Original Research

MRA Contrast Bolus Timing With Ultrasound Bubbles

Martin R. Prince, MD, PhD,* Yoshimi Anzai, MD, Mohammed Neimatallah, MD, Qian Dong, MD, and Jonathan M. Rubin, MD, PhD

The purpose of this study was to determine the feasibility of using an ultrasound contrast agent test bolus to determine optimum bolus timing for three-dimensional (3D) gadolinium (Gd)-enhanced magnetic resonance angiography (MRA). Small test doses of ultrasound contrast agent (0.3 ml Optison) were injected intravenously followed immediately by a 20 ml saline flush. Arrival of the contrast agent was detected by spectral Doppler ultrasound (US). This technique was implemented in patients undergoing peripheral vascular MRA and carotid MRA. Arrival of the US contrast agent test bolus was readily detected by the change in amplitude of the Doppler spectrum and by a huge increase in the audio signal amplitude. This contrast travel time measurement accurately guided bolus timing for 3D Gd MRA. Bolus timing for 3D contrast-enhanced MRA can be performed using US, thereby eliminating the problems and MR scanner time required for injecting a test bolus of Gd contrast. J. Magn. Reson. Imaging 1999;10:389–394.
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Index terms: ultrasound contrast; gadolinium; MR angiography; peripheral vascular disease; carotid artery; atherosclerosis

THREE-DIMENSIONAL, contrast-enhanced magnetic resonance angiography (MRA) is increasingly used for diagnosing vascular pathology because of its relatively low risk and expense compared with conventional arteriography (1–3). This technique requires timing of the intravenous contrast injection so that imaging is performed while contrast is in the vessel of interest. Usually, this is during the arterial phase of the bolus in order to image the arteries without the confounding effects of venous enhancement. Several strategies have emerged for optimizing bolus timing. These include a "best guess" based on patient history, fluoroscopic (4) or automatic triggering (5,6), ultrafast imaging (7,8), and use of a test bolus (9,10). The "best guess" approach works well when combined with a large contrast dose infused over a sufficiently longer time to compensate for timing errors. Floroscopic and automatic triggering and ultrafast multiphase imaging require specialized hardware and software. The test bolus approach has a simple logic and can be used on any scanner. For these reasons, the test bolus is one of the more popular approaches. A small amount of additional contrast and additional scanner time are required for the test bolus, but the improvement in consistency of MRA image quality often makes this a worthwhile trade-off.

This study investigates the feasibility of optimizing MRA contrast bolus timing by using ultrasound to detect an ultrasound contrast agent instead of gadolinium. This method of determining contrast bolus timing can be performed prior to entering the magnet, thereby reducing the MR scanner time. It eliminates unwanted enhancement of background tissues caused by a gadolinium test bolus. It also allows all the gadolinium contrast to be used for the actual MRA sequence. One final advantage is that it can be easily repeated multiple times if there is uncertainty about the results from the first test bolus measurement or if it is necessary to measure the contrast travel time to a number of different vessels of interest.

MATERIALS AND METHODS

A standard ultrasound unit (Diasonics, San Jose, CA) was used with 3.5 curved linear array or 5 MHz linear array transducers depending on the vessels being interrogated. Initially gray scale and color flow imaging was used to find the artery or vein of interest. Then spectral Doppler mode was used to obtain flow velocity information via both audio and spectral presentation. The initial Doppler gain was set at as low a level as possible to guarantee continuous detection and yet maximize dynamic range. A large dynamic range was necessary to allow detection of both the initial bolus arrival and the bolus peak. Since scanning was performed near a suite of three operating magnets, there was considerable radio frequency (RF) interference in the line voltage that was visible in the Doppler spectrum. A high wall filter setting helped suppress this RF noise. The change in ultrasound signal upon arrival of the ultrasound contrast agent was so prominent that this high filter setting was not a significant problem. We did not limit ourselves to scanning at low mechanical indexes since we were only interested in the first pass of the bubbles, and

Department of Radiology, University of Michigan, Ann Arbor, MI 48109-0030 and Weill Medical College of Cornell University, New York, NY 10021.

