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Original Article

Optimization of breathing instructions and timing of late arterial phase acquisition on gadobutrol-enhanced MRI of the liver

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ABSTRACT

Purpose: To compare a protocol with higher concentration macrocyclic gadolinium-based contrast agent (GBCA) [study group] to the traditional protocol with lower-concentration linear GBCAs [control group] for breath-held arterial phase magnetic resonance imaging.
Material and methods: A total of 136 patients were quantitatively evaluated for image quality (IQ), breathing artifacts (BA), and timing of the arterial phase (Tap). Quantitative analysis was also performed.
Results: No significant differences in IQ, BA and Tap ($P>.05$). Study group exhibited less enhancement of the aorta ($P=.0091$) and smaller standard deviation for the portal vein enhancement ($P=.0173$).
Conclusion: Similar arterial-phase image quality can be achieved with a macrocyclic GBCA compared to traditional linear GBCA.

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1. Introduction

Multiphasic contrast-enhanced (MCE) magnetic resonance imaging (MRI) is an established method for the detection and characterization of liver disease in clinical practice [1–6], and involves image acquisition before and after a bolus intravenous injection of gadolinium-based contrast agent (GCBA) during the arterial, portal-venous, late-venous, and equilibrium phases of liver enhancement. Acquisition of an optimally timed hepatic arterial phase is a critical component of the examination. For example, arterial phase enhancement and subsequent venous phase washout in a lesion is sufficient for the diagnosis of hepatocellular carcinoma in patients with cirrhosis, with no need for biopsy [7]. Similarly, an optimally timed hepatic arterial phase can be crucial in the evaluation of patients with hypervascular primary malignancies in whom the detection of metastatic lesions may be possible only during this phase of the MRI examination [8–10].

The quality of arterial phase imaging depends critically on the timing of the acquisition matched to the arterial enhancement of the liver parenchyma, as well as patient motion during acquisition. Ideally, these images should demonstrate strong aortic and hepatic artery enhancement, mild portal venous enhancement, faint hepatic parenchyma enhancement and no hepatic vein enhancement [11]. Accomplishing this is however not without challenges.

First, most MCE MRI protocols used over the last two decades were optimized for first generation of linear GBCAs with an intravenously (IV) injectable formulation of 0.1 mmol/kg body weight at a concentration of 500 mmol/ml, such as gadopentetate dimeglumine (Magnevist, Bayer Healthcare, Berlin, Germany) and Gadodiamine (Omniscan, Nycomed, Princeton, NJ, USA). However, compared to these traditional GBCAs, some of the more recently approved GBCAs are of different formulations and have higher concentrations, and therefore are injected as shorter boluses. Examples of the latter include gadobutrol (Gadovist, Bayer Healthcare), gadofosveset trisodium (Ablavar, Lantheus, North Billerica, MA, USA), and gadoxetate disodium (Eovist/Primovist, Bayer HealthCare). Macrocyclic agents such as gadobutrol (Gadavist, Schering, Berlin, Germany), gadoterate meglumine (Dotarem, Guerbet, Paris, France) and gadoteridol (Prohance, Bracco Diagnostics, Princeton, NJ) are considered safer in patients with renal failure because of their theoretical lower risk of nephrogrenic systemic fibrosis compared to the first generation of linear agents [12,13]. For this reason, these agents are an attractive option as the workhorse GBCA in clinical practice for routine abdominal MRI.

Gadobutrol is approved for abdominal imaging with a recommended dose at 0.1 mmol/kg of body weight and a formulation of 1000 mmol/ml. At the recommended dose, patients receive the same molar dose of gadolinium with gadobutrol (1000 mmol/ml) as with traditional GBCAs (500 mmol/ml), but in half the volume, typically at the same injection rate. This results in shorter (i.e. half) bolus duration with gadobutrol compared to traditional lower-concentration GBCAs for the same dose. Same molar dose of higher concentration formulations should have a comparable performance to that of lower concentration formulations because the concentration of the contrast agent has no impact on the extracellular distribution [14,15] in the equilibrium phase of enhancement. However, for the arterial phase imaging the optimal

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acquisition timing may require adjustments with higher concentration GBCAs, as the bolus duration is proportionately shorter.

Second, for three-dimensional (3D) spoiled gradient recalled echo (SPGR) acquisitions, the method used in most institutions for MCE liver MRI, the acquisition of the center of k-space must be timed to the arterial phase of the liver [16–21]. Consequently, for Cartesian 3D SPGR sequences the initiation of the acquisition must occur several seconds prior to the arrival of contrast to the liver. Timing of the acquisition is possible with a test bolus of a small dose of GBCA and application of a timing formula [21]. Alternatively, real-time MRI fluoroscopy-like techniques have gained popularity over the last decade and allow for the fast detection of the arrival of gadolinium to the abdomen without the need to administer a test bolus [11]. In either strategy, correct timing of arterial phase acquisition would be more challenging in shorter bolus duration of higher-concentration GBCA.

Third, a standardized protocol is necessary to ensure optimal breath-held imaging during a 15–20 s acquisition for most traditional Cartesian 3D SPGR acquisitions. End-expiration imaging is frequently preferred because it provides for a more consistent position of the abdominal organs compared to end-inspiration and facilitates anatomic co-registration for subtraction imaging of the abdominal organs [22]. Hyperventilation prior to suspension of the respiration can increase by up to 30% the individual's breath-hold capacity [22]. Accordingly, the use of two sets of breathing instructions followed by a breath-hold instruction (i.e. 'breath-in, breath-out, breath-in, breath-out, and hold your breath') has been previously recommended [22,23]. To accomplish this, however, the breathing instructions must be initiated approximately 10–12 s prior to starting the acquisition. It is thus crucial to initiate the breathing instructions in a timely manner such that the image acquisition timing coincides with the arterial phase enhancement of the liver, using the real-time MRI-fluoroscopy as the guide.

