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Original Research

Can MR Fluoroscopic Triggering Technique and Slow Rate Injection Provide Appropriate Arterial Phase Images With Reducing Artifacts on Gadoxetic Acid-DTPA (Gd-EOB-DTPA) -Enhanced Hepatic MR Imaging?

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Purpose: To evaluate whether using MR fluoroscopic triggering technique and slow rate injection improves the quality of arterial phase images in gadoxetic acid-DTPA-enhanced (Gd-EOB-DTPA) MR imaging because of proper acquisition timing and reduction of artifacts.

Materials and Methods: Two hundred sixteen patients undergoing examination for liver diseases were retrospectively reviewed. All MR images were obtained with two Gd-EOB-DTPA injection protocols: (i) a combination protocol, in which the MR fluoroscopic triggering technique and slow rate injection (1 mL/s) were used; and for comparison, (ii) a conventional protocol, in which adjusted fixed scan delay and ordinary rate injection (2 mL/s) were adopted. Signal-to-noise ratio (SNR) of aorta, portal vein, and liver parenchyma on arterial phase images were calculated. Two blinded readers independently evaluated the obtained arterial phase images in terms of acquisition timing and degree of artifacts.

Results: The SNRs of aorta and portal vein on arterial phase images were significantly higher in the combination protocol group (aorta/portal: 221.9 ± 91.9/197.1 ± 89.8) than that in the conventional protocol group (aorta/portal: 169.8 ± 97.4/92.7 ± 48.5) ($P < 0.05$). The acquisition timing for arterial phase images with the combination protocol was significantly better than that with the conventional protocol ($P < 0.01$). The image quality of the combination protocol was significantly higher than that of the conventional protocol ($P < 0.01$). The occurrence rate of moderate or severe degree of artifacts in the conventional protocol (38.0%) was more prominent than that in the combination protocol (18.5%).

Conclusion: The combination of the MR fluoroscopic triggering technique and slow rate injection provides proper arterial phase images and reduces the artifacts in Gd-EOB-DTPA MR imaging.

Key Words: MRI; liver; gadoxetic acid-DTPA (Gd-EOB-DTPA); MR fluoroscopic triggering technique; injection rate
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GADOXETIC ACID-DTPA (Gd-EOB-DTPA) has recently been introduced into clinical practice as a liver-specific hepatobiliary contrast agents. Gd-EOB-DTPA is categorized as a dual-acting agent, which simultaneously allows for dynamic imaging like an extracellular agent and a liver-specific imaging agent. In addition to the highly specific properties of Gd-EOB-DTPA for hepatocytes, the higher T1 relaxivity of the agent in human blood due to its weak protein binding (10%) provides prominent enhancement in arterial phase images, which indicates an advantage in detecting and characterizing hypervascular tumors, such as hepatocellular carcinoma (HCC) (1,2). Moreover, a recent study showed that the sensitivity and specificity of Gd-EOB-DTPA-enhanced MR imaging is superior to that of multi-detector computed tomography (MDCT) for the diagnosis of HCC (3). Although Gd-EOB-DTPA-enhanced MR imaging shows the high utility with quite small injection volume, which is 0.1 mL per 1 kg (e.g., 5 mL for a patient with 50 kg) , this small volume, in turn, can causes, if not properly timed, acquisition timing error and peculiar artifacts, namely

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truncation artifacts (ringing artifacts, Gibbs phenomenon), on arterial phase images (4).

The MR fluoroscopic triggering technique is real-time monitoring with two-dimensional (2D) fluoroscopic sequence after bolus administration of a contrast agents to detect arrival of the contrast in the vessel of interest (5,6). Thus, the operator can easily decide to start the acquisition at the appropriate arterial phase timing. Although the MR fluoroscopic triggering technique was originally applied to 3D MR angiography (MRA) (5,6), it can also be applied for abdominal dynamic imaging with 3D acquisition (e.g., VIBE sequence) to obtain reproducible arterial phase images without the influence of individual distinctions.

