

MR Diagnosis of a Pulmonary Embolism: Comparison of P792 and Gd-DOTA for First-Pass Perfusion MRI and Contrast-Enhanced 3D MRA in a Rabbit Model

Shella D. Keilholz, PhD¹
Ugur Bozlar, MD^{2,3}
Naomi Fujiwara, MD^{2,5,6}
Jaime F. Mata, PhD²
Stuart S. Berr, PhD²
Claire Corot, PhD⁴
Klaus D. Hagspiel, MD²

Index terms :

Pulmonary embolism
P792
Angiography, perfusion

DOI:10.3348/kjr.2009.10.5.447

Korean J Radiol 2009; 10: 447-454

Received July 11, 2008; accepted after revision February 12, 2009.

¹Department of Biomedical Engineering, Emory University and Georgia Institute of Technology, Atlanta, GA; ²Department of Radiology, University of Virginia Health System, Charlottesville, VA; ³Department of Radiology, Gulhane Military Medical Academy, Ankara, Turkey; ⁴Guerbet Research, Aulnay-sous-Bois, France; ⁵Department of Radiology, Kagawa University Faculty of Medicine, Kagawa, Japan; ⁶Department of Diagnostic Radiology, Osaka Neurosurgical Hospital, Kagawa, Japan

Address reprint requests to:

Klaus D. Hagspiel, MD, Department of Radiology, University of Virginia Health System, Box 800170, Lee Street, Charlottesville, Virginia 22908, USA.
Tel. +1 434 924 9401
Fax. +1 434 924 8698
e-mail: kdh2n@virginia.edu

Objective: To compare P792 (gadomelitol, a rapid clearance blood pool MR contrast agent) with gadolinium-tetraazacyclododecanetetraacetic acid (Gd-DOTA), a standard extracellular agent, for their suitability to diagnose a pulmonary embolism (PE) during a first-pass perfusion MRI and 3D contrast-enhanced (CE) MR angiography (MRA).

Materials and Methods: A perfusion MRI or CE-MRA was performed in a rabbit PE model following the intravenous injection of a single dose of contrast agent. The time course of the pulmonary vascular and parenchymal enhancement was assessed by measuring the signal in the aorta, pulmonary artery, and lung parenchyma as a function of time to determine whether there is a significant difference between the techniques. CE-MRA studies were evaluated by their ability to depict the pulmonary vasculature and following defects between 3 seconds and 15 minutes after a triple dose intravenous injection of the contrast agents.

Results: The P792 and Gd-DOTA were equivalent in their ability to demonstrate PE as perfusion defects on first pass imaging. The signal from P792 was significantly higher in vasculature than that from Gd-DOTA between the first and the tenth minutes after injection. The results suggest that a CE-MRA PE could be reliably diagnosed up to 15 minutes after injection.

Conclusion: P792 is superior to Gd-DOTA for the MR diagnosis of PE.

Pulmonary embolisms (PE) affect an estimated 600,000 patients annually in the US alone (1, 2). Since treatment reduces the mortality by a factor of 10 (3), timely diagnosis is mandatory. A number of tests have been introduced to help diagnose a PE. Namely, the ventilation-perfusion (V/Q) scintigraphy, which, for the last two decades, has been the initial test of choice at most medical centers worldwide and has been extensively evaluated (4). The diagnosis of a PE is primarily based on the presence of a perfusion defect following a vascular territory in the absence of a ventilation defect in that area. However, clearly concordant clinical and scintigraphic findings are only present in a minority of patients and thus, either empiric treatment or further imaging is required. More recently, the CT pulmonary angiography (CTPA) has largely replaced V/Q-scanning as the first line imaging modality for patients suspected of sustaining a PE. Unlike a scintigraphy which detects perfusion defects, the CTPA detects a thrombus as a filling defect within the pulmonary arterial branches. A contrast-enhanced (CE) pulmonary MR angiography (MRA) has been shown in a number of small studies to allow the diagnosis of PE with

