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Feasibility of Combining MR Perfusion, Angiography, and ^3He Ventilation Imaging for Evaluation of Lung Function in a Porcine Model

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Abstract

Rationale and Objective— To assess the feasibility of combining magnetic resonance (MR) perfusion, angiography, and ^3He ventilation imaging for the evaluation of lung function in a porcine model.

Materials and Methods— Fourteen consecutive porcine models with externally delivered pulmonary emboli and/or airway occlusions were examined with MR perfusion, angiography, and ^3He ventilation imaging. Ultrafast gradient-echo sequences were used for 3D perfusion and angiographic imaging, in conjunction with the use of contrast-agent injections. 2D multiple-section ^3He imaging was performed subsequently via the inhalation of hyperpolarized ^3He gas. The diagnostic accuracy of MR angiography for detecting pulmonary emboli was determined by two reviewers. The diagnostic confidence for different combinations of MR techniques was rated on the basis of a 5-point grading scale (5 = definite).

Results— The sensitivity, specificity, and accuracy of MR angiography for detecting pulmonary emboli were approximately 85.7%, 90.5%, and 88.1%, respectively. The interobserver agreement was very strong ($k = 0.82$). There was a clear tendency for confidence to increase when first perfusion and then ventilation imaging were added to the angiographic image (Wilcoxon signed ranks test, $P = 0.03$).

Conclusion— The combination of the three methods of MR perfusion, angiography, and ^3H ventilation imaging may provide complementary information on abnormal lung anatomy and function.

Keywords

Angiography; pulmonary embolism; lung perfusion; lung ventilation; magnetic resonance

Contrast-enhanced magnetic resonance pulmonary angiography (MRPA) and MR pulmonary perfusion (MRPP) are emerging imaging techniques for identifying pulmonary arterial structure (1–8). Subsecond temporal resolution and submillimeter spatial resolution can be achieved with state-of-the-art clinical magnetic resonance imaging (MRI) systems. Ultrashort repetition time/echo time (TR/TE) gradient-echo sequences can be applied to obtain volumetric lung imaging within a single breath-hold. The short TE of such sequences is particularly important because of a very short $T2^*$ in lung tissue (9–12). This technical advantage was reflected in two pulmonary artery applications: simultaneous assessment of lung perfusion and flow in the major pulmonary vasculature, and MRPA with relatively high spatial resolution by means of

first-pass MR data acquisition during the arterial phase of contrast enhancement (13–15). The latter technique has shown a high signal-to-noise ratio (SNR), and permits the visualization of pulmonary arteries beyond the subsegmental branches. On the other hand, assessment of regional lung ventilation with hyperpolarized noble gas has emerged as an imaging technique for evaluating lung diseases, including tumors, emphysema, bronchiectasis, cystic fibrosis, and asthma (16–23). A promising MR technique for visualizing the air spaces of the lung is the use of ^3He gas as a contrast agent. Many reports have pointed out that ^3He MRI can provide a high SNR and contrast-to-noise ratio (CNR), with image intensity directly proportional to the local concentration of inhaled ^3He . Integration of MR proton and ^3He imaging will allow the simultaneous assessment of unique lung arterial architecture and air ventilation. This is of particular interests in the study of pulmonary embolism (PE), in which mismatched perfusion/ventilation defects can be found embolism (10,24).

To date, MR techniques employing conjoint proton and ^3He imaging to visualize lung structure have been reported for assessing perfusion and ventilation in rat lungs (25) and in human lungs (26,27), and in a feasibility study with pigs (28). In the study reported here, we sought to assess the efficacy of combining three MR techniques for evaluating lung perfusion and ventilation in a porcine model of PE.