Truncation artifacts occur because of insufficient sampling at high spatial frequencies in *k*-space, and these artifacts may alter the intensity, shape, and anatomic detail of the structures (7,8). For proper arterial phase imaging, *k*-space filling should match the enhancement peak while avoiding abrupt changes in the concentration. The latter can in fact lead to truncation artifacts. In the case of small volumes of contrast media administered (e.g., Gd-EOB-DTPA) the matching of the peak with proper *k*-space filling may be insufficient and cause peculiar truncation artifacts (7). This should be considered when performing Gd-EOB-DTPA-enhanced MR imaging. To make the matching easier, recent studies proposed the contrast dilution method with saline to reduce truncation artifacts and maintain *k*-space homogeneity during signal acquisition (4). On the other hand, the slow injection rate followed by a saline chaser might have similar effects on the contrast dilution method. The latter can be called "intravenous dilution method," but its utility has not been intensively investigated.

The purpose of this study was to determine whether the MR fluoroscopic triggering technique and slow rate injection (1 mL/s) improve the quality of arterial phase images with proper scan timing and reduction of the artifacts on Gd-EOB-DTPA-enhanced MR imaging.

MATERIALS AND METHODS

This study endorsed the principles of the Declaration of Helsinki and subsequent amendments (9). Our institutional review board deemed that approval of this study was not necessary due to the retrospective nature of the evaluation. Written informed consent was obtained from all patients. All data and information derived from and pertaining to the study were under the exclusive control of the investigating radiologists.

Patients

We retrospectively and randomly listed 121 eligible patients using conventional injection protocol from April 2006 to December 2006 and 127 eligible patients using combination protocol from January 2007 to March 2008 on dynamic Gd-EOB-enhanced MRI for the evaluation of liver disease. Among these patients, 32 patients (13 in conventional protocol, 19 in combination protocol) were excluded from the study because of (a) having multiple focal liver lesions (more than 10 lesions) (n = 12) or a large liver lesion (more than 60 mm in diameter) (n = 9), (b) massive portal vein thrombosis (n = 6), and (c) inadequate examination (n = 5) (extravasation or severe adverse events to the contrast agent) and we selected the same number of patients (n = 108) examined with conventional or combination protocols. Finally, a total of 216 patients (124 male, 92 female; age range, 19–83 years; mean, 57.5 years) were enrolled in this study. Ninety-two patients had chronic liver disease (22 chronic hepatitis and 70 liver cirrhosis). In 128 patients with malignant hepatic lesions, the histopathologic diagnosis was made by surgical resection (n = 47) and fine needle biopsy (n = 59). The diagnosis of the remaining patients were obtained with characteristic image findings (n = 14) and identified increased tumor size on the follow-up examinations (n = 8). These included HCC (n = 90), cholangiocellular carcinoma (n = 8), metastases of colorectal cancer (n = 18), metastases of other primary tumors (n = 10), and lymphoma (n = 2). Among a total of 69 patients with benign focal liver lesions, 37 patients were histopathologically verified. The remaining patients were confirmed by characteristic image findings (n = 19) and stability in size of tumors on follow-up examinations (n = 13). The patients had focal nodular hyperplasia (n = 39), hemangioma (n = 20), adenoma (n = 3), nodular regenerative hyperplasia (n = 3), and other (n=4; inflammatory pseudotumor, abscess, cyst, and hamartoma).

MR Examination

MR imaging was performed with a 1.5 Tesla (T) scanner 18-channel system (Avanto, Siemens Medical Systems, Erlangen, Germany) with a 45 mT/m gradient strength (peak slew rate of 200 mT/m/ms) and a 12-element surface phased-array coil in all patients. Presaturation pulses were applied above and below the imaging volume to reduce flow artifacts from vessels. mSENSE (SENSE factor = 2) was also applied to reduce the scanning time. A T1-weighted 3D gradient-echo sequence with fat saturation and volumetric interpolated breathhold examination (VIBE; Siemens) image was acquired before and after the administration of Gd-EOB-DTPA (Primovist®, Bayer Schering Pharma, Berlin, Germany). The sequence parameters were as follows: repetition time/echo time (TR/TE) = 5.29/2.57 ms, slice thickness = 4 mm, intersection gap = 20%, field of view = 380–500 mm, effective matrix size = 176 × 256, signal averages = 1, acquisition time = 16 s, *k*-space trajectory, centric ordering. The 0.025 mmol/kg of body weight dose of Gd-EOB-DTPA was administrated in all patients. After precontrast images (e.g., T2WI, dual echo T1WI, etc.), T1-weighted VIBE images were obtained before administration of the contrast agent and during the arterial phase, during the portal venous phase at 70 s, during the equilibrium phase at 180 s, and during the hepatobiliary phase at 5 min, 10 min, 15 min, and 20 min, respectively. Dynamic MR images were obtained in the transverse plane covering the upper abdomen during