an equivalent accuracy as the CPTA (5, 6). Although preferable over CT for a number of reasons, particularly due to the lack of ionizing radiation and potentially nephrotoxic contrast agents, lack of availability, relatively long acquisition times, and difficulty in monitoring patients in the MR environment, it is not widely used. However, recent technical advances, namely, the introduction of parallel imaging techniques, have helped overcome many of those obstacles (7, 8). In addition, it has recently been shown that a time-resolved MRA technique employing sensitivity encoding (SENSE) to assess both intravascular filling defects and perfusion defects, has higher sensitivity than the CTPA alone and was equivalent to a combined strategy involving CTPA and V/Q scanning (9). A shortcoming of all currently available MR contrast agents is that they are extracellular and thus do not allow for the acquisition of true perfusion maps (10, 11). More importantly, their contrast kinetics only allow for very short acquisition windows during the first pass, thus limiting the maximum achievable spatial resolution and accuracy that could theoretically be achieved.

Intravascular contrast agents have the potential to improve the MR-based diagnosis of a PE because they provide true perfusion images and prolong the imaging window.

In this paper, we compare a rapid clearance blood pool agent (RCBPA), P792, with a standard extracellular agent, Gd-DOTA, based on its suitability for pulmonary MRA and perfusion imaging in a rabbit model in which the left pulmonary artery occlusion (PAO) is used as a model of PE.

MATERIALS AND METHODS

Contrast Agents

Gd-DOTA (gadoterate acid, Dotarem[®], Guerbet-France) is a nonspecific macrocyclic chelate which diffuses freely into the interstitium (except for the brain), and is freely excreted through the kidneys. The molecular weight of Gd-DOTA is 0.56 kDa, while the relaxivity (R1) is 2.9 L · mmol⁻¹ · s⁻¹ at 1.5 Tesla (12).

P792 (gadomelitol, Vistarem[®], Guerbet-France) is a monodispersed monogadolinium macromolecule and a tetrasubstituted derivative of Gd-DOTA. The structural characterization of P792 has been described in detail in past reports (12, 13). In summary, P792 is a RCBPA characterized by the limited diffusion across normal endothelium, while its clearance is equivalent to the glomerular filtration rate. The molecular weight of P792 is 6.47 kDa, whereas the R1 is 29 L · mmol⁻¹ · s⁻¹ at 1.5 Tesla.

The pharmacokinetic parameters of the two contrast agents were previously determined in rabbits (13). The volumes of the distribution were 187 ± 10 ml · kg⁻¹ for Gd-DOTA and 101 ± 10 ml · kg⁻¹ for P792, respectively; whereas, the total body clearances were 2.8 ± 0.2 ml · min⁻¹ · kg⁻¹ for both compounds. The ratios of the blood concentration at 5 minutes divided by the theoretical initial concentration were 19.3% ± 0.8 for Gd-DOTA and 41.7% ± 2.6 for P792, respectively (12).

Animal Preparation

All experiments were performed with the approval of the Institutional Animal Care and Use Committee.

A total of 17 experiments were performed in 13 New Zealand white rabbits (weight 3–5 kg). The rabbits were anesthetized with ketamine (60 mg · kg⁻¹) and xylazine (6 mg · kg⁻¹) (administered intramuscularly). Anesthesia was maintained via intravenous sodium pentobarbital. Temporary occlusion of the pulmonary artery was induced in five of the rabbits using a non-detachable silicon balloon (NDSB) filled with sterile saline. This animal model was described in detail in a previous study (14). Briefly, a 5 Fr sheath was placed in the surgically isolated right femoral vein. Under fluoroscopic control, a 5 Fr angiographic catheter (Cook, Bloomington, IN) was advanced over a Terumo guide wire (0.038", Terumo Corp., Tokyo, Japan) into the inferior vena cava. Following the removal of the guide wire, the NDSB (Occlusion Balloon Catheter with Hieshima Taper, Boston Scientific Corp., Fremont, CA) was advanced through this angiographic catheter as a guide into the left pulmonary artery. Once the NDSB was properly positioned, a test occlusion was created and an X-ray pulmonary angiography performed. Iodinated contrast agent (Omniscan 300, Nycomed, Princeton, NJ) was injected through the guiding catheter using the digital subtraction technique. Next, the balloon was deflated and the rabbit was placed in the MR system. The advantage of this model is that alternating occlusion and reperfusion of the pulmonary artery could be achieved by inflating and deflating the balloon, respectively. Multiple cycles of occlusion and reperfusion could be accomplished without removing the rabbit from the magnet. The NDSB catheter and all other components, used in vivo, were tested to ensure that their magnetic susceptibility was negligible prior to their use, and that sterile water was used to inflate the balloon.

