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Real-time Projection MR
Angiography: Feasibility
Study

Intraarterial injections of small doses of gadopentetate dimeglumine were combined with a fast spoiled-gradient-echo magnetic resonance (MR) sequence to obtain real-time projection angiographic images of the rabbit aorta and canine coronary arteries. Arterial filling and washout, as well as venous and perfusion phases, were clearly displayed, demonstrating that arterial fluoroscopy in which an MR technique is used is feasible.

Central to the success of vascular interventional procedures, such as transluminal angioplasty or embolization, is the accurate depiction of the vascular tree and interventional instruments. Such depiction has been accomplished by means of x-ray fluoroscopy. However, the disadvantages of x-ray fluoroscopy, including the toxicity of ionizing radiation, the risk of adverse reaction due to the use of iodinated agents (1,2), the inability to image cross-sectionally, and the difficulty of characterizing surrounding soft tissue (3), have led to the exploration of alternative strategies.

The potential to perform accurate two-dimensional and three-dimensional angiography (4), obtain high-spatial-resolution MR images with excellent soft-tissue contrast (5,6), and track interventional devices (7–9) make magnetic resonance (MR) imaging a potential alternative. By allowing the imaging of plaque morphology and composition, as well as the assessment of related organ function during a single vascular intervention, MR imaging may modify the management of vascular interventions and improve the clinical outcome for patients with athrosclerosis.

However, conventional MR angiography sequences (time-of-flight angiography, phase-contrast angiography, and contrast medium–enhanced angiography), when used for the guidance of vascular intervention devices through the arterial tree (10–12), have general limitations. First, acquisition times are longer than 1 second, which precludes obtaining information about the local hemodynamic condition. Second, long postprocessing analysis is required to generate road maps; and third, contrast-enhanced angiography necessitates the use of large amounts of contrast medium, which precludes the possibility of multiple injections because of increased background signal intensity. Recently, some authors have reported that two-dimensional projection techniques coupled with intravenous injections of gadopentetate dimeglumine can depict arterial flow in large arteries (13,14).

The goal of this study was to evaluate whether the combination of selective intraarterial injections of small doses of gadopentetate dimeglumine with a fast two-dimensional gradient-echo sequence could generate sufficient information to guide vascular interventions and allow analysis of local hemodynamic conditions. A twodimensional projection technique with no section selection was used to avoid problems relative to arterial localization and to enable imaging of a tortuous vessel in a single image.

I MATERIALS AND METHODS

Sequence Optimization: Preliminary Study

In a preliminary study, the pulse sequence and the gadopentetate dimeglumine concentration were optimized by using phantoms to maximize gadopentetate dimeglumine signal intensity and background signal suppression. The contrast medium used was gadopentetate dimeglumine (Magnevist; Berlex, Wayne, NJ). In vitro phantom experiments, which were performed with a 1.5-T imager (Signa; GE Medical Systems, Milwaukee, Wis), showed that the highest image contrast-to-
A noise ratio could be attained with a gadopentetate dimeglumine concentration of 31.25 mmol/L and a fast spoiled gradient-echo sequence with parameters set as follows: 4.4/1.4 (repetition time msec/echo time msec); rectangular field of view, 32 × 16 cm; matrix, 256 × 128; flip angle, 90°; bandwidth, 64 KHz; number of signals acquired, 1; and imaging time per image, 300 msec (Fig 1). These parameters allowed imaging at a rate of 3.5 frames per second.

Experiments
Experiments were performed in one human volunteer, three rabbits, and two dogs. In the first experiment, we injected gadopentetate dimeglumine into a tube, with pulsatile flow provided by a pump, which was taped vertically on the chest of a volunteer. The objective was to evaluate the imaging protocol in vitro, particularly to determine whether there was adequate tissue signal suppression and tube enhancement. In the second experiment, we assessed the technique in vivo, which consisted of imaging the aorta in three rabbits. The aim was to assess the technique in vivo in optimal conditions to determine enhancement in a large nonmoving vessel. In the third experiment, the coronary arteries of two dogs were imaged to assess the efficiency of the technique in small moving vessels.

For all these experiments, imaging parameters were used that were identical to those described in the preliminary study. However, a projection technique, disabling the section-selective gradients, was used. All animals were treated according to the principles of laboratory animal care of the National Society for Medical Research and the National Institutes of Health (15). The experimental protocol was approved by the animal care and use committee and by the institutional review board at Johns Hopkins University. Oral informed consent was obtained from the volunteer.

