung disease has been demonstrated (3,4,18). Although recent small animal studies suggest promise for joint lung structure and perfusion visualization, the combination of dynamic 3D radial imaging with the structural imaging capability of UTE has not yet been investigated for dynamic perfusion and structural imaging in large animals or humans.

The purpose of this work was to develop and demonstrate a method to simultaneously acquire both high-resolution vascular and structural images with intrinsically co-registered perfusion images using a single breath-held 3D radial UTE acquisition.

METHODS

Nine canine subjects (8 males: 1 female; weight 10.7 ± 1.2 kg; mean age 13 months) underwent dynamic-contrast enhanced MR imaging using a time-resolved 3D radial UTE pulse sequence. Each animal was scanned twice, separated by 2–4 days, resulting in a total of eighteen UTE perfusion acquisitions. Animals were mechanically ventilated and placed in the scanner in the supine position. Due to the requirements of a separate study being conducted simultaneously on the same dogs, the anesthesia used on the two study visits differed. Each dog received midazolam and fentanyl on one visit, and dexmedetomidine on the other. Eight of the animals were healthy and showed no cardiopulmonary abnormality; however, the one female animal had an incidentally discovered membranous ventricular septal defect causing a small left to right cardiac shunt. Our Institutional Animal Care and Use Committee approved this study.

MR Protocol and Post-Processing

All imaging was done on a commercial 3T scanner (MR750, GE Healthcare, Milwaukee, WI, USA) with gradient peak slew rate of 200 T/m/s and maximum gradient strength of 50 mT/m. Twenty elements of a clinical 32-channel chest phased array coil (Torso Array, Neocoil, Pewaukee, WI, USA) were used, providing for complete lung coverage. Two acquisitions were performed: a 33 second dynamic breath-hold acquisition during contrast injection and a 5 min respiratory-gated acquisition immediately following.

Temporally interleaved 3D radial UTE images were acquired starting simultaneously with the injection of 2.3 mL (~ 0.1 mmol/kg) of gadobenate dimeglumine (Multihance; Bracco Diagnostics, Princeton, NJ) followed by a 17 mL saline flush at 2 mL/sec in the cubital vein. Relevant acquisition parameters included: TR/TE = 3.3/0.08 ms, receiver bandwidth = ± 125 kHz, total number of readout points = 682 (1.4 ms readout time), flip angle = 15° , 0.94

mm isotropic spatial resolution, 8,000 total projections, and 1 sec time frames acquired over a 33 sec breath-hold at end expiration. The breath-hold was performed by stopping mechanical ventilation to allow for scanning. A slab-selective radiofrequency excitation with limited field of view, variable read-out gradients, and radially oversampled (2 times oversampled) projections were used to improve the quality of the lung images. Additional details regarding the design and optimization of the 3D radial UTE pulse sequence have been previously published (18).

The 3D radial UTE data was reconstructed using an iterative sensitivity encoding algorithm (iSENSE) (16) at full 0.94 mm isotropic resolution on a 256^3 matrix. As the breath-held perfusion acquisition is composed of 33 undersampled time frames, each consisting of a pseudo-random interleaved projection scheme for relatively uniform k-space coverage, a k-space adaptive filter was used as a temporal view-sharing method for reconstruction (20). This filter has a width of 1 second at the center of k-space increases to 7 seconds with a quadratic weighting function from the center to the edge of k-space. Therefore the effective frame rate is 1 second with a temporal footprint of 7 seconds.

For structural analysis, a composite dataset consisting of all 8,000 projections acquired during the dynamic acquisition was reconstructed at full 0.94 mm isotropic resolution. This 8,000 projection breath-held composite image acquired in 33 sec was compared with the reconstruction of a respiratory-gated image consisting of 38,000 projections acquired over a 5 min acquisition; hereafter referred to as “breath-held” and “respiratory-gated” scans respectively. The respiratory-gated, 3D radial structural UTE scan was acquired with the same pertinent acquisition parameters during tidal breathing after the dynamic breath-held acquisition. Prospective respiratory gating to end-expiration was used with adaptive feedback from the respiratory bellows signal used to define a 50% acceptance window. Due to the 50% acceptance window, the scan efficiency was 50% as the number of projections remained fixed. Each subject’s respiratory pattern determined the total number of projections acquired during each expiratory phase.