MR Imaging

All images were obtained on 1.5 Tesla scanners (Siemens Magnetom Vision or Sonata, Siemens Medical Systems, Malvern, PA).

Perfusion Imaging

A perfusion MRI was performed on six animals without PAO (DOTA: n = 3; P792: n = 3), and five animals with PAO (DOTA: n = 2, P792: n = 3). In two animals, an MRA was performed.

Scout images were acquired and used to select a transverse slice. Five images (to reach steady state) were acquired using an inversion recovery turbo fast low-angle shot (turboFLASH) according to the following parameters: TI 300 ms, TR 3.3 ms, TE 1.4 ms, flip angle 8°, field of view (FOV) 250 mm × 250 mm, matrix size 128 × 128, and 1 acquisition. The gains were set and kept constant for each of the five images. The rabbit was then injected with 0.1 mmol · kg⁻¹ Meglumine Gadoterate (n = 5) or 13 μmol · kg⁻¹ P792 (n = 6) through the sheath of the femoral vein in a bolus fashion, followed by 3 cc of saline as a bolus chaser. Since the relaxivity of P792 is 8 to 10 times higher than Gd-DOTA, the injected dose of P792 was correspondingly decreased in order to administer the agents with equivalent T1 efficacy. Images were obtained at every second after injection for 30 seconds. Moreover, images were also acquired once per minute for the first 10 minutes and every five minutes for the next 20 minutes, for a total of 30 minutes. The signal was measured for the aorta, pulmonary artery, and both lungs in the CE images, and plotted as a function of time.

Contrast-Enhanced Magnetic Resonance Pulmonary Angiography

Three animals had P792 MRA's (one with a PE and two

without a PE), whereas three animals had Gd-DOTA MRA (one with a PE and two without a PE). All the rabbits were hand-injected with a triple dose of either P792 or Gd-DOTA. In four of the animals, angiograms were acquired at 3 seconds, 5 and 15 minutes using a 3D FLASH sequence with the following parameters: TR 4.6 ms, TE 1.8 ms, flip angle 3°, FOV 390 mm, matrix size 135 × 512, 60 mm slab with 46 partitions (voxel size 2.8 × 0.8 × 1.3 mm) on a Vision Scanner (scan duration = 20 seconds).

Two rabbits underwent an MRA on a Sonata system, using an 8-channel high resolution knee array coil (MRI Devices Corporation, Waukesha, WI) and a 3D FLASH sequence with a TR of 4.54 ms, TE 1.6 ms, flip angle 30°, FOV 200 mm, matrix 256 × 384 and a voxel size of 0.8 × 0.5 × 0.9 mm at a scan time of 7 seconds. Parallel imaging (GeneRalized Autocalibrating Partially Parallel Acquisitions (GRAPPA) (8), was used with an acceleration factor of 3, thus resulting in a scan duration of 7 seconds. One animal was injected with P792, while the other was injected with Gd-DOTA. Angiograms were acquired for both techniques at 3 seconds, 30 seconds, 1, 3, 5, 10, and 15 minutes.

Statistical Analysis

The signal intensities at the different time points were plotted. Differences between the two contrast agents were tested for significance using an unpaired *t*-test.

Enhancement curves were plotted for the first 20 seconds after the start of the injection and washout curves for up to 30 minutes after injection. The decay contents

