Lung perfusion impairments in pulmonary embolic and airway obstruction with noncontrast MR imaging

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Suga, Kazuyoshi, Nobuhiko Ogasawara, Munemasa Okada, Toshinobu Tsukuda, Naofumi Matsunaga, and Mitsue Miyazaki. Lung perfusion impairments in pulmonary embolic and airway obstruction with noncontrast MR imaging. J Appl Physiol 92: 2439–2451, 2002; 10.1152/japplphysiol.00900.2001.—A noncontrast electrocardiography (ECG)-gated, fast-spin-echo magnetic resonance imaging was applied to noninvasively define perfusion impairments in pulmonary embolic and airway obstruction dog models. Two-phase ECG-gated lung images of the minimal lung signal intensity during systole and maximal signal intensity during diastole were acquired by using optimized R-wave triggering delay times in seven dogs anesthetized with pentobarbital sodium before, soon after, and 2 mo after embolization with enbucrilate and in another eight dogs before and after bronchial occlusion with balloon catheters, in combination with a gadolinium diethylenetriaminepentaacetic acid-enhanced dynamic study. An ECG-gated subtraction image between the two-phase lung images provided a uniform but gravity-dependent perfusion map in normal lungs. Furthermore, it defined all 13 variable-size perfusion deficits associated with pulmonary embolism and the dynamically decreased perfusion with time after bronchial occlusion in all the airway obstruction models. These results were consistent with contrast-enhanced pulmonary arterial perfusion phase images. This noncontrast imaging could be equivalent to a contrast-enhanced dynamic study in the definition of regionally impaired pulmonary arterial perfusion in pulmonary embolism and airway obstruction. The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

THE ASSESSMENT OF REGIONAL lung perfusion is essential for the evaluation of a variety of lung disorders. Although a perfusion scintigram with technetium-99m-labeled macroaggregated albumin (99mTc-MAA) has been a screening tool as a first choice for evaluating impaired perfusion, this modality has disadvantages due to poor spatial and temporal resolution and the use of radioactive substances. Recently, various high temporal- and spatial-resolution magnetic resonance (MR) imaging strategies for assessing lung perfusion, including a first-pass MR study with gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA), have been implemented in clinical and experimental studies (1, 2, 4, 5, 8, 12, 29, 31). However, the use of an exogenous contrast agent increases the cost of the exam and poses some risk to patients. The most advanced MR techniques enable the acquisition of a pulmonary perfusion map without contrast agents by using magnetically labeled water in blood as an endogenous contrast agent (13, 16–19, 23, 24). The arterial spin-labeling MR technique using a flow-sensitive alternating inversion recovery sequence with an extra radiofrequency pulse is one of the noncontrast perfusion MR imaging methods, and its potential in the detection of perfusion deficits in pulmonary embolism has been reported (18, 19). This imaging method, however, requires special hardware for producing an extra radiofrequency pulse, and the image quality is often degraded by a flow ghosting artifact from the large vessels. A short-echo-spacing half-Fourier fast-spin-echo (FSE) technique enables the image acquisition of the pulsatile lung signal intensity (SI) changes during a cardiac cycle (13, 16, 17, 23, 24). An electrocardiography (ECG)-gated subtraction image between the systolic and diastolic phase images acquired by this technique may also provide a perfusion MR imaging without contrast agents.

In this study, we conducted an animal study to evaluate the ability of this noncontrast ECG-gated perfusion imaging to provide normal lung perfusion and impaired perfusion in the fundamental dog models of pulmonary embolism and airway obstruction, compared with an intravenous Gd-DTPA-enhanced dynamic MR study. In the pulmonary embolic models, the findings were also compared with bronchial and/or intercostal arteriographies and intra-aortic Gd-DTPA-enhanced MR study after injection of Gd-DTPA via the catheter placed in the ascending thoracic aorta. This was done to investigate the effect of systemic circulation within the embolized lungs on the appearance of this noncontrast perfusion MR imaging.

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MATERIALS AND METHODS

Animal preparation. A total of 15 beagle dogs (10.4 kg ± 2.3, mean ± SD) were intubated by use of a 7- or 7.5-mm cuffed endotracheal tube after receiving pentobarbital sodium (25 mg/kg) and pancuronium (0.1 mg/kg). Small supplementary doses of pentobarbital sodium (the total dose ranged from 3.2 to 6.4 mg/kg) were intermittently administered during the course of the experiment as needed to maintain adequate levels of sedation. Each anesthetized animal initially underwent the baseline ECG-gated perfusion MR study in combination with an intravenous Gd-DTPA-enhanced dynamic MR study. The ECG-gated perfusion MR study was repeated with a 7-day interval in four of these normal animals to evaluate the reproducibility of the results.