Image Analysis and Measurement

Dynamic Contrast Enhanced Measures—To evaluate regional qualitative pulmonary perfusion 3D peak lung enhancement maps were calculated. The peak lung enhancement maps were calculated by simply performing a maximum intensity projection along the time dimension on a voxel-by-voxel basis. These peak lung enhancement maps were used to calculate the gravity dependent anterior-posterior (AP) gradient within the lungs, measured by comparing the mean signal in a region of interest (ROI) placed in the anterior right lung with the mean signal in an ROI placed in the posterior right lung, each normalized to the mean signal within ROIs placed in nearby muscle. The anatomic locations of the ROIs were determined by axially scrolling through the volume dataset to locate a slice superior to the heart.

The right ventricle (RV) to aorta transit time was calculated by manually placing circular ROI’s centered in the RV and descending aorta to determine their enhancement as a function of time. Transit times were determined by the time interval between peak enhancement in the RV and in the aorta.

Relative lung enhancement was calculated on a voxel-wise basis by subtracting precontrast signal derived from the first time frame, and then dividing by this precontrast signal. The first time frame is more likely a noise measure of stochastic and image artifact than true precontrast signal; therefore these calculations are a mixed metric of both signal and noise. Again, a circular ROI that avoided large vessels was manually positioned within the right lung to determine average relative lung enhancement for each dog.

Vascular Contrast and Structural Measures—Vessel edge width (to assess vessel sharpness), relative vascular signal (to assess the amount of vascular enhancement), and relative lung signal (to assess how well lung tissue is visualized) were used as structural image quality metrics. The dynamic breath-held acquisition and the respiratory-gated acquisition were compared using these measures.

Vessel edge width was chosen in order to evaluate potential blurring which can occur both due to motion and due to changing contrast dynamics during the scan (21). Using multiplanar reformations, cross-sectional images of two representative pulmonary arteries just distal to their origins were generated: the left main pulmonary artery and the first medially branching segmental pulmonary artery arising from the caudal lobe of the right lung (Figure 5). The vessel edge width was measured along 12 evenly spaced radial edge profiles beginning at the center of the specified vessel (demonstrated on Figure 5). Vessel edge width was defined to be the distance from 20% to 80% of the peak value. Edge profiles that failed to drop below 20% were excluded from the analysis due to insufficient contrast between the measured vessel and adjacent background structures.

Relative vascular and lung signal were calculated through manual placement of circular ROIs. Both measurements were normalized to the standard deviation of airway signal as a “pseudo-noise” metric. Relative vasculature signal (rVS) was calculated using the mean signal in ROIs placed in the vessels used for the vessel edge width measurements and in nearby lung tissue:

$$rVS = \frac{\text{Vessel} - \text{Lung}}{\sigma_{\text{Airway}}}, \quad (1)$$

Similarly, relative lung signal (rLS) was calculated using the mean signal in six circular ROIs placed in anterior, middle, and posterior in both lungs and an ROI in nearby airway using the equation:

$$rLS = \frac{\text{Lung} - \text{Airway}}{\sigma_{\text{Airway}}}. \quad (2)$$

Image measurement and statistical analysis was performed using MATLAB (The Mathworks Inc.; Natick, MA, USA). The quantitative measures are reported as mean $\pm$ standard deviation and were compared using a paired Student's t-test. A p-value less than 0.05 was considered statistically significant.