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*Address reprint requests to: M.R.P., at his present address, Cornell MRI, 416 East 55th Street, New York, NY 10022.
E-mail: map2008@mail.med.cornell.edu

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bubble destruction was to our benefit if we needed to perform further injections.

This study was approved by the hospital institutional review board, and all patients gave written informed consent before participating. After obtaining consent, the artery of interest was localized on ultrasound, and a dose of 0.3-ml ultrasound contrast agent (Optison, Mallinckrodt, St. Louis, MO) was introduced into the IV tubing within 20 cm of the IV site. This dose, which is less than the lowest recommended dose (0.5 ml) in the package insert, was chosen based on prior experience with this agent. The ultrasound contrast agent was then advanced into the bloodstream by flushing 20-ml normal saline through the intravenous line at a rate of 2 ml/sec. The arrival of this ultrasound contrast agent in the vessel of interest was noted by listening for a change in the audio amplitude of the Doppler signal and by visualizing a change in the Doppler frequency spectrum (see Fig. 2). The time of arrival of the leading edge of the bolus and the time to the peak of the bolus were both noted. The time to peak was defined as the point when the spectral display first saturated.

For peripheral vascular studies the contrast travel time was measured at the aorta (Fig. 1), the common femoral artery, and the popliteal artery. For carotid artery imaging the contrast travel time was measured at the common carotid artery proximal to the carotid bifurcation (Fig. 2) and the internal jugular vein (Fig. 3) on the side corresponding to the patient's symptoms. For portal venous studies the contrast travel time was measured to the abdominal aorta and also to the portal vein. Whenever there was any difficulty determining the contrast travel time precisely, the injection was repeated after a delay of 3–4 minutes to allow clearance of the agent that had already been injected.