MATERIALS AND METHODS

Animal Models

The animal experimental protocol used in the study was approved by the Animal Study Committee of Washington University. Fourteen consecutive domestic pigs (weight, 22.0 ± 2.4 kg [mean $\pm$ SD]) were used for the study. The pigs were premedicated by intramuscular injection of a cocktail of atropine (0.05 mg/kg), xylazine (2 mg/kg), and ketamine (20 mg/kg). An intravenous access line was secured in the ear for the injection of contrast agent and saline flushing. The pigs were then anesthetized with intravenous injections of pentobarbital (25 mg/kg), and underwent endotracheal intubation. A 9-F Pinnacle introducer sheath (Medi-tech, Watertown, MA) was inserted through the right internal jugular vein and passed into the superior vena cava in 9 of 14 pigs for the delivery of blood clots to create artificial pulmonary emboli.

The creation of emboli has been described in detail previously (29). The diameter of each thrombus was approximately 3 mm and its length was from 1–4 cm. To deliver the blood clots to the pulmonary vessels of the pigs, the clots were inserted into a 1-mL syringe and then injected manually into the 9-F catheter, followed by a flush with normal saline (0.9%). Bronchial obstructions were created in 5 of 8 pigs without pulmonary emboli and 3 of 8 pigs with pulmonary emboli. To do this, an 8-F balloon catheter was used to block one of the bronchial branches. The balloon was first filled with a small amount of diluted gadolinium contrast agent for localizing the catheter and partially dilating the balloon. The catheter was then inserted into the lung of the pig through the endotracheal tube and extended into either the right or the left lung. After resistance of the catheter was detected in the lung, the balloon was inflated completely to fully block the bronchi distal to the balloon. A 3D proton fast low-angle shot (FLASH) image was acquired to identify the location of the balloon.

After this procedure, the pigs were placed in the supine position in the magnet bore, and were mechanically ventilated through a small-animal ventilator (Harvard Apparatus, South Natick, MA) at a rate of 15 breaths/min, a stroke volume of 300 mL, and an inspiration/expiration time ratio of 40/60. Normal saline (0.9%) was administered through the established intravenous line at the rate of 300 mL/kg/hr to maintain hydration. Anesthesia was maintained with a mixture of isoflurane/oxygen during the imaging procedure. A 4-lead electrocardiogram (ECG) patch

was attached to the chest of the pig. During breath-hold scans, ventilation was stopped when the pig's diaphragm was in the inspiration position.

Imaging Protocol

Six of 14 pigs received only pulmonary emboli, and 5 of 14 had airway blocking without given emboli. The remaining 3 pigs had both blood emboli and airway blocking. For pigs with blood emboli, X-ray angiography was performed at the end of the study to confirm the existence and location of the emboli. All pigs underwent MR perfusion and angiographic imaging, which were performed on a 1.5-T Magnetom Sonata system (Siemens Medical Systems, Erlangen, Germany) with a high-performance gradient system (maximum gradient strengths of 40 mT/m and maximum slew rate of 200 mT/m/msec).

The perfusion images were obtained through a 3D gradient-echo sequence with asymmetric k-space sampling in the readout, phase-encoding, and partition-encoding directions. In the slice direction, sinc interpolation was applied to increase the slice display by a factor of two (7). A rectangular RF pulse with a duration of 100 μ sec was used for imaging, allowing TR and TE to be shortened to 1.64 and 0.6 msec, respectively. Other imaging parameters were: flip angle = 15°, readout bandwidth = 1,295 Hz/pixel, in-plane field of view (FOV) = 320 $\times$ 200 mm², slab thickness = 80 mm, data-acquisition matrix = 256 $\times$ 120 pixels and 12 partitions (interpolated to 24), with a voxel size of 1.3 $\times$ 1.7 $\times$ 3.3 mm³. The orientation of the 3D slab was oblique in the coronal-to-transverse direction to fully cover both lungs. The temporal resolution was 1.98 seconds per 3D data set, with a total of 13 data sets collected continuously during the first-pass of the contrast agent. During the acquisition of perfusion data, a single dose of 0.1 mmol/kg gadopentate dimeglumine (Magnevist; Schering-Plough, Erlangen, Germany) was injected as a bolus over a 2-second interval through the established ear vein catheter, and was followed by a 10-mL saline flush. The injection was performed after acquisition of the first 3D perfusion data set.