Pulmonary embolic models. After these normal animal studies, under fluoroscopic control, the lobar (n = 6) and segmental (n = 7) pulmonary arterial branches were selectively embolized at the lower lung level of the unilateral (n = 5) or bilateral (n = 4) lungs in 7 of the 15 animals, by administration of enbucrilate (Histoacryl, B. Braun Surgical, Melsungen, Germany) via a 6-French pulmonary angiographic catheter (Cook, Bloomington, IN). Enbucrilate released from a catheter produces a coagulant soon after contact with blood, resulting in variable-size pulmonary emboli (26). The embolization was confirmed by a pulmonary arteriography. Soon after pulmonary arterial embolization, bronchial and/or intercostal arteriographies were also performed by using a 6-French angiographic catheter to investigate systemic arterial blood supply to the embolized lung areas. This catheter was inserted from the femoral artery by use of a Seldinger technique. The catheterization and embolization were successfully performed in all the animals. The only complication was hypoxic reactions in the animals with large emboli. The tip of the catheter remained within the ascending thoracic aorta for the subsequent, intra-aortic Gd-DTPA-enhanced MR study. Then each animal was placed on the table of the MR system, and, at ~20 min after embolization, the ECG-gated noncontrast perfusion and intravenous and intra-aortic Gd-DTPA-enhanced MR studies were serially performed. All these MR studies were repeated at 2 mo after embolization in these animals to evaluate the hemodynamic alteration in the embolized lungs.

After completion of the experiment, each animal was killed to investigate histological changes in the embolized lungs. The postmortem short-echo-spacing half-Fourier FSE MR images were obtained in two of these animals before resection of the lungs, to investigate whether the detected lung signals were related to pulmonary perfusion. The lungs of each animal were resected en bloc and were fixed with formalin solution. The formalin-fixed lungs were cut along the transaxial planes to approximately correspond to the lung level assessed by the MR studies. The tissue samples were sequentially embedded in paraffin and were sectioned and stained with hematoxylin-eosin for light microscopic observation.

Airway obstruction models. In the remaining eight animals, the lobar (n = 6) or segmental bronchus (n = 4) in the unilateral lower lung level was occluded by use of a 5-French balloon catheter under fluoroscopic control, by inflating the balloon with an injection of 0.3–1.5 ml of physiological saline. These obstructions were loose to maintain as much lung volume on the occluded area as physiologically possible. After confirmation of adequate placement of the catheter in the bronchus under fluoroscopy, the proximal site of the catheter was fixed to the head of the animals, and the balloon was deflated. Each animal was then placed in the supine position on the table of the MR system. The animal then underwent an ECG-gated noncontrast perfusion MR study before and after inflation of the balloon, followed by an intravenous Gd-DTPA-enhanced MR study. Soon after the MR study, all these airway obstruction models underwent chest X-ray fluoroscopy, without withdrawal of the inflated balloon catheter from the obstructed bronchus to evaluate the volume change of the obstructed lungs.

All these experiments were performed in accordance with the Guide for the Care and Use of Laboratory Animals (25) and were also approved by the Animal Care and Research Use Committee of Yamaguchi University.

Noncontrast ECG-gated perfusion MR imaging. All the MR experiments were performed with the use of a 1.5-T MR scanner (VISART/EX, Toshiba Medical, Tokyo, Japan). Each animal was placed in the supine position on a quadrature radiofrequency knee coil, and two cutaneous copper electrodes were placed on the anterior chest wall for ECG gating. A localizer fast-gradient T1-weighted image of the lungs was initially acquired at the midcoronal plane, which was used to select a transaxial lower lung plane in the normal animals and to select the lower lung plane including the embolized region in the embolic models. Then a preparation scan of the noncontrast ECG-gated perfusion MR image was initially obtained at these selected lower lung levels by using a two-dimensional short-echo-spacing half-Fourier FSE sequence. In this sequence, a train of multiple spin echoes is generated from repeated selective 180° radiofrequency pulses spaced to provide multiple echoes or views from a single 90° radiofrequency excitation pulse. The sequence parameters were as follows: effective repetition time (TR eff) = effective echo time (TE eff) = 80 ms, echo train spacing = two R-R wave intervals × 4 ms, matrix = 224 × 256 columns, field of view = 30 × 30 cm, and slice thickness = 30 mm. The very short echo train spacing of 4 ms (the time between the delays between the beginning of each dephase period and the end of the corresponding refraction period) was applied because it was expected to show high SI in relatively slow and steady flow during cardiac diastole and low SI in high blood flow during systole. Furthermore, it was expected to reduce motion-related artifacts because scan times were significantly reduced (13). In this preparation scan, to determine the optimized trigger times for obtaining the diastolic image showing the maximal lung parenchymal SI and the systolic image showing the minimal lung parenchymal SI in each animal, multiphase images were acquired by ECG triggering with incremental delay time of 20 ms over a cardiac cycle, with eight shots and two numbers of excitation (NEX). The repetition time varied according to the heart rate of each animal, ranging from 678 to 1,012 ms (mean: 877 ± 84 ms). After the optimized trigger times for systolic and diastolic phases were determined, a two-phase scan was obtained by using 8 shots and 12 NEX to increase the signal-to-noise ratio. In the airway obstruction models, after acquisition of the baseline ECG-gated perfusion images, the balloon of the intratracheal catheter was inflated by injection of the same dose of physiological saline as was injected in the fluoroscopy. Localized fast-gradient T2-weighted images were then obtained at the midcoronal lung plane to confirm adequate placement and inflation of the balloon within the bronchus. Thereafter, the ECG-gated MR images were obtained at the transaxial lower lung plane, including the lung regions distal to the bronchial occlusion, with an interval time of 10 min over 45 min after bronchial occlusion. Although the heart rate of the animals varied from 102 to 190 beats/min and the single-shot acquisition time varied by the R-R wave interval in each animal, the ECG-gated MR image acquisition could...
be completed within 6 min. The systolic phase image was then subtracted from the diastolic phase image, yielding a perfusion-weighted MR image. The lung images of the two postmortem animals were also obtained by using the same sequence parameters as in the living animals, but without cardiac triggering.