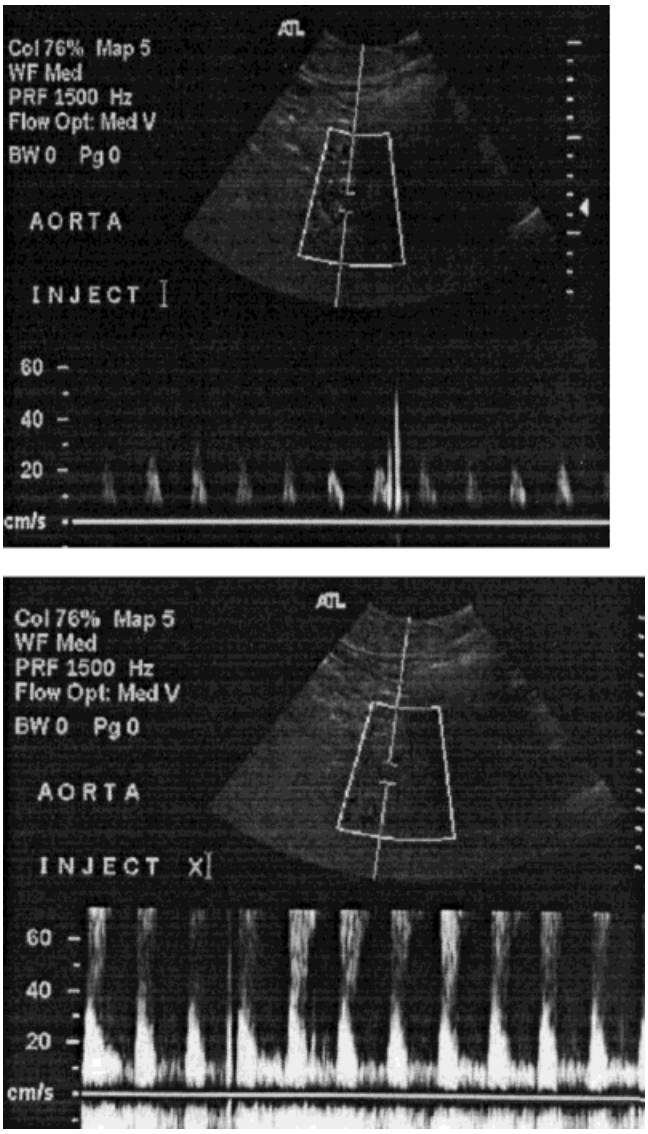

Figure 1. Spectral Doppler ultrasound of the abdominal aorta pre (top) and post (bottom) microbubbles shows the characteristic increase in spectral Doppler signal upon arrival of the bolus.

Bolus Chase Peripheral MRA

All imaging was performed on a 1.5 T magnet (LX Horizon, GE Medical Systems, Waukesha, WI) equipped with echoplanar gradients. The body coil was used for signal transmission and reception. After the ultrasound measurement of contrast travel times, the patient was positioned supine and feet first on the scanner table. The ankles and knees were elevated with cushions so the arteries of the legs were horizontally aligned with the aorta. By landmarking on the sternum and disengaging the table from the drive mechanism, the "dog house" moved out the back end of the magnet, allowing free manual movement of the table from the abdomen down to the ankles.

Ten axial two-dimensional time-of-flight (2D TOF) localizer slices were obtained spread out from mid-abdomen to mid-calf by manually moving the table about 10 cm in between acquisition of each slice. Then the table was manually positioned for imaging the pelvis and abdomen, and a sagittal single-shot fast spin-echo (SSFSE) localizer sequence was obtained.

A 3D fast spoiled gradient-echo volume acquisition was prescribed using the sagittal SSFSE and axial 2D TOF localizer images to determine the optimal anterior and posterior coverage. The following parameters were utilized: TR/TE 6/2.1 msec, flip angle 45°, bandwidth 32 kHz, field of view 44 cm, and 36 partitions, each 3 mm thick with zero filling interpolation to obtain a total of 60 coronal images per 3D volume. The acquisition time was 30 seconds for each 3D volume of MRA data. Three seconds were required to move the table from station 1 (abdomen-pelvis) to station 2 (thigh), and another 3 seconds were needed to move from station 2 (thigh) to station 3 (calf). Thus, the total imaging time was 96 seconds.

A positioning pole was used to fix the table precisely at each of the three stations to ensure that the precontrast and during contrast images were acquired at exactly the same table locations, thereby allowing digital subtraction. To minimize the total amount of table motion, the precontrast, 3D volumes of data (used as a mask for subtraction) were obtained in reverse order starting at the calf, then the thigh, and finally the abdomen/pelvis. This was followed by contrast injection and acquisition