end-expiratory breathhold. Although other precontrast sequences (e.g., T2WI, dual echo T1WI etc) and other dynamic phase (portal venous phase and equilibrium phase) and hepatobiliary phase images at 5 min, 10 min, 15 min, and 20 min were acquired in clinical protocols, in this study, we evaluated only pre–T1-weighted and arterial phase images with VIBE sequence.

Gd-EOB-DTPA Injection and Arterial Phase Acquisition Methods in the Two Protocols

We designed two Gd-EOB-DTPA injection protocols for comparison in this study.

(a) Combination protocol (MR fluoroscopic triggering technique and slow injection rate, n = 108): Gd-EOB-DTPA was administrated at a rate of 1 mL/s with a mechanical power injector (MedRad Spectris Solaris EP) through an 20-gauge catheter inserted into an antecubital vein, followed by 20-mL saline flush at the same injection rate. After injection of the contrast, real-time monitoring with the MR fluoroscopic triggering technique (CARE Bolus; Siemens) in the sagittal plane was simultaneously started and, when the operator decided that the contrast arrived around the bifurcation of celiac artery, arterial phase imaging was initiated after 10 s, which represents the estimated duration from abdominal aorta to peripheral intrahepatic arterial branches, from the operator decisions. Timing was, therefore, always consistent and individual. As information, the mean starting timing of arterial phase images over 108 patients was 30.3 s (range, 26–38 s).

(b) Conventional protocol (adjusted two kinds of fixed scan delay and ordinary injection rate, n = 108): Gd-EOB-DTPA was administrated at a rate of 2 mL/s in the same way as in the combination protocols. Arterial phase imaging was started at two kinds of adjusted fixed scan delay as follows; 25–28 s for young patients (19–50 years) without cardiovascular disorders and 30–35 s for middle age or older patients (51–83 years) or patients with cardiovascular disorders after injection of the contrast.

Imaging analysis

Quantitative Analysis

For quantitative analysis, signal intensities (SI) of aorta, portal vein, and liver parenchyma on arterial phase images were measured by one radiologist, who did not attend each reading session to minimize bias on the measurements. Regions of interest (ROIs) were drawn as large as possible, which was at least 1 cm in diameter, in the structure of interest, avoiding vessels for measurements of liver parenchyma. The means and standard deviations (SDs) of each target were recorded. Image noise was measured as SD of an ROI in outside the body volume along the phase-encoding direction (10). Signal-to-noise ratio (SNR) of each organ was then calculated as follows: SNR = SI (target structure)/Noise (SD of background).

Qualitative Analysis

All MR images were interpreted by two experienced abdominal radiologists with 12 and 14 years experience, respectively, who were blinded to all clinical information. The MR images were analyzed separately by each radiologist in two different reading sessions. The each one session was also divided into three parts to reduce the reading overload, which might induce a misjudgment. In case of discrepancies between the two readers, they were discussed in additional reading session until a consensus was reached. To assess optimal acquisition timing for the arterial phase, provisions were made in the scoring to allow for some scans which may have been initiated too early as well others initiated too late. A three-point scoring system was used, with 3 corresponding to appropriate timing, 2 as moderately inaccurate, and 1 as markedly inaccurate. Appropriate timing (a score of 3) was defined as the hepatic arteries and portal vein being sufficiently enhanced for interpretation. A score of 2 was defined as "moderately early" triggering if there was small enhancement in the hepatic arteries and portal vein. A score of 1 was defined as "markedly early" if there was no portal vein enhancement. Similarly, for late triggering, a score of 2 was defined as "moderately late" if there was slight hepatic vein enhancement, and a score of 1 as "markedly late" for hepatic parenchymal and hepatic vein enhancement.