In addition, a simplified water-flow phantom study was performed to evaluate the effect of flow velocity on the SI of the present FSE MR image. A water stream with constant flow in a tube with a diameter of 5 mm, which was embedded in the gelatin-containing soft sponge, was produced by use of an electric pump. A single-shot image of this water stream was obtained at the fixed transaxial section with different flow velocities ranging from 0 to 56 cm/s by using the same FSE sequence applied for the above preparation scan of the ECG-gated perfusion MR image. The SI measurement of the flow was performed in the same tube area by using a small region of interest (ROI) that fits within the flow signal.

Gd-DTPA-enhanced dynamic MR study. Approximately 5 min after the ECG-gated perfusion MR study, each animal underwent a contrast-enhanced dynamic MR study along the same, transaxial lung planes after an intravenous bolus injection of gadopentetate dimeglumine (Gd-DTPA) (Magnevist, Nippon Shering, Osaka, Japan). The dynamic images were acquired by using a three-dimensional fast-gradient echo sequence after a 3-s bolus injection of a 0.1 mmol/kg dose of Gd-DTPA via power injector, which was immediately followed by a 20-ml saline solution. Sequence parameters were as follows: repetition time/echo time = 2.6/0.9 ms, flip angle = 30°, slab thickness = 8 cm, slice thickness = 8 mm, matrix size = 96 × 256, rectangular field of view = 270 × 360 mm, acquisition time = 2.8 s/scan. Breath holding was performed with the lungs inflated to a tidal inspiration level and was kept steady at this level with positive air pressure through careful compression of the air bag connected to the intubated tracheal tube. Cardiac gating was not used. The injection technique of Gd-DTPA was based on our previous analysis of the linearity between the lung enhancement effect and different administration doses and rates of this contrast agent in two normal dogs, which revealed that the present injection procedure was appropriate to enhance the lung tissue without competing effects on T1 and T2 shortening (4). The contrast injection was synchronized to the start of the dynamic MR sequence, with a 2-s delay to obtain two or three precontrast lung images. A total acquisition time of 35 s produced a series of 12–13 transaxial lung images in each section. The time course of the lung enhancement was assessed by the time-ΔSI curves, in which the relative SI increases from the precontrast SI [ΔSI_{Gd-DTPA} = (lung SI-background noise SI)_{post} – (lung SI-background noise SI)_{pre}] was plotted against time (4). The term (lung SI – background noise SI)_{pre} stands for the averaged SI of the lung in the precontrast image before the arrival of the contrast bolus, and (lung SI-background noise SI)_{post} stands for the SI of the lung on each of the successive postcontrast images. Noise was measured similar to the ECG-gated perfusion study. All the ROIs were placed independently by the two interpreters (K. Suga and N. Ogasawara), and the data were taken as an average of the two measurements. Data are expressed as means ± SD. Significance of the differences of the data comparisons were

Image interpretation and MR signal analysis. The location and extent of perfusion impairment on the ECG-gated perfusion-weighted images in the animal models were interpreted independently by two chest MR specialists (M. Okada and T. Tsukuda) blinded to the information about the embolized and bronchus-occluded lung regions. Thereafter, the matching of the perfusion impairment between the ECG-gated perfusion and intravenous Gd-DTPA-enhanced dynamic studies was assessed. The final image interpretation was recorded after consensus was established.

On the ECG-gated preparation scan of the baseline normal lungs, the SI of the pulmonary arteries and veins, descending aorta, and inferior vena cava were measured by use of manually defined ROI on these vessels. Lung parenchymal SI was also measured by using the ROIs placed in the peripheral lung portions of both lungs and in two different zones (dorsal and ventral) to minimize any contribution from large vessels and from the noticeable artifacts caused by fast cardiac motion. In the pulmonary embolic and airway obstruction models, the signal was measured for each ROI in the affected regions and in the contralateral symmetrical nonaffected regions. The same ROIs were placed for the interstudy comparisons. The areas of the ROIs varied from 0.7 to 1.9 cm², but within individual animals all ROIs were of the same size. The time course of SI changes was then obtained for each ROI, and the percentage of the delay time after trigger R-wave showing the minimal and maximal SI against R-wave interval time (%Tmin and %Tmax), and the difference between the maximal and minimal SI [ΔSI_{ECG} = (maximal SI – background noise SI) – (minimal SI – background noise SI)] were estimated (Fig. 1). The background noise was measured with a large ROI that encompassed the entire image background lateral to the animals.

In the Gd-DTPA-enhanced dynamic study, the mean lung SI was estimated in regional lungs of each animal by use of the same ROIs as placed for ECG-gated perfusion study. The time course of the lung enhancement was assessed by the time-ΔSI curves, in which the relative SI increases from the precontrast SI [ΔSI_{Gd-DTPA} = (lung SI-background noise SI)_{post} – (lung SI-background noise SI)_{pre}] was plotted against time (4). The term (lung SI – background noise SI)_{pre} stands for the averaged SI of the lung in the precontrast image before the arrival of the contrast bolus, and (lung SI-background noise SI)_{post} stands for the SI of the lung on each of the successive postcontrast images. Noise was measured similar to the ECG-gated perfusion study. All the ROIs were placed independently by the two interpreters (K. Suga and N. Ogasawara), and the data were taken as an average of the two measurements. Data are expressed as means ± SD. Significance of the differences of the data comparisons were