In addition to the parametric measurements previously mentioned, two cardiothoracic radiologists with 6 (SN) and 7 (CF) years of experience in cardiovascular MRI scored the structural breath-held and respiratory-gated composites by consensus. The structural anatomy of the pulmonary arteries was evaluated on a 4-point scale, indicating the smallest well visualized vessels (1 = Main, 2 = Lobar, 3 = Segmental, 4 = Subsegmental). Two components of structural quality of the lung were scored on a binary scale: one for differentiating airways from the lung and the second for identifying an AP gradient. Lastly, subjective measurements of the noise in the composites were also scored on a 3-point scale. (1 = “Severe: renders images non-diagnostic for PE or consolidation”, 2 = “Moderate: diagnostic but decreased confidence”, 3 = “Mild: diagnostic with high confidence”, 4 = “No significant noise”).

RESULTS

Both the time-resolved dynamic 3D radial UTE perfusion and the respiratory-gated structural UTE acquisition were successfully performed in all 18 experiments (2 experiments per animal). The first two (2) experiments were performed using different scan parameters than the remainder and were therefore excluded, resulting in a total of sixteen (16) datasets for analysis. Reconstruction of both perfusion and structural images from the same dataset eliminated the need for image registration (Figure 1).

Figure 2 shows coronal MIP images of the first pass contrast dynamics from a typical scan, reconstructed at 1.0 frame/sec and 2.3 mm isotropic spatial resolution. Figure 3 illustrates the relative enhancement of the right ventricle, lung, and left ventricle over the breath-hold time in the same experiment. Mean relative lung enhancement was a factor of 8.4 ± 1.5 (Table 1). Mean RV to aorta transit times was 7.4 ± 2.0 sec (Table 1) with a typical example shown in Figure 3. The normalized anterior lung signal was 0.80 ± 0.13 and the normalized posterior lung signal was 1.76 ± 0.30 (Table 1), resulting in a statistically significant AP gradient ($p \ll 0.05$).

An unsuspected membranous ventricular septal defect was discovered in one of the presumed healthy dogs using data acquired for an unrelated study. This resulted in altered temporal dynamics compared to the other animals (Figure 4). The full-width-at-half-maximum (FWHM) of the right ventricular enhancement peak was greater than measured in the other dogs, indicating a left-to-right cardiac shunt consistent with the animal's ventricular septal defect. As seen in Figure 4 the measured FWHM was 12.6 sec compared to an average of 8.7 ± 1.4 sec for healthy individuals administered under midazolam and fentanyl anesthesia. Similar results were seen for the exams performed under dexmedetomidine anesthesia. This result illustrates that despite the use of a k-space temporal filter, abnormalities in enhancement curves can be detected.

Figure 5 demonstrates typical cross-sectional appearances of the left main pulmonary artery and the right segmental pulmonary artery used for structural assessment. Table 2 summarizes the results of the structural analysis of both composite breath-held and respiratory-gated acquisitions. The vessel edge width of both large and small arteries differed significantly ($p = 0.003$) between the acquisitions. The vessel edge width was

greater (ie. vessels were more blurred) on the composite breath-held acquisitions for both the large (left main) and small (segmental) pulmonary arteries ($p < 0.05$ for both vessels). There was no statistically significant difference in relative vascular signal in either the left main pulmonary artery ($p = 0.16$) or in the smaller segmental pulmonary artery ($p = 0.19$). Likewise, there was no statistically significant difference ($p = 0.48$) in the relative lung signal between both acquisitions.

Radiologist scoring showed that both the breath-held and respiratory-gated acquisitions presented similarly excellent depiction of the pulmonary arteries to the subsegmental level ($p = 0.33$). Radiologist scoring showed similarly excellent depiction of the pulmonary arteries to the subsegmental level in 15/16 (94%) of the breath-held and 16/16 (100%) of the respiratory-gated acquisitions ($p = 0.33$). The one breath-held case was visualized to the segmental level (score of 3) instead of the subsegmental level. Differentiation between lung tissue and airways was possible for both acquisitions, whereas the AP gradient was clearly seen in the breath-held composites. Breath-held composites were significantly more compromised by noise (median score of 3) than the respiratory-gated images (median score of 4) at $p < 0.001$.