For the evaluation of image quality (degree of artifacts) on arterial phase image, we used a 4-point rating scale (0–3). The quality was assigned as excellent if no artifacts were observed; good when mild artifacts were shown, but it did not interfere diagnostic interpretation; poor when moderate artifacts were observed and they did interfere with the interpretation; and nondiagnostic, when severe artifacts were observed impairing the assessment.

Statistical Analysis

The differences in mean age and gender distinctions of the two groups were evaluated by t-test and chi-square test, respectively. Interobserver variability among the two readers was assessed by the unweighted kappa statistics. K value range of 0.81–1.00 was indicated as excellent agreement; 0.61–0.81, as good; 0.41–0.60, as moderate; 0.21–0.40, as fair; and 0.00–0.20 as poor. SNR of each organ between the two protocols was compared using an unpaired t-test. Differences in the grading score of the timing and the image quality on arterial phase images with the two injection protocols were assessed using chi-square test. A P value of <0.05 was considered to indicate a statistically significant difference. For statistical analysis, commercially available software (SPSS release 15.0, SPSS) was used.

RESULTS

Interobserver Agreement

Good to excellent reader agreements (0.76–0.94) were achieved concerning assessment of timing and image

Table 1
Results of Agreements Between the Two Readers

	Conventional	Combination
Timing of arterial phase	0.94	0.76
Image quality (Degree of the artifacts)	0.80	0.81

quality (degree of artifacts) on arterial phase images with the two protocols (Table 1).

Patient Population (Background Factor)

There were no significant differences in terms of mean age ($P = 0.263$, t-test) and gender distinction ($P = 0.116$, chi-square test) of the patients between the two groups (Table 2).

Quantitative Analysis

The SNRs of each in the two protocols are shown in Table 3. The SNRs of the aorta and portal vein in combination protocol (aorta/portal vein: 221.9 ± 91.9/197.1 ± 89.8) on arterial phase was significantly higher than that in the conventional protocol (aorta/portal vein: 169.8 ± 97.4/92.7 ± 48.5, $P < 0.05$). The SNR of the liver was not significantly different between the two protocols.

Assessment of Optimal Acquisition Timing for Arterial Phase Images

The acquisition timing for the arterial phase imaging with the combination protocol was significantly better than that with the conventional method ($P < 0.01$) (Fig. 1; Table 1). The acquisition timing for the arterial phase image was assigned as appropriate for 91.7% (99/108) and 31.5% (34/108) of the patients in the combination protocol and conventional protocol, respectively, and significant differences were observed in the results ($P < 0.01$) (Table 2). Of the patients assigned as inappropriate timing, 100% (9/9) and 93.2% (69/74) of the patients were judged as "early" or "too early" in the combination protocol and conventional protocol, respectively (Fig. 2). Whereas, of these groups, none and only 6.8% (5/74) of the patients were judged as "too late" in the combined protocol and conventional protocol, respectively (Fig. 3).

Table 3
Results of Quantitative Analysis on Arterial Phase Images in the Two Protocols

	Mean ± SD		
SNR of each organ	Conventional (n = 108)	Combination (n = 108)	*P* value
Aorta	169.8 ± 97.4	221.9 ± 91.9*	<0.05
Portal vein	92.7 ± 48.5	197.1 ± 89.8*	<0.01
Liver	81.8 ± 40.1	87.3 ± 37.9	n.s.

*Significant difference between two protocols.
n.s. = not significant.

Image Quality (Degree of Artifacts)

The results of image quality of the two protocols are shown in Figure 4. The image quality of the combination protocol was significantly better than that of the conventional protocol ($P < 0.01$) (Fig. 1). The occurrence rate of moderate or a severe degree of artifacts in the conventional protocol (38.0%, 41/108) was significantly higher than that in the combination method (18.5%, 20/108) ($P < 0.01$).