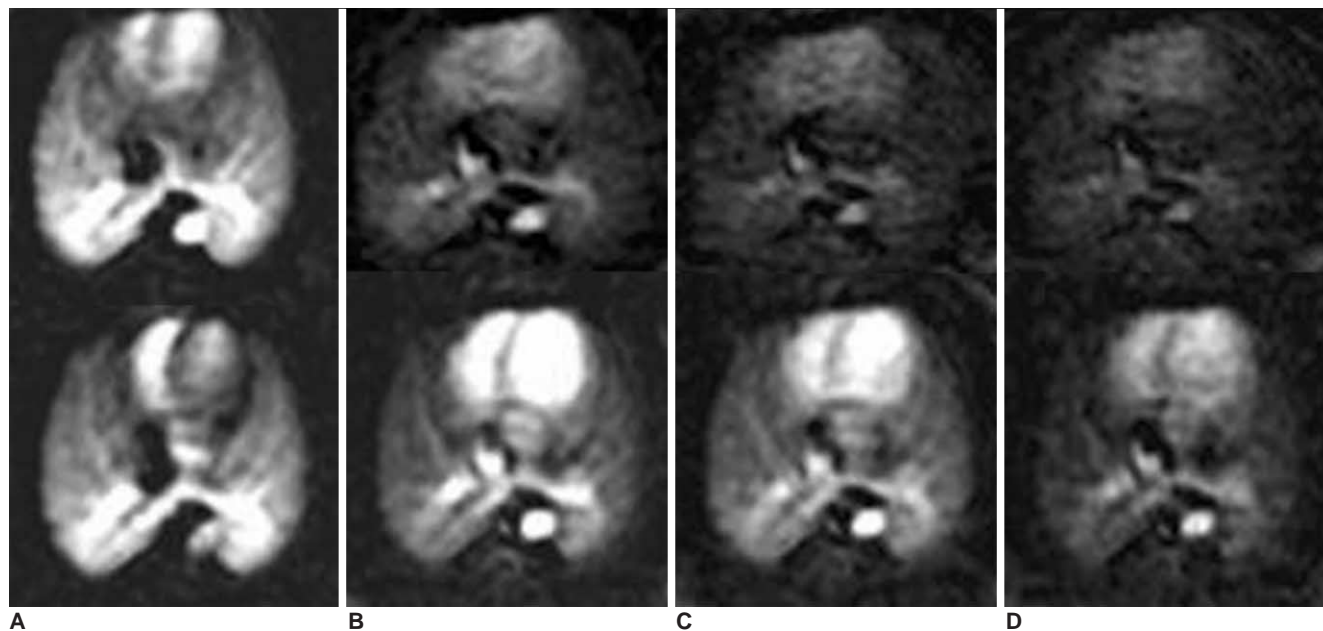


Fig. 1. Gd-DOTA (0.1 mmol · kg⁻¹ bw) (top row) and P792-enhanced (0.013 mmol · kg⁻¹ bw) (bottom row) images of normal rabbit lungs at time of peak contrast (A), and 1 minute (B), 5 minutes (C) and 10 minutes (D) after injection.

were calculated for the washout curves by fitting the data to $y = Ae^{-Rt} + C$, where R is the washout rate, and t is the time in minutes.

RESULTS

Perfusion Imaging

Perfusion images were successfully obtained in all 11 experiments with both contrast agents. Typical CE perfusion images of a rabbit without a PE obtained with Gd-DOTA and P792 at the time of peak contrast and at 1, 5, and 10 minutes post-injection are shown in Figure 1.

The images have a comparable signal at the time of peak contrast, but the P792 image has a higher signal at later time points. The heart and vessels are more visible in the P792 image at five minutes after the contrast injection than in the Gd-DOTA image at one minute post-injection. The initial rates of enhancement for both contrast agents are similar. In addition, no significant difference was found between the maximum signal obtained in either the aorta ($p = 0.25$) or the pulmonary artery ($p = 0.41$) (*t*-test).

Washout curves from 1 to 30 minutes post-injection are shown in Figure 2. The signal is significantly higher in the P792 images of the aorta and the pulmonary artery for the

Table 1. P Values for Difference in Signal Intensity between Gd-DOTA and P792 Enhanced Images at Various Time Points.

Time (min)	Aorta	Pulmonary Artery	Right Lung	Left Lung
1	0.01	0.1	0.47	0.43
5	0.002	0.03	0.20	0.44
10	0.03	0.04	0.16	0.23
15	0.12	0.11	0.01	0.01
20	0.26	0.15	0.48	0.21
25	0.48	0.44	0.4	0.33
30	0.19	0.38	0.44	0.09

Note.— Those considered significant ($p \leq 0.05$) are shaded.

Table 2. Decay Constants for Washout Curves Shown in Figure 3.