DISCUSSION

This study demonstrates the feasibility of simultaneously acquiring co-registered pulmonary perfusion and pulmonary artery structure images using a 3D radial UTE sequence. Prior results have shown that lung disease, such as pulmonary embolism, can be identified by both the qualitative changes in pulmonary perfusion and by direct visualization of embolus in the pulmonary artery (7,22–24). Using a single 3D dataset acquired during a single breath-hold to reconstruct images of both lung structure and function allows direct spatial correlation between the findings on each. This avoids the need for retrospective image registration, shortens total scan time by eliminating the need for a second breath-hold, and eliminates a second contrast injection.

Reasonable first-pass contrast dynamics and lung enhancement was seen in all of the animals scanned using this dynamic 3D UTE acquisition. The circulation of the contrast bolus through the right ventricle, pulmonary arteries, lung, and left ventricle could be clearly differentiated despite a temporal footprint of seven seconds that incorporated view sharing in the periphery of k-space. Observed temporal dynamics allowed for quantification of the transit time of contrast between the right ventricle and the descending aorta. Lung enhancement showed the expected gravitational gradient in AP direction, consistent with normal physiology (25,26). The presence of contrast during the breath-held scan most likely created a more defined AP gradient than in the respiratory-gated composites. The observed left-to-right shunt was later confirmed to be a membranous ventricular septal defect, and this serendipitous result suggests that temporal filtering imposed by view sharing may not compromise quantitative measures.

Vessel edges were sharper on the respiratory-gated acquisition than on the breath-held acquisition. We suspect that the primary cause for the increased blurring on the breath-held acquisition is the time-varying contrast bolus imposing a low-pass filter during data

acquisition. This can introduce artifacts, analogous to the ringing and widening of vessels edges that can be seen in Cartesian acquisitions (21). However the blurring of the vessel edge width during the breath-hold was relatively mild since good visualization of the pulmonary arteries to the subsegmental level was appreciated by the radiologist readers.

Relative vascular signal trended slightly higher in the respiratory-gated images than in the breath-held images. Intuitively, it would seem that the relative vascular signal should be higher in the breath-held acquisition due to the higher concentration of contrast present in the vessel, but the aggressive under-sampling introduces more streak artifacts. Despite this, the relative vascular signal did not differ significantly between the two scans. Finally, relative lung signal measurements trended slightly lower in the breath-held versus respiratory-gated images, likely due again, to the streak artifacts arising from the more aggressive radial under-sampling, causing the standard deviation of the airway signal to be higher in the breath-held acquisition. Indeed, scoring by radiologists demonstrated that the breath-held scans were “noisier” than the respiratory-gated scans; however, the breath-held scans were still considered “reasonably diagnostic”. Nevertheless, the relative lung signal did not differ significantly between the scans, suggesting that these under-sampling artifacts are relatively minor.

This study has several limitations. As data used to reconstruct each 3D volume in the perfusion time-course are under-sampled, an adaptive k-space filter was necessary in order to mitigate radial streak artifact. Therefore, absolute quantification of the arrival times of the contrast bolus may be compromised. Similarly, quantitative hemodynamic parameters such as pulmonary blood flow, pulmonary blood volume, and mean transit time derived from this acquisition may be similarly compromised. The application of compressed sensing reconstruction methods to this technique may improve the true temporal resolution (ie, temporal footprint) of the method, potentially enabling this method to be used for more quantitative pulmonary perfusion measurements. Compressed sensing also could mitigate the subjective noise seen in the breath-held composites. In addition, to ensure linearity between contrast agent concentration and signal in the arterial input function (typically the pulmonary artery), quantification demands a small contrast bolus and correct pulse sequence parameters (e.g. flip angle) both of which were outside the scope of the present study. For these reasons we chose 3D peak enhancement maps to qualitatively assess pulmonary perfusion since this metric has been used in other studies (27). Finally, this feasibility study was performed only in a small population of presumed healthy animals.