DISCUSSION

Our study demonstrated that combined MR fluoroscopic triggering technique and slow rate injection provided proper arterial phase images with reduction of artifacts on Gd-EOB-DTPA MR imaging. Among serial phase images on dynamic Gd-EOB-DTPA MR imaging, the quality of arterial phase images has a tendency to become worse, influenced by several factors, in particular, acquisition timing and the artifacts, such as truncation artifacts are notable in these factors.

In the past, several methods have been proposed to determine optimal acquisition timing in liver imaging (6,7,11). In general, a fixed scan delay method is adopted to determine arterial phase acquisition timing on dynamic MR imaging, but the timing error may often occur under injection of a small amount volume of contrast, like Gd-EOB-DTPA with the influence of individual variation (blood circulation, a history of cardiovascular disease, etc.). In this study, only 31.5% (34/108) of the patients with the conventional protocol were assigned as appropriate acquisition timing for arterial phase, although we used not one but adjusted two kinds of scan delay, thus somehow considering individual variation, and most of these (93.2%) were categorized as " too early."

Table 2
Results of the Two Injection Protocols

	Injection protocols		
	Conventional (n = 108)	Combination (n = 108)	*P* value
Mean age	57.4 ± 15.5	57.5 ± 14.7	n.s.
Gender	68 M 40 F	56 M 52 F	n.s.
Mean score (timing of arterial phase)	1.80 ± 0.89	2.92 ± .028*	<0.01
Appropriciate acquisition timing	31.5% (34/108)	91.7% *(99/108)	<0.01
Occurrence rate of moderate or severe artifacts	38.0%% (41/108)	18.5% *(20/108)	<0.01

*Significant difference between two protocols n.s. = not significant.

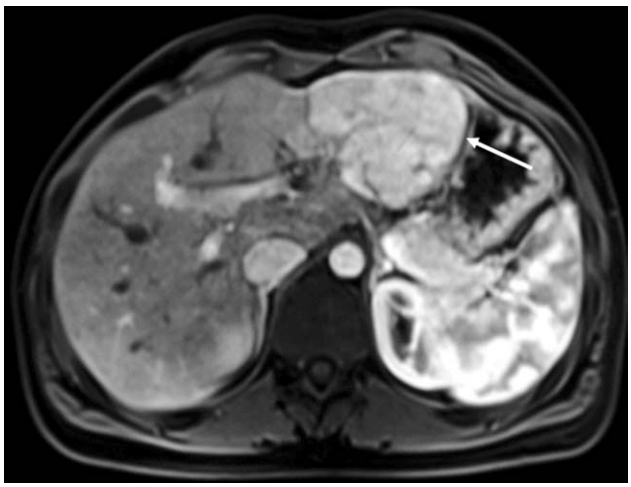

Figure 1. Images obtained by a combination protocol in a 24-year-old woman with typical focal nodular hyperplasia. The acquisition timing for the arterial phase image was appropriate, and an intense enhanced mass (arrow) in the lateral segment of the liver is clearly demonstrated. Excellent quality images without any artifacts were obtained. A score of 3 was assigned by both readers.

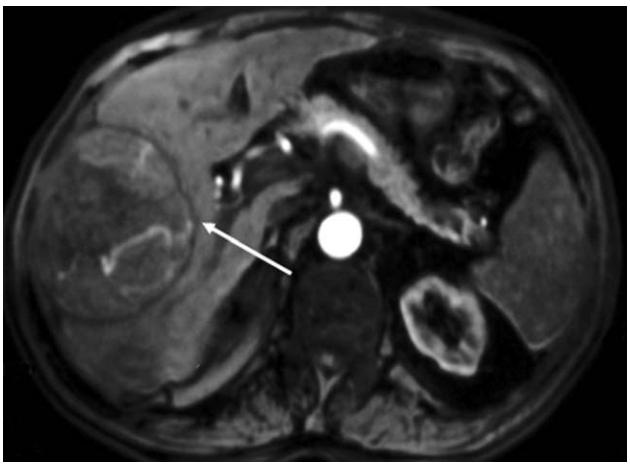

Figure 2. Images obtained by a conventional protocol in a 71-year-old man with hepatocellular carcinoma (HCC) and liver cirrhosis (HCV and alcohol). A large HCC tumor with a thin capsule (arrow) in the right anterior segment of the liver was faintly enhanced due to the inappropriate "too early" acquisition timing. The image quality was excellent without any artifacts.