![Image](https://example.com/image.jpg)
Table 1. Analysis of the time-to-signal intensity curves on ECG-gated preparation scan in 15 normal dog lungs

<table>
<thead>
<tr>
<th>Location</th>
<th>%Tmin</th>
<th>%Tmax</th>
<th>ΔSI_{ECG}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung parenchyma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vental</td>
<td>16.4±4.7</td>
<td>54.8±13.4</td>
<td>136.5±48.6</td>
</tr>
<tr>
<td>Dorsal</td>
<td>16.2±4.1</td>
<td>54.7±13.8</td>
<td>237.8±49.4</td>
</tr>
<tr>
<td>Mean</td>
<td>16.3±4.9</td>
<td>54.7±9.8</td>
<td>187.1±70.5</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>16.3±4.3</td>
<td>54.4±8.3</td>
<td>911.1±169.1</td>
</tr>
<tr>
<td>Pulmonary vein</td>
<td>26.4±9.6*</td>
<td>44.7±12.0*</td>
<td>349.0±83.5*</td>
</tr>
<tr>
<td>Aorta</td>
<td>11.6±3.8*</td>
<td>57.3±6.3</td>
<td>317.3±374.5*</td>
</tr>
<tr>
<td>Inferior vena cava</td>
<td>9.6±4.2*</td>
<td>52.3±8.1</td>
<td>740.4±437.9*</td>
</tr>
</tbody>
</table>

Values are means ± SD. ECG, electrocardiography; SI, signal intensity; %Tmin and %Tmax, percentage of delay time after trigger R-wave showing minimal and maximal SI, respectively, against R-wave internal time. %Tmin = (delay time after trigger R-wave showing the minimal SI/R-R wave interval) × 100; %Tmax = (delay time after trigger R-wave showing the minimal SI/R-R wave interval) × 100; ΔSI_{ECG} = (maximal SI – background noise SI) – (minimal SI – background noise SI). *P < 0.0001 compared with the mean parameter values in the lung parenchyma. †P < 0.0001 compared with ventral lung parenchyma values.

assessed by paired or unpaired Student’s t-test. Significance levels were accepted with a P value of <0.05.

RESULTS

Normal lungs. In the normal lungs, the SI of the lung vessels and parenchyma was apparently decreased during the systole compared with that of the diastole on the time-SI curves of the ECG-gated preparation scans (Fig. 1). Both the ventral and dorsal lung ROIs in the diastolic phase had significantly higher SI than those in the systolic phase (380.3 ± 62.7 vs. 246.0 ± 37.8, P < 0.0001, and 501.4 ± 55.5 vs. 263.5 ± 37.8, P < 0.0001, respectively). The dorsal lung ROIs had higher SI than ventral lung ROIs in both diastolic and systolic phases (both P < 0.0001). The ΔSI_{ECG} was significantly greater in the dorsal lung than in the ventral lung (237.8 ± 49.4 vs. 136.5 ± 48.6, P < 0.0001), although there were no significant differences (NS) between the same gravitational portions (Table 1). The ΔSI_{ECG} of the aorta was higher than that of the pulmonary vein, and that of the lung parenchyma was significantly lowest. The time course of SI changes was synchronized between the lung parenchyma and pulmonary artery, without significant differences in %Tmin and %Tmax. However, the %Tmin and/or %Tmax values in the lung parenchyma were significantly different from those in other structures (Table 1). The subtracted ECG-gated perfusion-weighted images showed uniform but gravity-dependent SI in the lung parenchyma, with only minimal respiratory motion artifacts and vascular ghosting (Fig. 2). The pulmonary arteries at least to the subsegment levels were usually visualized as high-signal structures, whereas

Fig. 2. Baseline normal dog magnetic resonance (MR) study. The transaxial ECG-gated MR image during the diastole of cardiac cycle (TR cuff /TE cuff = 856/80 ms, 8 shots, and 12 NEX) (a) shows apparently higher SI of the lung parenchyma and pulmonary arteries compared with those during the systole (b). The subtracted perfusion-weighted image (c) shows uniform SI in the lung parenchyma but with greater SI in the dorsal lung, similar to the subtracted, intravenous gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA)-enhanced pulmonary arterial perfusion phase image (d).
the pulmonary veins appeared as lower signal structures. The uniform but gravity-dependent perfusion appeared similarly on the intravenous Gd-DTPA-enhanced pulmonary arterial perfusion phase images (Fig. 2). However, the dorsal-to-ventral lung ΔSI_{Gd-DTPA} ratio of 2.18 ± 1.11 at this phase on these contrast-enhanced images were significantly greater than the ratio of ΔSI_{ECG} of 1.97 ± 1.1 on the ECG-gated perfusion images (P < 0.01).

The repeated, ECG-gated perfusion studies in four normal animals showed almost consistent results, without significant differences between the two measurements of the signal-to-noise ratio in each lung region on the perfusion-weighted images (NS).