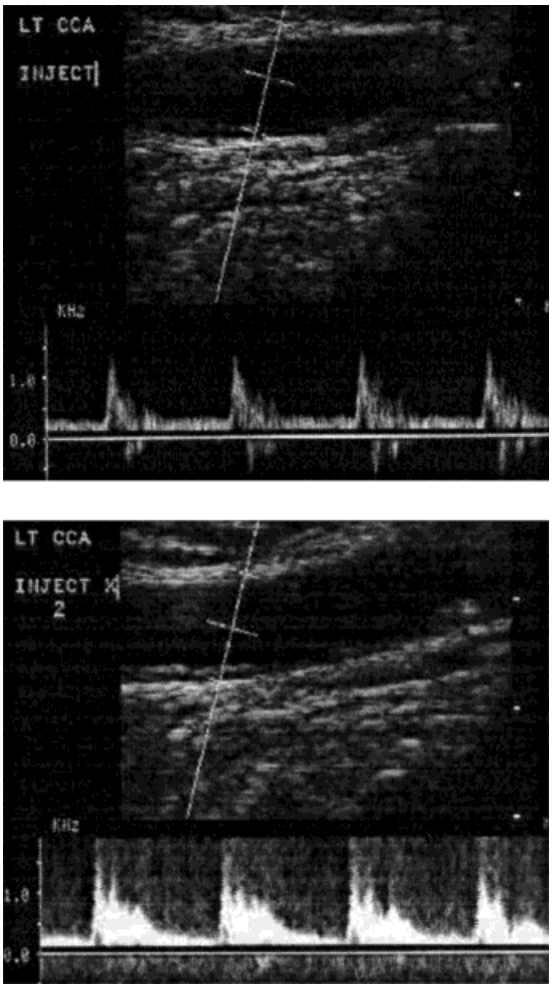

Figure 2. Spectral Doppler ultrasound of the common carotid artery pre (top) and post (bottom) microbubbles shows the characteristic increase in spectral Doppler signal upon arrival of the bolus.

of the same three stations beginning at the abdomen/pelvis, then the thigh, and finally the calf all during the arterial phase of the bolus.

Before initiating contrast injection, the optimum contrast injection rate and delay time were calculated as follows:

$$\text{scan delay} = \text{time to aorta peak bolus} - \text{scan time}/4$$

$$\text{gadolinium bolus duration} = 2.5 \times \text{scan time} + \text{table movement time} - (\text{popliteal peak time} - \text{aortic peak time}) - \text{ultrasound bolus duration}.$$

The scan delay is defined as the time between initiating the injection and initiating the scan. The injection rate was determined by taking the total volume of gadolinium to be administered to the patient based on a dose of 0.3 mmol/kg divided by the injection duration. After a few cases, however, we found it was easier simply to give every patient 60 ml. Ordering of k-space was adjusted to acquire central k-space data for the first station toward the end of the first acquisition. This was done by selecting 0.5 averages, (partial Fourier imaging). Thus, the central half of k-space was acquired during the second half of the acquisition. The injection was then timed to have contrast reach peak concentration at about 15 seconds (midway) into the scan. Immediately following this first acquisition of 3D coronal data, a control variable (phorder) was changed in order to activate centric phase encoding. In this way, the second and third stations acquired data centrically with the center of k-space at the very beginning of the scan. This reduced the injection duration required and also reduced venous enhancement on the third station. The total duration of bolus required was also reduced by taking advantage of the delayed arrival of the contrast in the calf compared with its arrival in the aorta. These factors are all incorporated into the above equations.

Following acquisition of the three stations of data, digital subtraction of the precontrast image data was performed on a computer workstation (Advantage Windows, GE Medical Systems). Performing digital subtraction on this computer workstation required all acquisi-