High-spatial-resolution 3D angiography was obtained by another 3D gradient-echo sequence, with a TR/TE of 3.2/1.1 msec. The readout bandwidth was 432 Hz/pixel and the flip-angle was 30°. The 3D slab was prescribed to have the same orientation as in the perfusion study. The data-acquisition matrix was 512 $\times$ 24 $\times$ 96 pixels (interpolated partition number), resulting in a voxel size of 0.66 $\times$ 0.82 $\times$ 0.8 mm³. The scanning time for the angiography procedure was 25 seconds. For angiographic data acquisition, the same gadopentate dimeglumine contrast agent as used in the perfusion study, but with a doubled dose of 0.2 mmol/kg, was injected over a 20-second interval, followed by a 10-mL saline flush at a rate of 1 mL/sec. The delay time for the start of the angiography data-acquisition procedure was calculated (30) on the basis of the transit time of the bolus in the perfusion imaging study. In all of the animals studied, an 8-second delay between the start of injection and the start of data acquisition yielded the best enhancement of the pulmonary arteries. Angiographic MR differs primarily from the perfusion MR in giving a higher degree of spatial resolution and requiring a longer time for acquisition of a 3D data set.

The ventilation portion of the imaging was performed on a 1.5-T Magnetom Vision whole-body scanner (Siemens). After perfusion and angiographic imaging, pigs were immediately transferred to the adjacent 1.5-T Magnetom Vision whole-body scanner (Siemens), in which ³He gas ventilation imaging was performed to visualize the lung ventilation distribution. A home-made Helmholtz coil pair operating at both 48.47 MHz and 63.63 MHz was used to acquire ³He and proton MR scout images, respectively.

Hyperpolarized ³He gas was prepared by depopulation optical pumping of Rb and spin exchange between the Rb electrons and ³He nuclei (31). A 40-W diode laser array was used to polarize the ³He in valved Pyrex cells, with equipment constructed in our research group.

Three dedicated polarizers were used, each generating 0.45 L of ^3He under standard temperature and pressure (STP) at approximately 45% polarization. The cells were then transported over a distance of 4 km to the imager in a hand-carried, battery-powered holding field of 30 G. Negligible losses in polarization occurred during transport, but care must be taken near the large field gradients close to the imager to avoid significant demagnetization of the ^3He gas (32).

A complete set of coronal proton scout images was made at full inspiration for comparison to the gas-space images and for anatomical reference. Just prior to ^3He imaging, the ^3He gas was mixed with 0.5 L N_2 in a polyethylene bag. The gas mixture was delivered to the pig through a set of valves connected to the Harvard ventilator used in the study. When the imager had been switched to the ^3He frequency, 0.3 L of gas was removed from the lungs at functional residual capacity (FRC) by opening a valve leading to a partially evacuated plastic container. This removed some O_2 , reducing the oxygen-induced relaxation rate of the ^3He (33). The 1-L ^3He - N_2 mixture was then delivered by opening a valve to the polyethylene bag containing the mixture and squeezing the bag at a constant pressure of about 10 inches of water. At full inspiration, all valves were closed to suspend breathing, and imaging began.

To image ^3He gas, a two-dimensional gradient-echo sequence was used. Thirteen slices with a slice thickness of 8 mm were collected during a 13-second breath-hold. These slices were in locations similar to those used in the perfusion study. Other imaging parameters included a TR/TE = 11 ms/4.2 ms, flip angle = 15° , readout bandwidth = 130 Hz/pixel, FOV = $320 \times 240 \text{ mm}^2$, and data acquisition matrix = 128×96 pixels, resulting in a voxel size of $2.5 \times 2.5 \text{ mm}^2$.