**Pulmonary embolic model.** Soon after embolization, the SI of the embolized lung areas was persistently high throughout the systolic and diastolic phases on the ECG-gated preparation scans, although the signal loss during the systolic phase was apparently seen in the nonembolized lung areas. The subtracted, ECG-gated perfusion-weighted images visualized all 13 lobar/segmental perfusion deficits as markedly hyposignal areas in the seven animals, with a good accordance between the two observers (Figs. 3–5). The locations of these perfusion deficits were well appreciated by the simultaneously depicted pulmonary arteries in the surrounding lungs and were matched with those on the intravenous Gd-DTPA-enhanced pulmonary arterial perfusion phase images in 10 lesions, although the remaining three lesions appeared slightly smaller in size (Figs. 3–5). However, the perfusion maps differed from the subsequent Gd-DTPA aortic perfusion phase images after the pulmonary arterial perfusion phase images in 10 of the 13 lesions, in which some Gd-DTPA reperfusion enhancement was seen within the embolized areas (Figs. 3–5). These 10 lesions were also enhanced to variable degrees on the subtracted, intra-aortic Gd-DTPA-enhanced images immediately after injection of the contrast material from the ascending thoracic aorta, although the bronchial/intercostal arteriographies did not show noticeable vascular developments in these areas (Figs. 3–5).

At 2 mo after embolization, all of the 13 embolized areas appeared to be persistently and markedly hyposignal on the subtracted ECG-gated perfusion-weighted images, as soon after embolization (Fig. 5A). The ΔSI_{ECG} ratio of the embolized area to the contralateral nonembolized area at this time was not significantly changed from that of soon after embolization (0.36 ± 0.14 vs. 0.31 ± 0.14; n = 11, NS). The perfusion

![Image](https://via.placeholder.com/150)

**Fig. 3.** MR study soon after embolization in a pulmonary embolic dog model with a small embolized area in the left lung. The ECG-gated perfusion-weighted image (TR_{eff}/TE_{eff} = 931/80 ms, 8 shots, and 12 NEX) (a) shows a perfusion deficit as a marked hypointensity area (arrow), which is matched with that on the subtracted, intravenous Gd-DTPA-enhanced pulmonary arterial perfusion phase image (b; arrow). The perfusion map, however, differs from that on the subsequent aortic perfusion phase image (c), where the embolized area is enhanced (arrow). The subtracted, intra-aortic G-DTPA-enhanced image immediately after injection of the contrast agent from the catheter placed within the ascending aorta (d) shows some enhancement within the embolized area (arrow), indicating the presence of systemic circulation.
maps were well consistent with the intravenous Gd-DTPA-enhanced pulmonary arterial phase images in all these animals. The embolized-to-nonembolized lung ΔSI_{Gd-DTPA} ratio at this phase was also not significantly changed from that of soon after embolization (0.14 ± 0.15 vs. 0.06 ± 0.08; n = 11, NS). However, the subsequent aortic perfusion phase images after the pulmonary arterial phase images showed prominent enhancement in all these embolized areas, indicating the prominent increases in systemic circulation within the embolized areas (Fig. 5A). The embolized-to-nonembolized lung ΔSI_{Gd-DTPA} ratio of 2.39 ± 0.83 at this phase.

Fig. 4. MR study soon after embolization in a pulmonary embolic model with a large embolized area in the right lung and a moderate size embolized area in the left lung. The ECG-gated perfusion-weighted image (TR_{eff}/TE_{eff} = 819/80 ms, 8 shots, and 12 NEX) (a) shows perfusion deficits in both lungs as marked hypointensity areas (arrows), which are matched with those on the subtracted, intravenous Gd-DTPA-enhanced pulmonary arterial perfusion phase image (b; arrows). This perfusion map, however, differs from that on the subsequent aortic perfusion phase image (c), where the right embolized area is enhanced (open arrows). The subtracted intra-aortic Gd-DTPA-enhanced image (d) also shows apparent enhancement in the right embolized area (open arrows), indicating the presence of systemic circulation. In contrast, the left embolized area is not enhanced on either image (c and d; arrows).

Fig. 5. A: MR studies soon after embolization (top) and at 2 mo later (bottom) in a pulmonary embolic model with a relatively large embolized area in the right lung. Top: ECG-gated perfusion-weighted image (TR_{eff}/TE_{eff} = 963/80 ms, 8 shots, and 12 NEX) (a) shows a large perfusion deficit in the right lung as a markedly hypointensity area (arrows), which is matched with that on the subtracted, intravenous Gd-DTPA-enhanced pulmonary arterial perfusion phase image (b; arrows). The perfusion map, however, slightly differs from that on the subsequent aortic perfusion phase image (c), where some portion of the embolized area is enhanced (open arrow). The subtracted, intra-aortic Gd-DTPA-enhanced image (d) also shows some enhancement within the embolized area (open arrow), indicating the presence of systemic circulation. Bottom: similar to the appearance soon after embolization, the embolized area appears as a persistently hypointensity area on the ECG-gated perfusion-weighted image (TR_{eff}/TE_{eff} = 923/80 ms, 8 shots, and 12 NEX) (a), which is also well consistent with that on the subtracted, intravenous Gd-DTPA-enhanced pulmonary arterial perfusion phase image (b; arrows). This perfusion map, however, apparently differs from that on the subsequent aortic perfusion phase image (c), where the embolized area is prominently enhanced (open arrows). The subtracted, intra-aortic Gd-DTPA-enhanced image (d) also shows prominent enhancement within the embolized area, indicating the presence of a large amount of systemic circulation. B: pulmonary (left) and bronchial (middle) arteriographies soon after embolization, and bronchial arteriography (right) 2 mo later in the same pulmonary embolic model represented in A. Pulmonary arteriography showed an embolization of the right lower pulmonary arteries with embucrilate (left; arrows). Bronchial arteriography shows only slight enhancement in the embolized area soon after embolization (middle; open arrow) but demonstrates prominent vascular development within this area 2 mo later (right; open arrow).
phase, which reflects the relative amount of systemic circulation in the embolized lungs against the nonembolized lungs, was significantly greater than that of $0.23 \pm 0.22$ soon after embolization ($n = 11, P < 0.0001$). The intercostal/bronchial arteriographies revealed a marked development of bronchial arterial branches or the collateral vessels from the intercostal arteries supplying blood flow to the embolized areas, compared with those soon after embolization (Fig. 5B). This increased systemic arterial circulation was also confirmed by the prominent enhancement of the embolized areas on the intra-aortic Gd-DTPA-enhanced images (Fig. 5A). The $\Delta SI_{ECG}$ ratio of the embolized to nonembolized areas was significantly lower than the $\Delta SI_{Gd-DTPA}$ ratio on the intravenous Gd-DTPA-enhanced pulmonary arterial phase images both soon and 2 mo after embolization ($P < 0.0001$ and $P < 0.01$, $n = 11$, respectively).