Human volunteer experiment.—A 2-cm-diameter tube was taped on the chest of a 30-year-old male volunteer (weight, 80 kg; height, 1 m 80 cm). A roller flow pump provided a pulsatile flow compatible with the human pulse rate (70 beats per minute) and aortic flow (3 L/min) (Fig 2). A 60% stenosis was created by tightening a string around the tube. Since the obtained images were essentially projection images, the tube on the chest of the body was expected to generate a signal intensity similar to that of a human aorta. To simulate an intraarterial injection, a 4-F introducer was connected to the descending flow tube, upstream from the stenosis. The body coil was used for imaging. Injection of 10 mL of gadopentetate dimeglumine through the introducer was performed simultaneously to obtain images at variable concentra-
tions of gadopentetate dimeglumine: 31.25, 62.50, 125.00, 250.00, and 500.00 mmol/L. The signal intensity of the vessel was measured by a radiologist (J.M.S.) for each injection, and the concentration that provided the best vascular signal intensity compared with that for adjacent tissues was recorded.

Rabbit aorta experiment.—Three New Zealand white rabbits (3.5–4.5 kg; Robinson Services, Winston-Salem, NC) were used in this initial in vivo application. The rabbits were first anesthetized with a mixture of ketamine hydrochloride (35 mg per kilogram of body weight; Ketaset; Fort Dodge Animal Health, Fort Dodge, Iowa) and acepromazine maleate (0.75 mg/kg; Acepromazine; Vedco, St Joseph, Mo), as well as atropine sulfate (0.5 mg/kg; Atropine Sulfate; American Regent Laboratories, Shirley, NY), administered intramuscularly. Pentobarbital sodium (25 mg/kg; Sodium Nembutal; Veterinary Laboratories, Lenexa, Kan) was later administered intravenously to bring the animal to a level of anesthesia sufficient for performance of surgery. The right carotid artery was dissected free, and a 4-F introducer sheath (Boston Scientific, Natick, Mass) was inserted against the flow direction.

The rabbit was then placed in a supine position in the imager and aligned with the main magnetic field. An extremity coil was used to obtain the images. Coronal projection images were obtained first to determine the anatomic position of the rabbit. Transverse and sagittal scout images were obtained to prescribe the angulation of the projection. The next step was to inject contrast medium intravenously to obtain a road-map image and allow positioning of a catheter in the aorta. 1.5 mL of gadopentetate dimeglumine (250.00 mmol/L; Sodium Nembutal; Veterinary Laboratories) was injected into the ear vein of the rabbit. There were 60 images obtained in 17 seconds.

An MR-compatible 3-F angiographic catheter constructed in-house was then used to introduce up to the ascending aorta to allow intraarterial injections of gadopentetate dimeglumine. Injections of 1 mL of gadopentetate dimeglumine with variable concentrations were administered through the catheter, followed by 3 mL of an iso-osmolar saline solution flush. We tested concentrations of 31.25, 62.50, 125.00, 250.00, and 500.00 mmol/L. The signal intensity of the vessel was measured for each injection by a radiologist (J.M.S.), and the concentration that provided the best vascular signal intensity compared with that for adjacent tissues was recorded.

By using the optimal gadopentetate dimeglumine concentration, images with a 24- and a 12-cm field of view were obtained to determine whether higher spatial resolution angiography could be achieved.

Canine coronary experiment.—Two healthy 30-kg mongrel dogs (Biomedical, Friedensburg, Pa) were studied for this experiment and killed at the end of the experiment. Anesthesia was induced by administering 25 mg/kg of pentobarbital sodium (Sodium Nembutal, Veterinary Laboratories) intravenously and was maintained by means of general inhalational anesthesia (1%–2% isoflurane; Isoflurane; Abbott Laboratories, North Chicago, Ill). A 9-F introducer sheath (Boston Scientific) was placed through a right carotid arterial cutdown. The left main coronary artery was engaged with a 7-F magnetically compatible catheter (Cordis Endovascular, a Johnson & Johnson Company, Miami Lakes, Fla) with radiographic guidance.

After each dog was transported to the magnet, a cardiac phased-array coil (GE Medical Systems) was placed around its chest. The previously determined rabbit protocol was used, but with a smaller field of view (20 and 16 cm), with no intravenous injection, and with 4 mL rather than 1 mL of gadopentetate dimeglumine injected for each acquisition because of the larger diameter of the angiographic catheter. The signal intensity of the vessel was measured for each injection by a radiologist (J.M.S.). The concentration that provided the best vascular signal intensity compared with that for adjacent tissues was recorded. Multiple projection images were obtained, which included standard right anterior oblique images and left anterior oblique images with or without cranial or caudal angulation to assess the left coronary artery.