Image Analysis

The 3D perfusion sequence was designed to perform on-line subtraction (subtracting the first 3D data set from all later data sets) and to automatically reconstruct a maximum-intensity projection (MIP) image for each subtracted 3D data set. For 13 total sets, there were 12 subtracted data sets. MIP and multiplanar reformat (MPR) images were also generated from the 3D angiographic data sets to assist visualization of pulmonary arteries and emboli. All MR source images were reviewed independently, at an MR satellite console, by two chest radiologists with experience in pulmonary MR imaging. The two reviewers had no knowledge of the findings in the X-ray angiography or animal surgical procedures. Each 3D data set was reviewed in a slice-by-slice manner, with the MIP and/or MPR images also reviewed. The angiographic, perfusion, and ventilation images (if present) were reviewed in that order. The pulmonary system of each pig was divided into 6 areas, as follows: right upper (RU), right middle (RM), right lower (RL), left upper (LU), left middle (LM), and left lower (LL) areas (Fig 1).

The reviewers were first asked to grade the quality of each image on a 5-point scale in which 1 = non-diagnostic (or unevaluable), 2 = poor image contrast with severe motion artifacts, 3 = moderate image contrast with some motion artifacts, 4 = good image contrast with little motion artifacts, and 5 = excellent image contrast and no motion artifacts. The reviewers then identified the presence and location of pulmonary emboli. Following this, the reviewers gave a confidence score to three methods for depicting each PE: MR angiographic imaging, MR angiographic imaging + perfusion imaging, MR angiographic imaging + perfusion imaging + ventilation imaging. The score was defined as: 1 = highly doubtful, probable artifacts or no embolism, 2 = 50% likelihood of either PE or artifacts, 3 = 50% likelihood of PE for a non-artifactual reason (no vessel visualized), 4 = clear vessel cut-off and no intraluminal filling defects, and 5 = definite PE. A suspected PE that was given a confidence score of ≥ 3 was considered as a positive finding.

An experienced interventional radiologist (J.R.L.) reviewed the images made by X-ray angiography as the “gold standard” for the diagnosis of PE. The presence and location of each PE were indicated.

Statistical Analysis

Sensitivity, specificity, and positive and negative predictive values for the detection of PE were calculated and compared for MR angiography versus X-ray angiography. Interobserver variability was assessed by using kappa (k) analysis. Distribution of confidence was analyzed with contingency tables, and patterns were tested for statistical significance with the Wilcoxon signed-ranks test.

RESULTS

The surgical procedures and MR imaging scans were well tolerated by all 14 of the pigs used in the study. The examination time for the combined MR imaging acquisitions was approximately 1 hour, including the time for injection of pulmonary emboli. MR angiography, perfusion, and ventilation received mean ratings of 3.5, 4.0, and 4.5, respectively, for image quality.

Table 1 lists the x-ray angiographic findings and findings with the three MR imaging techniques for the 14 pigs in the study. Twenty-one pulmonary emboli in 9 pigs with induced emboli were detected by X-ray angiography, with 11 of these emboli being in right lungs and 10 in left lungs. MR angiograms depicted the filling defects in pulmonary arteries of these 9 pigs with induced emboli. Ventilation defects were found only in the 8 pigs that had bronchial obstruction, and perfusion defects in lung parenchyma were detected in all 14 pigs in the MR perfusion scan. Ventilation/perfusion-mismatch defects were found only in the pigs with pulmonary emboli.

As described above, the pulmonary arteries of each pig were assessed in 6 segments distributed across the upper, middle, and lower areas of the left and right lungs. MR and X-ray angiography for the detection of PE were compared directly for the detection of PE in each of the 84 ($= 14 \times 6$) pulmonary segments of the 14 pigs in the study (Table 2). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of MR angiography for detecting PE were 85.7%, 87.3%, 69.2%, 94.8%, and 86.9%, respectively, for the first reviewer, and 81.0%, 90.5%, 73.9%, 93.4%, and 88.1%, respectively, for the second reviewer. The agreement between the two reviewers was very strong ($k = 0.82$).

Table 3 shows the distribution of diagnostic confidence by reader and imaging procedure. The readers were very similar in their confidence scores and in the tendency of their confidence scores to increase with the added imaging modalities. The change in the distribution of confidence values with the addition of each imaging method was statistically significant (Wilcoxon signed-ranks test, $P = 0.03$).