The histology of all 13 embolized areas revealed obstructions of pulmonary arterial branches by granulomatous tissues surrounding the bluishly stained embucrilate, with heterogeneous oligemia in the alveolar microvasculatures. However, no noticeable infarction was seen in any of the embolized lung areas, despite the slight, focal alveolar hemorrhage in the minority of the cases. Arterial vessels with a thick, elastic wall developed along the bronchi and/or the subpleural portion in these embolized areas.

In the two postmortem pulmonary embolic models, the lung vascular and parenchymal SI was persistently high on the FSE MR images obtained with the same acquisition parameters as in the living animals. The subtracted images did not show noticeable signals throughout the lung vessels and parenchyma.

**Airway obstruction model.** Before inflating the intra-bronchial balloon, there was no significant difference in the $\Delta SI_{ECG}$ between the lung regions distal to the bronchial obstruction and the contralateral, nonaffected lung regions in the eight animals ($208 \pm 64.5$ vs. $212.3 \pm 60.2$; NS), and the ECG-gated perfusion-weighted images were similar to those in the normal animals. However, after balloon inflation, these images showed gradual decreases in SI corresponding to the hypoventilated lung areas with time in all these animals (Figs. 6 and 7). The affected-to-nonaffected lung $\Delta SI_{ECG}$ ratio was decreased with time after bronchial occlusion and was significantly lower compared with the preocclusion value beyond 25 min after bronchial occlusion (Fig. 8). The relatively large proximal pulmo-
nary arteries within the affected lung areas, however, were usually seen on these images.

The locations of this decreased perfusion were nearly consistent with those on the Gd-DTPA-enhanced pulmonary arterial perfusion phase images (Figs. 6 and 7). The affected-to-nonaffected lung ΔSI_{ECG} ratio of 0.27 ± 0.22 at 45 min after bronchial occlusion was not significantly different from the ΔSI_{Gd-DTPA} ratio of 0.35 ± 0.17 at 50 min. The large proximal pulmonary arteries within the affected lungs were also usually seen on these Gd-DTPA-enhanced images, similar to the ECG-gated perfusion-weighted images. No noticeable over-inflation or volume loss was seen on the chest X-ray fluoroscopy taken after MR studies in all these animals.

**DISCUSSION**

The present FSE MR sequence allowed the image acquisition of the cardiac-dependent, pulsatile lung parenchymal signal changes, and the subtracted ECG-gated image between the systolic and diastolic phase...
images provided a uniform but gravity-dependent perfusion map in the normal dogs, similar to the intravenous Gd-DTPA-enhanced pulmonary arterial perfusion phase image. This image also defined the perfusion deficits and reduction in the pulmonary embolic and airway obstruction models, consistent with the Gd-DTPA-enhanced pulmonary arterial phase images. Although these results were obtained from a single slice of the lower lung level, and from the dog lungs with some anatomic and physiological characteristics different from human lungs (21, 29), this noncontrast perfusion MR imaging thus seems to have the characteristics different from human lungs (21, 29), this noncontrast perfusion MR imaging thus seems to have the potential to express normal pulmonary blood flow and an excellent ability equivalent to a Gd-DTPA-enhanced dynamic MR study to define regionally impaired pulmonary arterial perfusion in pulmonary embolism and airway obstruction.