Another timing technique commonly used is "test bolus," in which a small amount of (i.e., 1 mL) of contrast medium is injected before the full bolus to determine aortic peak enhancement (11). Although this method is effective for CT or MRA, the acquisition timing determined by test injection may be sometimes different to actual scan timing because circulatory dynamics are variable at any given time. Moreover, unlike nonspecific distributed extracellular contrast agents, test injected Gd-EOB-DTPA is rapidly taken up into hepatocytes and may induce unfavorable increased liver signal, leading to less lesion-liver contrast.

The MR fluoroscopic triggering technique easily makes the operator decide appropriate acquisition timing for the arterial phase without unnecessary preinjection of the contrast (5,6). This method is a relatively operator-dependent technique, but the best results can be achieved if conducted by accomplished operators. In this study, successful results (91.7%) were obtained for determining acquisition timing of arterial phase with significant differences to that of the conventional protocol.

Another key point for obtaining sufficient good quality arterial phase images is the reduction of artifacts of several origins.

It is worth reminding that liver imaging is commonly affected by motion-related artifacts (body motion, respiratory movement, etc.). These artifacts could be reduced by shortening the acquisition time, for example, by using parallel imaging (SENSE etc).

As presented in this study, recent investigators pointed out that Gibbs or truncation artifacts, which are also called "ringing artifacts," are also an important factor in image degradation of arterial phase on dynamic Gd-EOB-DTPA MR imaging (4). They appear as bright or dark lines parallel to the edge of the interface, experiencing abrupt intensity changes (7). They seem to be related to abrupt concentration changes during the *k*-space filling. They can be avoided matching the peak concentration homogeneous part with the time duration of the *k*-space filling. This is for example what the contrast dilution method does, decreasing the intensity change between arteries and surrounding soft tissues and proportional long inflow

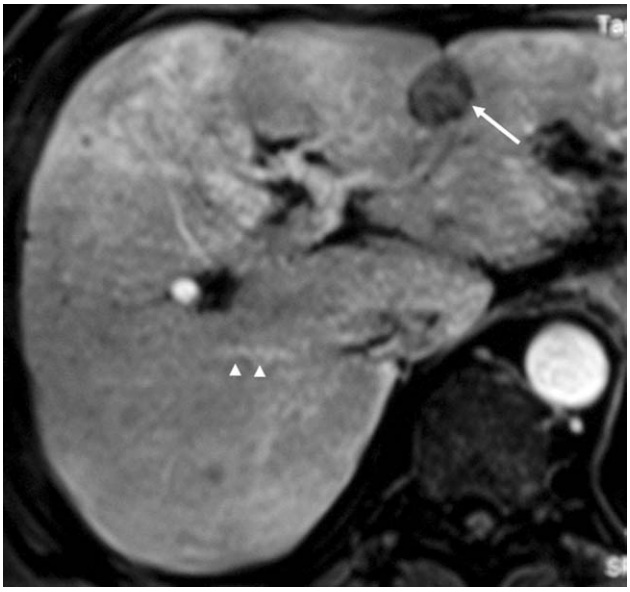

Figure 3. Images obtained by a conventional protocol in a 56-year-old man with hepatocellular carcinoma after partial resection and liver cirrhosis (HCV). In this patient, the acquisition timing for the arterial phase was "too late" and both hepatic vein (arrowheads) and liver parenchyma were already enhanced. Mild artifacts (truncation and motion-related artifacts) were also observed. Note the hypointense round area (arrow) was corresponding to the change after radiofrequency ablation.