The dynamic contrast enhancement measures demonstrated strong peak enhancement of lung tissue relative to the pre-contrast image (a factor of eight) and the expected physiologic AP gradient in perfusion was apparent. We therefore believe that sufficient signal is obtained on the perfusion reconstruction to support feasibility for detection of clinically significant perfusion defects; however, the performance of this imaging approach in the setting of lung disease remains to be assessed and is indeed the subject of an ongoing study. Furthermore, the 33 second breath-hold acquisition currently implemented in our animal study will be difficult to translate to human studies. It was chosen as such to insure sufficient number of projections for the composite structural reconstruction. In translating this method

to humans, the scan time maybe further shortened by constrained reconstruction methods and pulse sequence optimization.

In conclusion, we have demonstrated the feasibility of using time-resolved 3D radial UTE MRI for simultaneous imaging of lung function (perfusion) and co-registered pulmonary vascular structure during a single breath-hold. This approach to structure-function imaging is achieved in a short exam and is relatively robust to motion due to the use of a 3D radial acquisition. It is well suited for clinical situations in which rapid assessment of pulmonary perfusion and pulmonary artery structure is needed since it requires only a single breath-held with a small dose of contrast.

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Figure 1. Perfusion weighted peak parenchymal 3D maps (hot metal) are co-registered with their structural images acquired simultaneously (axial, coronal, and sagittal orientations) in the top row. Corresponding structural images are shown in the bottom row.

Figure 2.
Coronal MIP images demonstrating the dynamic passage of the contrast bolus at a 1 frame/sec rate with 0.94 mm isotropic spatial resolution.

Figure 3. Typical temporal behavior the first pass temporal waveforms visualized in the pulmonary artery (solid line), lung (solid line with *), and aorta (solid line with open circles).

Figure 4.

Prolonged transit time (double arrow measured value of 12.6 sec) illustrates a membranous ventricular septal defect in one of the presumed healthy dogs (dashed black line). Typical enhancement curves for the healthy normal dogs are indicated by the gray solid lines for comparison (average transit time of 8.7 ± 1.41 sec).

Figure 5. Oblique reformatting of 3D composites (left column = breath-held; right column = respiratory-gate) for vessel measurements of the pulmonary artery (first row) and a right segmental lobe (second row). Insert shows the placement of six radial lines used for vessel measurements.

Table 1

Perfusion Analysis

	Mean $\pm$ SD	p-value
Relative Lung Enhancement	8.4 $\pm$ 1.5	--
RV to Aorta Transit Times	7.4 $\pm$ 2.0 sec	
AP Gradient		
Normalized Anterior:	0.80 $\pm$ 0.13	1.40E-08
Normalized Posterior:	1.76 $\pm$ 0.30	

Relative lung enhancement was visualized and calculated for all twelve subjects during the first-pass of contrast. Temporal behaviors of the first-pass of contrast were quantified from the right ventricle to the aorta. Additionally, a statistical difference is seen between the normalized signal measurements in the anterior and poster regions of the pulmonary perfusion maps.

Table 2

Structural Analysis

	Breath-Held Images	Respiratory-Gated Images	p-value
Left Main Pulmonary Artery			
Vessel Edge Width (mm)	1.72 ± 0.22	1.22 ± 0.46	0.003
Relative Vascular Signal	26.4 ± 8.78	29.8 ± 7.41	0.16
Right Segmental Vessel			
Vessel Edge Width (mm)	1.48 ± 0.10	1.29 ± 0.09	< 0.001
Relative Vascular Signal	18.1 ± 8.60	21.6 ± 4.52	0.19
Relative Lung Signal	5.86 ± 2.57	6.49 ± 1.88	0.48

Structural analysis results are presented here as mean ± standard deviation for vessel edge width and relative vascular/lung signal measurements.