	Aorta Gd-DOTA	Aorta P792	Pulm. Art. Gd-DOTA	Pulm. Art. P792
	0.109	0.095	0.197	0.090
	0.152	DNC	0.178	DNC
	0.182	0.071	0.148	DNC
	0.158	0.090	0.123	0.113
	0.147	0.092	0.173	0.095
		DNC		0.210
Average	0.150	0.087	0.164	0.127

Note.— Data were fit to $y = Ae^{-Rt} + C$. DNC indicates that fitting algorithm did not converge.

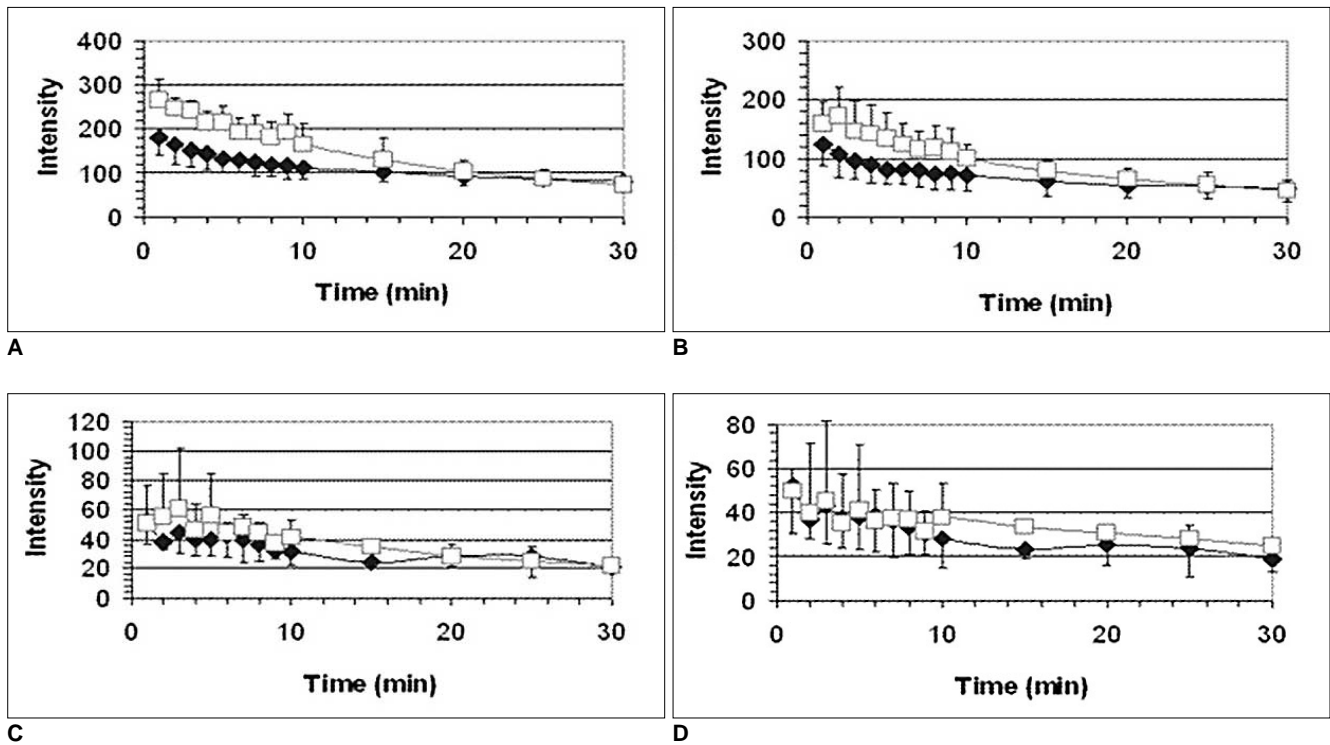


Fig. 2. Average washout curves for Gd-DOTA (diamonds) and P792 (squares) in aorta (A), pulmonary artery (B), right lung (C) and left lung (D). (Dose: Gd-DOTA 0.1 mmol · kg⁻¹ bw, P792 0.013 mmol · kg⁻¹ bw.) Data points for left and right lungs were obtained in rabbits without pulmonary artery occlusion.