Figure 2 shows images from one pig with blocked bronchi and PE. Both perfusion imaging and MR angiography were done after the interventions that produced these effects. Comprehensive evaluation of all three image data sets provided correct diagnoses.

DISCUSSION

Our results demonstrate the feasibility of acquiring both anatomical and functional volumetric lung MR images within a reasonable breath-hold time in a porcine model of PE. First-pass volumetric perfusion imaging clearly delineated blood perfusion in the pulmonary parenchyma as well as in the lobar and segmental arterial vessels. The MR volumetric perfusion technique

used in our study has already been used in humans to simultaneously provide low-spatial-resolution parenchymal perfusion maps and pulmonary angiography. However, high-spatial-resolution pulmonary angiography is still needed in some cases to accurately delineate sources of pulmonary flow defects, because our perfusion maps reveal “cut-off” signal voids for absent flow only in large vessels. The use of perfusion maps by themselves fails to ascertain the exact location and extent of emboli. With submillimeter resolution, contrast-enhanced MR angiography can readily determine the locations and sizes of small emboli, as shown in Figure 2. Subsegmental branches are also well depicted (Fig 2b,d).

It could be argued that high-spatial-resolution angio-graphic images may provide the same information as perfusion images. In our study, parenchymal perfusion was better delineated by perfusion imaging, particularly in regions without defects. Angiographic images may contain signal enhancement in both vessels and parenchyma, but the SNR of the parenchyma is substantially lower than that in perfusion images. It should be realized that during the first-pass angiographic imaging session, variability in timing of the data acquisition window after contrast injection will cause variations in the patterns of parenchymal enhancement, which may increase the possibility of false-positive diagnosis.

In our study, ^3He images provided high-quality lung-ventilation maps with a sufficient SNR and adequate sensitivity for detecting defects in ventilation. Although assessment of lung ventilation was also possible indirectly with inhalation of 100% oxygen as a paramagnetic T_1 relaxation contrast agent (34), only one slice was obtained with each oxygen inhalation, and the SNR of the O_2 ventilation image is much lower than that of the ^3He image. Other limitations of O_2 ventilation imaging include a relatively long imaging time (making this technique susceptible to respiratory motion) and the inability to perform dynamic ventilation imaging. In contrast, MR lung imaging with hyperpolarized ^3He MR provides multi-slice volume coverage within a single breath-hold time, and readily depicts regional defects in ventilation caused by stenosis or blockage of airways.

In the present study, perfusion defects corresponding to ventilation defects matched the size and shape of the ventilation defects very well. Other than CT imaging, the imaging approach presented here is the only one that can be repeated and used before and after an intervention without the need for ionizing radiation or injection of iodinated contrast medium. Because the ability to combine the three MR imaging techniques investigated in our study is not now available with a single scanner, our data were obtained separately, from two scanners. It is anticipated that our MRI system will be upgraded with broadband capability in the near future, allowing all of the perfusion, angiographic, and ^3He ventilation imaging to be performed in one setting. A single coronal slab could cover both the right and left lungs without complex slice localization. This volumetric data- acquisition strategy facilitates imaging and also permits simple registration of perfusion, angiographic, and ventilation images even though the resolutions of the three image sets are different.

In our study, the combination of three MR imaging techniques yielded reasonably good sensitivity and specificity for the detection of externally generated pulmonary emboli. It is noted that sensitivity and specificity should be determined separately with the three imaging techniques. However, even if the MR image are reviewed randomly, bias may be created if the reviewers remember previous images. We therefore determined the confidence scores for different combinations of the imaging techniques examined in our study. As expected, the combination of the three imaging techniques provided the best score, which differed significantly from that with one or two techniques.