Hepatic arterial phase imaging with short-bolus, higher-concentration GBCA is therefore technically more challenging compared to long-bolus lower-concentration GBCAs. Traditional acquisition strategies may be inadequate for short-bolus GBCAs as these were previously optimized for traditional long-bolus GBCAs. However, we hypothesize that, the short-bolus protocol can be optimized, with proper modification in the acquisition breath-hold strategies, to deliver at least equivalent image quality compared to the traditional long-bolus protocol for traditional GBCAs. The purpose of our study was to compare the performance of an optimized short-bolus protocol with a new higher-concentration GBCA to the traditional long-bolus protocol with lower-concentration GBCAs for the acquisition of breath-held arterial-phase MRI of the liver.

2. Material and methods

2.1. Study design

Institutional review board approval was obtained for this retrospective, Health Insurance Portability and Accountability Act-compliant study and requirement for informed consent was waived. The Picture Archiving and Communication System (PACS) (McKesson Horizon Rad Station, version 11.9) database was searched to find patients who had an MRI examination with our clinical 'abdominal MCE' protocol between January 2010 and January 2013. Prior to February 2012, both gadodiamide and gadopentetate dimeglumine were used at the authors' institution for this protocol. After that, the GBCA was changed to gadobutrol. Two different groups were included in this study: a *control* group for all patients who underwent MCE MRI during the months of January 2010 and January 2012, using either gadodiamide or gadopentetate dimeglumine) and a *study group* for all patients who underwent MCE MRI in September 2012 and January 2013, using gadobutrol). Two different non-consecutive months were selected for each group to account for potential drifts in clinical practice overtime. The exclusion criteria were all patients that didn't have a MCE MRI study performed in this period. The *control group* was comprised of 75 consecutive patients who received either gadodiamide or gadopentetate dimeglumine. The *study group* was comprised *of* 61 consecutive patients who received gadobutrol.

2.2. Optimization of breathing instructions and timing of acquisition

The initiation of the acquisition was timed with a MRI fluoroscopy acquisition in the coronal plane both for the control and study groups. Breathing instructions and timing of the contrast injection/image acquisition were not standardized in the control group. The predominant practice was to provide the patient with a single set of breathing instructions (i.e., "breathe in and hold it") after visualization of the arrival of contrast to the upper abdominal aorta on the MRI fluoroscopy acquisition. This was immediately followed by the initiation of the late-arterial phase image acquisition (i.e. performed in end inspiration).

MRI technologists received a training session 6 months prior to changing the contrast agent to gadobutrol to standardize the approach for giving breathing instructions and timing of the acquisition of the late arterial phase. Briefly, the initiation of the acquisition for the study group was also timed with an MRI fluoroscopy acquisition in the coronal plane positioned through the heart. After MRI fluoroscopic visualization of the contrast in the left ventricle, two sets of breathing instructions were given followed by a breath-hold instruction at end-expiration (i.e. 'breathe-in, breathe-out, breathe-in, breathe-out and hold it'), at which point the acquisition sequence was triggered. The MRI technologists routinely explain to the patient the breath-hold requirements and injection of contrast prior to the MRI examination at the authors' institution. However, in regards of patient education and instruction, no specific changes were made to ensure consistency between the control and study groups.

2.3. MRI technique

MRI studies were performed in three different 1.5 T MRI scanners at a single institution (Parkland Hospital, Dallas, TX): Optima 450x and Signa HDxT (General Electric Healthcare, Milwaukee, WI, USA) and Avanto (Siemens Healthcare, Erlangen, Germany). The protocol for MCE MRI of the abdomen included an axial 3D T1-weighted SPGR acquisition with fat-suppression, before and after the administration of contrast during the late arterial phase (timed with the protocol described above), and 40, 90, and 120 s after the initiation of the arterial phase acquisition. The acquisition parameters for the 3D acquisition are included in Table 1.

A single dose (0.1 mmol/kg body weight) of gadodiamide or gadopentetate dimeglumine was administered for the control group and a single dose of gadobutrol was administered in the study group at 2 ml/s. The weight-based dosing resulted in a 50% reduction of the injected volume for the study group, as well as of the bolus injection duration. For example, for a 80 kg patient, 20 ml bolus of gadodiamide/gadopentetate dimeglumine was administered in 10 s compared to 10 ml bolus of gadobutrol in 5 s. In both groups, the bolus was followed with a 20 ml saline flush at 2 ml/s.

2.4. Image analysis

2.4.1. Qualitative analysis

Three readers (DFP, NLC and HA) with 8, 6, and 6 years of experience in abdominal MRI interpretation, respectively, performed an independent review of all images on a clinical PACS workstation (Horizon Rad Station, version 11.9, McKesson, Richmond, BC Canada). Reviewers were blinded to the IV contrast used or when the MRI was obtained. The image quality of the arterial phase images was rated using a five-point scale (5 – excellent, 4 – good, 3 – moderate, 2 – suboptimal and 1 – non-diagnostic). The presence of breathing artifacts on the arterial phase images was rated also on a five-point scale (5 – no artifacts; 4 – mild artifact corruption, 3 – moderate artifact corruption, 2 – extreme artifact corruption, 1 – unreadable). The timing of hepatic arterial phase was

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