I RESULTS

Human Volunteer Experiment

The intravenous injection allowed the acquisition of dynamic angiographic images of the tube (Fig 2). The stenosis was depicted clearly. The rate of 3.5 frames per second allowed the depiction of tube filling and washout. Background signal suppression was efficient and did not preclude clear depiction of the angiogram. The best gadopentetate dimeglumine concentration was 500.00 mmol/L.

Rabbit Experiment

The intravenous injection allowed the acquisition of dynamic angiographic images of the aorta and its branches (Fig 3). Enhancement was seen first in the pulmonary artery, then in the heart chambers on the left side and the aorta. Body signal intensity, including that of fat and periarterial tissues, was suppressed completely on all images. The rate of 3.5 frames per second showed arterial filling and washout, as well as the venous contrast phase, visible in the portal vein. Intraarterial injections in the ascending aorta, with use of gadopentetate dimeglumine concentrations between 31.25 and 125.00 mmol/L, displayed arterial phases in the aorta. Carotid and renal vessels, which are as small as human coronary vessels, were depicted clearly. Concentrations of 250.00 and 500.00 mmol/L did not enhance the aorta. The best concentration was 62.50 mmol/L, because it allowed higher spatial resolution angiography with 24- and 16-cm fields of view; however, arterial signal intensity decreased. Overlapped tissues in acquisitions with a small field of view were not a problem, as their signal intensity was below the noise level. No substantial enhancement due to gadopentetate dimeglumine accumulation in background tissues was noticed during the experiment, which lasted approximately 1 hour.

Canine Experiment

Angiographic images of the left main coronary artery, the left anterior coronary artery, and the circumflex artery were obtained with a 20-cm field of view and gadopentetate dimeglumine concentrations of 31.25 and 62.50 mmol/L (Figs 4, 5). Spatial resolution per pixel was 0.8 × 1.5 mm. These arteries were outlined clearly. Body signal intensity, including that of fat and periarterial tissues, could be saturated below the noise level. As shown with the rabbit aorta, the rate of 3.5 frames per second showed filling and washout of the coronary arteries, followed by the venous contrast phase. With concentrations of more than 62.50 mmol/L, coronary arteries were not seen; but with a concentration of 125.00 mmol/L, veins were enhanced clearly.

Six projection images were obtained with a gadopentetate dimeglumine concentration of 31.25 mmol/L. This concentration allowed complete assessment of the left coronary arterial vasculature. The small doses and low concentration of contrast medium allowed performance of these multiple angiographic examinations, as no substantial enhancement of background tissue signal intensity could be detected. After 1 hour of study, the equivalent dose of 500.00-mmol/L gado-
pentetate dimeglumine injected was 9 mL, which corresponds to less than half of a single dose injected in humans for a standard gadolinium-enhanced MR angiographic examination. When used with a smaller field of view (16 cm), vessel signal intensity dropped substantially and did not improve the quality of the angiogram.

I DISCUSSION

Contrast-enhanced MR angiography has been shown to be the best MR technique for vascular imaging (16–19). On the basis of the intravenous injection of gadopentetate dimeglumine, which is associated with a low number of adverse reactions (20,21), contrast-enhanced MR angiography offers the best compromise between spatial and temporal resolution. After it is in the artery, the contrast medium dramatically lowers blood T1. The short repetition time and echo time of the sequence allows imaging of the low-T1 blood pool and simultaneously offers the advantage of saturating surrounding tissues that have a long T1.

The technique we present in this article was inspired by contrast-enhanced MR angiography; however, the existing technology is applied in a different manner. First, rather than obtaining three-dimensional high-spatial-resolution images in a few seconds, our technique allows the acquisition of a single-projection image in 300 msec. This method is similar to that of x-ray fluoroscopy. Second, instead of injecting large doses and concentrations of gadopentetate dimeglumine into veins, the optimal concentration of gadopentetate dimeglumine is attained within the artery by injecting low doses of low-concentration contrast medium directly into the arteries.

Figures 2–5 show the potential of such
an approach. Arterial filling and washout are clearly demonstrated. The anatomy of the left anterior descending coronary artery and the circumflex coronary artery of the dog is well displayed, with a spatial resolution per pixel of 0.8 × 1.5 mm. No postprocessing data viewing technique is needed. In addition, the technique provides easy acquisition of different projection images. Figure 2b and 2e illustrates this advantage by showing a lateral projection image that allows easy depiction of a 60% stenosis, which was not easy to quantify on the coronal image.