The three imaging techniques examined in our study can be easily used with an advanced clinical MR system having multinuclear capability. The volumetric data acquisitions allow

automatic registration among the three types of images obtained. Patient cooperation will require only three single breath-holds. Reliable and high-quality images can be obtained without apparent cardiac or respiratory motion. Non-perfused or incompletely perfused and non-ventilated lung regions can be readily detected and characterized with the volumetric data sets. The integrated three-technique MR method may provide an important diagnostic tool for accurate and non-invasive assessment of both lung vascular anatomy and parenchymal function in a single setting, without involvement of irradiation or iodinated contrast agents. However, its clinical utility and cost effectiveness remain to be determined.

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Figure 1.
Sketch of pulmonary artery system of the pig.

Figure 2.

Example of comprehensive evaluation of pulmonary emboli in a pig with both one ventilation defect and emboli. **(a)** MR angiography in an MIP format is in excellent agreement with **(b)** X-ray angiography showing the emboli in both the left and right lower lobes (**white arrows**). The **black arrow** indicates the contrast-agent-filled balloon used to block the right airway. The **white block arrows** point to the parenchymal perfusion defects, which are also clearly demonstrated in one source image **(c)** and a perfusion image **(d)**. However, the perfusion curves (ie, the signal intensity-vs-time curves) for the upper, middle, and lower lung at that slice location **(e)** clearly indicate different enhancement patterns, with much reduced and delayed perfusion in the upper lobe, which was not easily seen in the source image of angiography **(c)** (**long arrow**). At the same slice location, an ^3He ventilation image **(f)** shows the ventilation defects in the middle and upper lobes of the right lung, but not in the left lung. These observations show the ventilation/perfusion mismatch defects in the left lung, a typical feature for pulmonary emboli. However, the perfusion defects in the right lung might be caused by ventilation defects. After carefully review, a small PE was found in one of the pulmonary branches of the main right pulmonary artery, as indicated by a **long arrow** in **(g)**. This embolism

was not seen on X-ray angiography because the tip of the catheter blocked the view of the embolism.

Findings on X-ray Angiography, MR Angiography, MR Perfusion, and MR Ventilation Imaging in Pig Models of Pulmonary Embolism, Bronchial Obstruction, and Both Pulmonary Embolism and Bronchial Obstruction

Pig	Intervention	X-ray Angiography	MR Angiography	MR Perfusion	MR Ventilation
A	Pulmonary embolism	1 [*]	+ [‡]	+	— [‡]
B		1	+	+	—
C		4	+	+	—
D		2	+	+	—
E		3	+	+	—
F		1	+	+	—
G	Bronchial obstruction	—	—	+	+
H		—	—	+	+
I		—	—	+	+
J		—	—	+	+
K		—	—	+	+
L		4	+	+	+
M	Both	4	+	+	+
N		1	+	+	+

^{*} Number of pulmonary emboli detected.
[‡] Defects detected.
[‡] Negative finding.

Table 2
MR Angiography versus X-ray Angiography for Detecting Pulmonary Emboli in 14 Pigs

		X-ray Angiography		
		PE	Negative	Total
MR angiography (Reviewer 1)	PE	18	8	26
	Negative	3	55	58
	Total	21	63	84
MR angiography (Reviewer 2)	PE	17	6	23
	Negative	4	57	61
	Total	21	63	84

Table 3
Distribution of Confidence Scores by Reader and Imaging Modality for Two Readers

Reader	Confidence Score	Angiography Alone	Angiography + Perfusion	Angiography + Perfusion + Ventilation
1	5	18 (69%)	20 (80%)	22 (92%)
	4	4 (15%)	4 (16%)	2 (8%)
	3	3 (12%)	1 (4%)	0 (0%)
	2	0 (0%)	0 (0%)	0 (0%)
	1	1 (4%)	0 (0%)	0 (0%)
2	5	13 (59%)	16 (73%)	14 (82%)
	4	6 (27%)	4 (18%)	2 (12%)
	3	1 (5%)	2 (9%)	1 (6%)
	2	1 (5%)	0 (0%)	0 (0%)
	1	1 (5%)	0 (0%)	0 (0%)

Differences among imaging modalities are statistically significant (Wilcoxon signed-ranks test, $P = .03$).