P792 versus Gd-DOPA for Pulmonary Embolism MRI Diagnosis in Rabbit Model

data acquired between 1 and 15 minutes after injection, however, this was not the case in the lung parenchyma (see Table 1 for *p* values). There is a significant difference between the Gd-DOTA and P792 images of lung parenchyma at 15 minutes. By 30 minutes, the signal in both images attained a stable low point, suggesting that a decay curve can be fit to the series to determine a washout rate. The data were fit to $y = Ae^{-Rt} + C$, where *y* is the signal intensity, *A* is an amplitude constant, *C* is an offset constant, *R* is the washout rate, and *t* is the time in

minutes. The *R* for P792 was 42% lower than that of Gd-DOTA in the aorta and 23% lower in the pulmonary artery (Table 2).

In the subset of rabbits with occluded arteries (Gd-DOTA, *n* = 2; P792, *n* = 3), the signal is higher for both contrast agents in the perfused lung than in the unperfused lung during the initial enhancement and washout phase, although the effect was only significant for P792 because of the small number of studies.

Both contrast-agents were successful at delineating

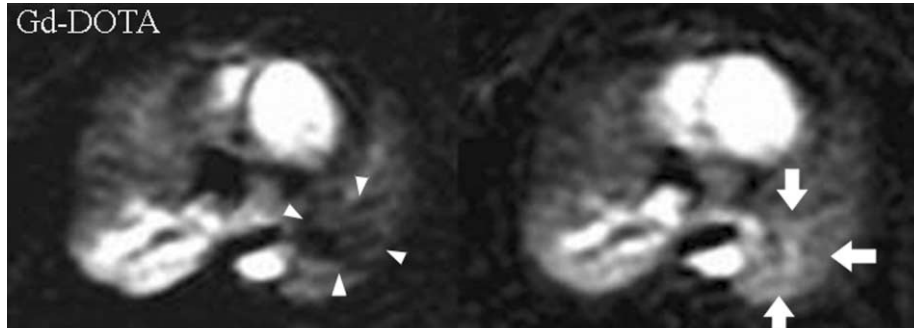


Fig. 3. Gd-DOTA (top row) and P792-enhanced (bottom row) perfusion images of rabbit with obstructed pulmonary artery at time of peak contrast (A) and one minute (B) after injection of contrast agent. Note that fill-in of occluded lung occurs for both agents at one minute, likely by systemic collaterals. (Dose: Gd-DOTA 0.1 mmol · kg⁻¹ bw, P792 0.013 mmol · kg⁻¹ bw.)

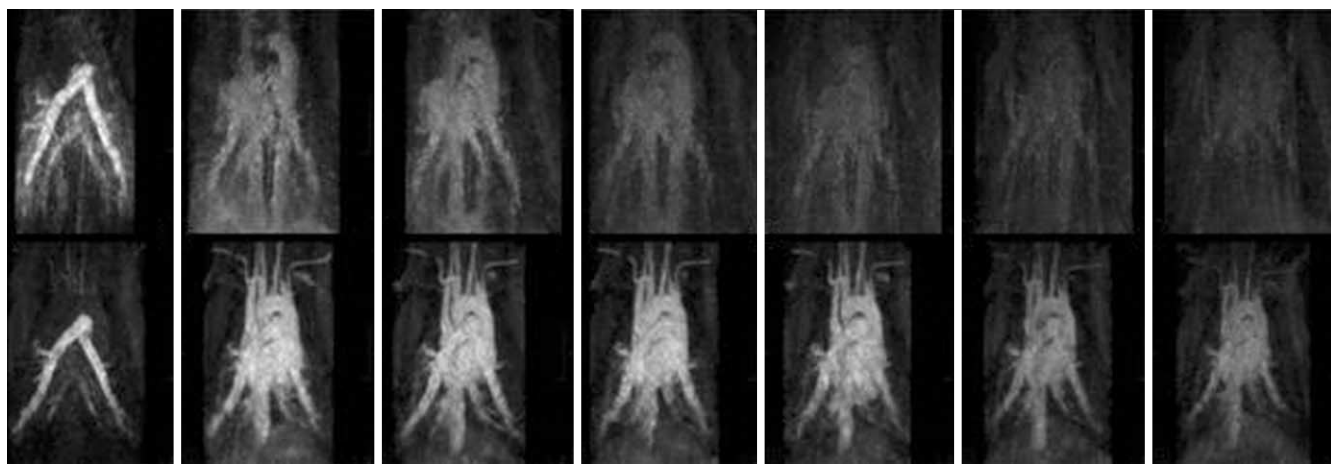
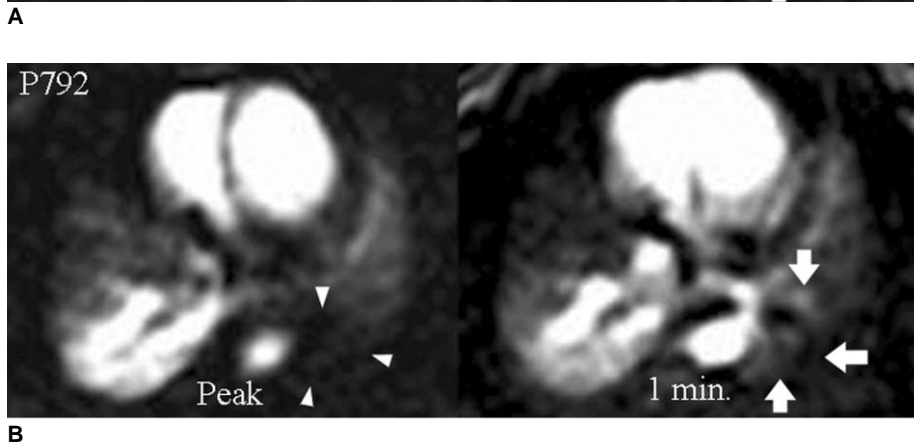