Another advantage of this method is the use of a low dose of gadopentetate dimeglumine injected per angiographic examination, which avoids background tissue enhancement, even if it is used multiple times during an interventional procedure. Figure 1 shows that when gadopentetate dimeglumine concentration is lower than 1 mmol/L, the signal intensity is low. Thus, as long as gadopentetate dimeglumine concentration in the background tissues is lower than 1 mmol/L, a vessel filled with a gadopentetate dimeglumine concentration of 15.60–62.50 mmol/L will be enhanced clearly (Fig 1). If we approximate the distribution volume of gadopentetate dimeglumine to 12 L in vascular and interstitial compartments (22) to maintain a concentration lower than 1 mmol/L, the radiologist is limited to a maximum injection of 10 mmol of gadopentetate dimeglumine in the body. In our experiment, angiography of a coronary artery necessitated the injection of 0.1 mmol of gadopentetate dimeglumine (3 mL of gadopentetate dimeglumine with a concentration of 31.25 mmol/L). It would have been possible, therefore, without even considering gadopentetate dimeglumine elimination by the kidneys, to perform 120 injections of gadopentetate dimeglumine without substantial background enhancement.

After dilution in the body, the dose is equivalent to one 500th of the standard gadopentetate dimeglumine concentration (0.125 mmol/L compared with 500.00 mmol/L) which, as shown in Figure 1, gives a negligible signal intensity. This small dose allows (a) multiple successive angiographic examinations and (b) assessment of small fields of view because overlapped tissues are always suppressed efficiently (Fig 3).

For x-ray angiography, the more concentrated the contrast medium injected, the better the arterial enhancement will be, whatever the contrast medium dilution after injection into the vessel. For MR angiography, high concentrations lead to susceptibility artifacts if dilution of contrast medium in the vessel is insufficient, which would preclude arterial enhancement (Fig 1). Thus, to calculate the appropriate gadopentetate dimeglumine concentration needed in the syringe to enhance the vessel, the radiologist needs to estimate the dilution level of gadopentetate dimeglumine after injection into the bloodstream. In theory, the dilution level depends on the ratio between blood flow in the vessel and the injection rate of gadopentetate dimeglumine in milliliters per second. As vessel flow is difficult to evaluate, such calculations were not considered in this study.

To achieve optimal vessel enhancement, a gadopentetate dimeglumine concentration of 31.25 mmol/L was always tested first, followed by more concentrated injections of gadopentetate dimeglumine, until the maximum vessel enhancement was reached. This method was efficient and rapid and could be applied easily in all animals. However, optimal concentration levels—500.00 mmol/L for the tube, 62.50 mmol/L for the rabbit aorta, and 31.25 mmol/L for the canine coronary vessels—correlated with vessel and catheter diameter ratios in all these experiments, which were 1:20, 1:5, and 2:3, respectively. For future clinical applications, this technique involves several issues. (a) An MR imager with a high-field-strength magnet and fast and high gradients is required, and not all imagers are so equipped. (b) For interventional procedures, an open magnet or short magnet is required to obtain easy access to the patient. Despite dramatic progress in this direction, these open or short magnets currently are not available with high magnetic fields, which limits their actual use in clinics. (c) The spatial and temporal resolution are still lower compared with those attained with x-ray fluoroscopy, which may be insufficient for stenosis quantification in small vessels, such as coronary arteries. (d) For the depiction of coronary arteries, the acquisition time per image (300 msec) is too long and causes motion blurring of the vessels during the systolic phase (Fig 4). Acquisition time will have to be shortened to minimize this blurring. (e) For selective injection of contrast medium, it is necessary to determine the relationship of the catheter to the arterial structures, an issue that was not addressed in this experiment. Although the results of some studies (8,23) have shown the possibility of depicting this relationship with MR imaging guide wires, guiding catheters, or both, this issue will need to be assessed.

Assessing the anatomic and hemodynamic conditions of a vessel is the first step before placing or advancing any intravascular device during an interventional procedure. To date, this has been accomplished with x-ray fluoroscopy,
which allows high spatial and temporal resolution, with frequent updating of the data. The technique we present here shows that placement and monitoring of interventional devices also may be possible by using MR imaging. Arterial filling and washout, as well as venous and perfusion phases, were clearly displayed, demonstrating that real-time angiography with use of an MR technique is feasible. Even if 3.5 frames per second represents a low fluoroscopic rate, technologic evolution of gradient hardware and new pulse sequences will provide faster acquisition times in the near future (24,25), which will allow clinicians to take full advantage of the benefits of MR imaging in the field of interventional radiology and cardiology.

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