The lung has many of vessels and vascular networks that contain a large amount of blood flow, although there is little solid component. The present FSE MR sequence allows efficient acquisition of lung signals derived from intravascular water molecules, regardless of the low proton spin density and great magnetic susceptibility associated with the large air and tissue interface of the lung tissues (12, 13, 16, 17, 19, 23, 24). As seen on the ECG-gated preparation scan in the normal dog lungs, this sequence provides cardiac-dependent SI changes in the pulmonary vascular networks. These SI changes during a cardiac cycle may be attributed to blood flow velocity variations in the amount of dephasing and rephasing by magnetic field gradients. In a relatively fast flow, phase coherence generated with the 90° pulse in a multiecho sequence is not completely refocused for any subsequent echoes, resulting in substantial reduction in the SI (flow void effect). The SI loss during the systolic phase may result mainly from the fast flow velocity in the pulmonary vascular networks, and, conversely, the recovered high SI during the diastolic phase may result from the slow flow velocity (24). The complete absence of blood flow should result in no SI changes because of the lack of flow void effect, as seen in the two postmortem animals. The SI changes of the lungs may be largely related to the pulmonary arterial blood flow, because ~95% of the lung circulation is normally supplied from the pulmonary artery (21). In fact, the delay times after R-wave showing the minimal and maximal SI (Tmin and Tmax) were nearly synchronized between the pulmonary artery and parenchyma. In a Doppler echo study, the pulmonary artery shows a peak seep (inflow) at the middle phase of the cardiac systole (16), which is considered to correspond to the signal loss of the lung parenchyma during the systolic phase. On the other hand, the pulmonary veins have moderate speed flow during the ventricular contraction period, followed by a fast flow in the opposite direction during the atrial contraction period. There is, therefore, a short, slow-flow phase before the atrial contraction period in the vascular networks, which is considered to correspond to the highest SI of the lung parenchyma during the diastolic phase. As indicated by our flow phantom study, the flow void effect of the vascular networks, however, may not occur in very slow flow velocity on the present FSE MR image. The lung SI changes may reflect large blood flow changes in the relatively large vascular networks, because the blood flow velocity in the alveolar microvascularities is steadily low, less than ~0.3–0.5 mm/s (17, 20, 23, 24). The subtraction process stresses the SI difference of the lung parenchyma between systolic and diastolic phases (∆SI_ECG, the difference between the maximal and minimal SI) and suppresses the SI from the extravascular interstitial tissue, thereby providing a perfusion-weighted image. The appearance of the gravity-dependent dorsal-to-ventral gradient in the normal lungs on the subtracted perfusion-weighted image was almost consistent with the Gd-DTPA-enhanced pulmonary arterial phase image, although the gradient was relatively small, probably because the effect of signal averaging. The high pulmonary arterial pressure in the dorsal lung normally increases the transmural pressure of the vascular networks, which distends the greatly distensible vascular tubes and lowers the resistance to blood flow, resulting in greater pulmonary arterial blood flow and volume in this lung (7, 11, 27, 31, 33, 35, 36). In addition to the greater blood flow velocity in the vascular networks of the dorsal lung, the greater blood volume also may partly contribute to greater SI in this lung (16, 17).

In the pulmonary embolic models, the ECG-gated perfusion-weighted images efficiently defined the perfusion deficits, consistent with Gd-DTPA-enhanced pulmonary arterial perfusion phase images. These perfusion deficits appeared persistently hyposignal on the perfusion-weighted images soon and 2 mo after embolization, without significant changes in the ∆SI_ECG ratio of the embolized to nonembolized areas. This finding was also consistent with the Gd-DTPA-enhanced pulmonary arterial phase images. The perfusion map, however, often differed from the subsequent Gd-DTPA-enhanced aortic perfusion phase images, which showed some contrast enhancement within the embolized areas. This enhancement seems to be caused by systemic arterial circulation within the embolized areas.
areas, as shown by the arteriographies and intra-aortic Gd-DTPA-enhanced MR images and as indicated by the development of arterial vessels in the resected specimen. This systemic circulation appeared to increase in the chronic phase of pulmonary embolism to compensate the interrupted pulmonary arterial blood flow and to prevent the development of infarctions, as seen in the histology (9). The persistently hyposignal intensity of the embolized lungs on the ECG-gated perfusion-weighted image, regardless of this increased systemic circulation, may be caused by the limited sensitivity of the present ECG-gated perfusion imaging for slow blood flow, as described earlier. This failure also may be caused partly by the difference in the perfusion phase between the systemic and pulmonary arterial flows, because the present FSE MR image was obtained by triggering the Tmin and Tmax of the nonembolized lungs largely supplied from the pulmonary artery. This imaging feature of the ECG-gated perfusion-weighted images is disadvantageous compared with a Gd-DTPA-enhanced dynamic study that permits the detection of systemic circulation or collateral and/or anastomotic perfusion in the embolized lungs (1, 2, 29, 31). The persistently hyposignal appearance of the embolized lungs with a high contrast against the nonembolized lungs, however, may contribute to the sensitive detection of perfusion deficits in pulmonary embolism, as well as 99mTc-MAA perfusion scintigrams (29).

In the airway obstruction models, the delayed ECG-gated perfusion-weighted image showed apparently decreased perfusion in the hypoventilated lungs, almost similar to Gd-DTPA-enhanced pulmonary arterial perfusion phase image. Pulmonary arterial perfusion reduction associated with insufficient ventilation is a well-recognized, fundamental phenomenon (5, 8, 15, 19, 28, 30). Regional hypoxemia after airway obstruction has a direct action on the smooth muscle of the pulmonary arteries of a size 200–300 \( \mu \text{m} \) in diameter, partly on the small pulmonary veins, and elicits hypoxic vasoconstriction leading to regional hypoperfusion (8, 15, 28, 30). The degree of pulmonary perfusion reduction may vary depending on the time after bronchial occlusion (15, 30). The ECG-gated, subtracted perfusion-weighted images showed the gradually decreased SI with time after bronchial occlusion in the hypoventilated lungs. This seems to reflect the gradual decrease in pulmonary arterial blood flow due to the gradual increase in hypoxic vasoconstriction with time after bronchial occlusion. Therefore, this image appears to be able to measure the degree of reduction in pulmonary perfusion, although the flow velocity must be greater than the measurable, minimal limitation, as described earlier. The large proximal pulmonary arteries within the insufficiently ventilated lungs may be able to keep some blood flow because of the lack of hypoxic vasoconstriction, because these arteries were usually well delineated on the ECG-gated perfusion-weighted and Gd-DTPA-enhanced pulmonary arterial phase images. This delineation of these relatively large pulmonary arteries may indicate the still-remaining substantial pulmonary blood flow, although the present ECG-gated perfusion image could not well detect this slow blood flow, probably because of the limited sensitivity for slow blood flow. Despite the limitation for measuring slow blood flow, the ability of the easily repeatable noncontrast ECG-gated perfusion MR imaging to demonstrate dynamically changed perfusion over time in the hypoventilated lungs is superior to Gd-DTPA-enhanced MR study or 99mTc-MAA perfusion scintigrams, which cannot be repeated within a short time (4, 15). This easily repeatable test will be beneficial for monitoring perfusion changes after anticoagulation or thrombolysis therapies in pulmonary embolism.