Fig. 4. Gd-DOTA (top row) and P792-enhanced (bottom row) images of two different rabbits, acquired at 3 seconds (A), 30 seconds (B), 1 (C), 3 (D), 5 (E), 10 (F) and 15 minutes (G) after contrast injection. (Dose: Gd-DOTA 0.3 mmol · kg⁻¹ bw, P792 0.039 mmol · kg⁻¹ bw.) All images are filmed at identical window settings.



Fig. 5. P792-enhanced ($0.013 \text{ mmol} \cdot \text{kg}^{-1} \text{ bw}$) images of rabbit during balloon occlusion of left pulmonary artery at time of first pass (A), as well as 5 minutes (B) and 15 minutes (C) after injection.

perfusion defects caused by temporary balloon occlusion. Gd-DOTA and P792 perfusion-weighted images of rabbit lungs during occlusion are shown in Figure 3. Additionally, both agents demonstrated a perfusion defect in the lower left lung and, the defects became less conspicuous over time because the agents reached the portions of the occluded lung region, possibly via collateral circulation or incomplete occlusion of the artery.

Contrast-Enhanced Pulmonary MR Angiography

All CE-MR pulmonary angiography (MRPA) studies were technically successful; the MR angiograms acquired on the high-performance system with parallel imaging at 3 seconds, 30 seconds, 1, 3, 5, 10 and 15 minutes post-contrast injection are shown in Figure 4. The vessels are highly visible in both images at peak contrast; however, after one minute post-injection, the vessels in the P792 image has a stronger signal than those in the Gd-DOTA image. The P792 angiogram is readily readable even at 15 minutes post-injection. The images on the pulmonary arterial phase image (3 seconds delay) allowed for the delineation of the patent and occluded pulmonary arteries in all animals and with both contrast agents. The scans obtained at 5 and 15 minutes post-injection allowed the delineation of the occluded pulmonary artery on the P792 enhanced studies only (Fig. 5).

DISCUSSION

Contrast-enhanced MRA has potential for diagnosing PEs, despite its current shortcomings. Gadolinium-enhanced MR angiography is a technique sensitive to the method of contrast injection, the nature of the contrast

agent (nonspecific or blood pool agent), and to the acquisition parameters. Two distinct phases were identified for the MRA: the bolus phase and the post-bolus phase (15). The bolus phase is mainly sensitive to the injection parameters such as dose, rate of injection and volume of injection. Hence, the use of a blood pool agent (BPA) did not provide any advantage over a nonspecific agent. However, differences were observed between BPA and nonspecific agents during the post-bolus phase. Because of their vascular compartmentalization, plasma BPA concentrations during the post-bolus phase were much greater than those of the nonspecific agent (12, 13, 15, 16).