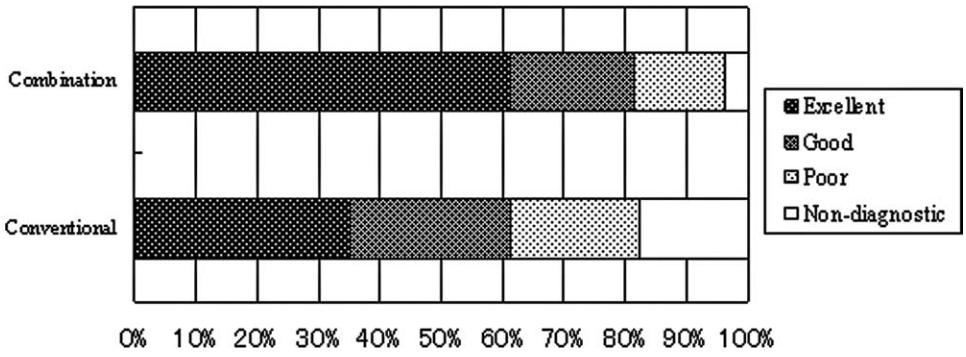

Figure 4. Results of image quality with the two protocols. The image quality of the combination protocol was significantly better than that of the conventional protocol ($P < 0.01$). The occurrence rate of poor or nondiagnostic image qualities in the conventional protocol (38.0%, 41/108) was significantly higher than that in the combination protocol (18.5%, 20/108) ($P < 0.01$).

of the contrast (half or one-third of total acquisition time), thus leading to *k*-space homogeneity, which results in reducing the artifacts (4). The slow rate injection (1 mL/s) followed by a sufficient volume of saline chaser may work the same way. Using the slow injection method, the contrast may be naturally diluted in intravascular space, as using the contrast dilution method, and thus lead to reduction of ringing artifacts as observed in this study. Another advantage of slow injection over dilution is that the diluted contrast with decreased the viscosity could be passed effectively through a venous dead space to heart and might accelerate a sufficient protein binding process of Gd-EOB-DTPA during the relative longer injection time, which are contributing to higher arterial enhancement (12–14). Because velocity of injection is supposed to affect the peak enhancement, a higher degree of abdominal aortic peak enhancement may be obtained by means of a fast injection rate protocol (e.g., 3 mL/s) (15,16). However, this mechanism may mainly apply to the enhancement on CT or MR images using conventional iodinated or Gadolinium-chelate agents (17). In this study, significant higher arterial enhancement was obtained with the combination protocol (1 mL/s) compared with the conventional protocol (2 mL/s). A recent study on pigs has shown that lowering the injection rate not only "compensated for the lower injection volume by stretching the bolus without decreasing the peak" but also that "an injection rate of 1 mL/s showed better results with regard to the arterial enhancement compared with 2 mL/s" (14). Therefore, this recent experience also could support our results in the human clinical study. Moreover, the effect of reducing the artifacts with slow rate injection is important for achieving sufficient enhanced high quality arterial phase images. In the present study, the enhancement of the portal vein in the combination protocol was also significantly higher than that in the conventional protocol, reflecting appropriate scanning timing.

This study has two main limitations. First, this study was retrospective in design and we did not compare the images obtained with the two protocols in the same patient, as we selected the materials from the patients who underwent MRI as routine clinical examination for diagnostic purposes. Although there is some bias on this evaluation, we believe that our results are valid because in this evaluation we used randomly selected and adequate number of patients, with a same number used in the two protocols. Second, we did not compare our combination method with the contrast agent dilution method in this study. Dilution is, as described above, another effective solution for improving quality of arterial phase images with reduction of artifacts in dynamic Gd-EOB-DTPA MR imaging. But this method may be not only time-consuming with regard to the preparation, because examiners have to take special care to avoid risk of contamination at any time, but may also be off-label without well-established evidence of safety.

In conclusion, the combination method of MR fluoroscopic triggering technique and slow rate injection contributes to proper arterial phase images with reduction of the artifacts. We believe that this method is the best practical solution without time-consuming preparation or risk of contamination, reducing the artifacts and ensuring best timing and higher image quality in the arterial phase of Gd-EOB-DTPA MR imaging.

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