Although the present ECG-gated perfusion-weighted MR image was obtained without breath holding, the sufficient NEX provided an excellent image quality with high signal-to-noise ratio and without significant motion artifacts and ghosting from the large vessels. This image provided good anatomical landmarks of the well-delineated pulmonary vessels which contributed to anatomic localization of the perfusion deficits or reduction in the animal models. Our ongoing clinical study indicates that a good image quality of ECG-gated perfusion image is possible by use of reduced NEX with a 35-s breath holding, but the present method without breath holding is clinically beneficial especially for patients with respiratory insufficiency. A pulsed arterial spin-labeling technique of flow-sensitive alternating inversion recovery sequence with an extra radiofrequency pulse using an ECG-gating subtraction technique and breath holding also has been reported to have an excellent ability in providing normal lung perfusion maps and perfusion deficits in pulmonary embolism, without using contrast agents (18, 19). This method, however, requires special hardware to produce an extra radiofrequency pulse and seems to be more affected by the flow ghosting from the large vessels.

A Gd-DTPA first-pass MR study is a promising screening method to detect perfusion impairment in pulmonary embolism and airway obstruction (1, 2, 4–6, 8, 12, 29, 31). In pulmonary embolism, this method appears to provide a better contrast between the embolized and nonembolized lungs compared with the ECG-gated perfusion imaging, with significantly greater embolized-to-nonembolized lung \( \Delta S_{\text{ECG}} \) ratios than the \( \Delta S_{\text{Gd-DTPA}} \) ratios or the \( \Delta S_{\text{ECG}} \) ratios on the pulmonary arterial perfusion phase. This method also permits separation of pulmonary arterial flow from the subsequent perfusion from the systemic circulation, arteriovenous anastomoses, and collaterals (1, 4, 6, 8, 29, 31) and may permit quantitation of significantly reduced pulmonary arterial perfusion in pulmonary embolism and airway obstruction, despite some limitations in application of the indicator dilution principle (14). However, the use of an exogenous contrast agent increases the cost of the examination and poses some risk to patients. Computed tomography angiography using a multidetector scanner is a new method of detecting intravascular emboli in pulmonary embolism, but it...
also uses iodinated contrast, and the ability to depict reduced perfusion in the lung parenchyma is uncertain (10). Although the most accurate test is pulmonary angiography (8, 10, 29), it is invasive, the need for catheterization poses some risk to patients, and it might be inferior in detecting periphery or capillary-type perfusion deficits. To date, positron emission tomography may be the only noninvasive method to quantify pulmonary perfusion. However, this method is expensive and its availability is limited.

The subtraction process contributes to provide purely perfusion-weighted MR images without contrast material. However, this process is sensitive to misregistration due to bulk motion, which can be a disadvantage of the present MR method, although cardiac and respiratory motion artifacts did not interrupt the detection of the perfusion deficits in the present models. The use of respiratory gating will improve these motion artifacts, although it prolongs the examination time. Another drawback of the present study includes the imaging of only a single slice of the lower lung level. However, additional orthogonal section imaging of the entire lungs is possible in this noncontrast imaging, but it prolongs the examination time. The lung signal changes associated with different R-R intervals among individual subjects may limit quantitative assessment of pulmonary perfusion and intersubject comparison. The image acquisition might be interrupted by severe arrhythmia. Another drawback of the present study is the lack of the comparison with $^{99m}$Tc-MAA perfusion scintigrams. The sizes of the perfusion defects might show discrepancies because of the large particle sizes of MAA (4, 6, 29). Because perfusion imaging alone is also not sufficiently specific to diagnose pulmonary embolism and airway obstruction, ventilatory MR imaging should be combined with inhalation of hyperpolarized gases, oxygen, or Gd-DTPA aerosol (2, 4–6, 8, 22, 32, 34).

In conclusion, these preliminary experimental results indicate that the noncontrast ECG-gated perfusion MR image can provide normal perfusion maps and may have excellent potential, equivalent to Gd-DTPA first-pass MR study, for detection of perfusion deficits or reduction associated with pulmonary embolism and airway obstruction. The ability of this repeatable test to demonstrate dynamically changed perfusion in the hypoventilated lung regions in airway obstruction model is noteworthy. The perfusion map appears to reflect mainly pulmonary arterial circulation and may not be significantly affected by systemic circulation compensatorily developed within the emobolized lungs. Although further evaluations and a test for clinical use are needed, this method may be an attractive, noninvasive screening tool for diagnosing pulmonary embolism and for demonstrating impaired perfusion associated with airway obstruction.

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REFERENCES