Our study demonstrates that excellent perfusion maps can be obtained with P792, and, at a quality comparable to those obtained with extracellular agents (14). The graphs in Figure 2 show that P792 washes out of the blood vessels significantly less quickly than Gd-DOTA. A look at Figure 3 reveals that it is also clear that the contrast between normal lung and occluded lung parenchyma is sufficient for diagnostic purposes in both the Gd-DOTA image and the P792 image only at peak contrast. However, at later time points, the differences disappear, likely due to collateral perfusion, which reduces the conspicuity of the defect. While these are important findings, we believe that perfusion imaging will likely not play a major role in the future, as the presence of perfusion defects is not specific to PEs.

The gold standard for the diagnosis of PEs is the demonstration of a filling defect in the pulmonary arteries. Current standard CE-MRA techniques can demonstrate these filling defects; however, the techniques are only reliable during the bolus phase, which makes accurate bolus timing absolutely critical. Even the most advanced

scanners do not provide adequately short scan times for the performance of breathhold exams in respiratorily compromised patients if isotropic resolution is desired. Typical scan times for MRPA's with 512 matrices are 15–20 seconds, with a slab thickness between 120–160 mm. This is usually not thick enough to completely cover the lung. In comparison, scan times on state-of-the-art 16 detector MDCT scanners are in the range of 5 seconds for full lung coverage with isotropic resolution and much faster on 64 detector systems (our own unpublished data). Some investigators have overcome this obstacle by acquiring two separate sagittal acquisitions rather than one coronal acquisition, thus necessitating two separate contrast injections, which is itself problematic because the second acquisition suffers from an increase in background signal resulting from the first injection (6). Others have utilized real-time imaging approaches with true fast imaging with steady-state precession (true FISP) sequences, demonstrating increased robustness from respiratory motion artifacts (17).

The development of time-resolved imaging and parallel imaging techniques has furthermore significantly improved our ability to diagnose PEs with MRI (7, 9, 18). With high acceleration factors, the studies can indeed be performed in less than 10 seconds breathholds, although this is still twice as long as on MDCT scanners. Also, the issues with bolus timing still remain, possibly rendering a study nondiagnostic. Nevertheless, it was recently shown by Ohno and coworkers (9) that a combined time-resolved perfusion-angiography study is as accurate in the detection of PE as a strategy combining CTPA and V/Q scanning.

The ability to acquire high-resolution images during the equilibrium phase is a major advantage of intravascular MR contrast agents for the diagnosis of PE. The prolonged imaging window can be used in many ways. It could allow for the acquisition of multiple overlapping high-resolution data sets with short separate breathholds, or the acquisition of high resolution images using navigator techniques at the lung bases, where the majority of PEs occur. In cases where the bolus was missed on first pass imaging, repetition of the scan is possible without penalty. The advantage of such an approach has already been demonstrated for MR coronary angiographies (19). The simultaneous enhancement of pulmonary arteries and veins is not really a diagnostic obstacle, since on 3D data sets, pulmonary veins can be easily traced to the left atrium.

The ability to obtain high-resolution pulmonary angiographic images not only during first-pass, but also during the equilibrium phase of P792, has clearly been demonstrated in our experiments. The results from our MR angiography cohort suggest that a diagnostic MRPA can be

obtained up to 15 minutes after the dynamic perfusion study using P792. This would allow to repeat sequences affected by respiratory or bulk motion and allow to employ both cardiac and respiratory gating.

In conclusion, we demonstrated that P792, a member of the RCBPAs, has potential for the detection of PEs using both a first-pass perfusion MRI as well as a CE-MRA in a rabbit model. Similarly, a P792 perfusion MRI is as effective as the first-pass perfusion MRI using Gd-DOTA, a standard extra-cellular agent, for the demonstration of perfusion defects caused by PAO. Further, at a steady-state, it significantly prolongs the time over which diagnostic high-resolution MR angiographic images can be obtained. Thus, for utilizing optimized imaging sequences with or without cardiac and/or respiratory gating, further studies seem warranted to fully explore the potential of this agent for the MR diagnosis of PE.

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