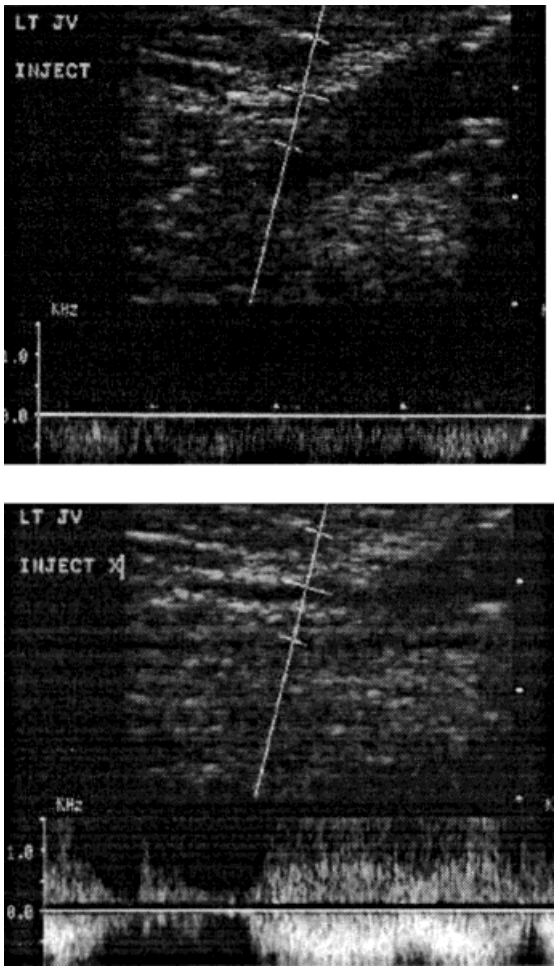

Figure 3. Spectral Doppler ultrasound of the internal jugular vein shows a typical venous pattern pre (top) and post (bottom) microbubbles with the typical increase in signal upon arrival of the bolus.

tions to be within the same series with no change in the acquisition parameters other than the ordering of k-space. Accordingly, care was taken during acquisition to ensure that all 3D volumes of data were within the same series. The initial prescanning was performed in the abdomen, as this was felt to be the most likely location to produce acceptable transmit and receiver gain settings for all three stations.

Carotid MRA

Contrast bolus timing considerations were different for carotid arteries compared with peripheral arteries. The rapid transit time through the cerebrovascular circulation and the low contrast extraction in the brain secondary to the blood-brain barrier tended to result in enhancement of the internal jugular veins, which obscured visualization of the carotid arteries. To avoid this problem of jugular venous enhancement, the gadolinium bolus was timed so that central k-space data were acquired while contrast was in the carotid arteries but not yet in the internal jugular veins. This required measuring the contrast travel time to reach the carotid arteries and the internal jugular veins. We used the ultrasound technique as described above to measure the time to arrival of the bubbles and also the time to the peak contrast effect in both common carotid artery and internal jugular vein.

Because of the potential for ringing artifacts with centric phase encoding, sequential mapping of k-space was employed. With sequential mapping of k-space, the central, low spatial frequential lines of k-space data are acquired in the middle of the scan. Actually they may be slightly offset from the middle of the scan by a fraction of a second due to the dummy (disdaq) pulses used at the beginning of the scan, which are meant to bring the tissue into dynamic equilibrium. Based on the ultrasound contrast travel time measurements, the bolus was initially timed so that contrast was arriving in the internal jugular vein 1 second after the mid-point of the scan as follows:

$$\text{scan delay} = \text{time to arrive in internal jugular vein} - (\text{scan time}/2 + 1).$$

Then we checked to be sure the peak carotid time would arrive well before the center of k-space. However, this resulted in excessive internal jugular venous enhancement and did not synchronize maximum arterial enhancement with the center of k-space. Accordingly, we adjusted the algorithm to synchronize the center of k-space with the center of the arterial peak. By keeping the total scan time under 30 seconds, jugular venous enhancement was not a problem. Thus,

$$\text{carotid artery peak time} \leq \text{scan delay} + \text{scan time}/2 - 1.$$

After deciding on the scan time, scan delay, and gadolinium contrast agent dose, the infusion duration and infusion rate were determined by setting the infusion duration to half of the scan duration and the rate equal to the dose divided by the infusion duration as follows:

$$\text{infusion duration} = \text{scan duration}/2$$

$$\text{infusion rate} = \text{dose}/\text{infusion duration}.$$

Eventually, to simplify and standardize all these parameters, we settled on a dose of 40 ml for all patients and a scan duration of 24–28 seconds. This scan duration required a difference between the peak carotid artery time and jugular venous arrival time of at least 7 seconds, which was just barely possible in most patients.

For carotid arteries, imaging was performed using a neurovascular head and neck coil (MRI Devices, Milwaukee, WI) designed to cover sufficiently inferiorly to include all the way down to the aortic arch with adequate signal-to-noise ratio. Coronal 3D gadolinium MRA with a fast spoiled gradient-echo pulse sequence was prescribed with the following parameters: TR/TE 6.2/1.4 msec, flip angle 45°, bandwidth 31.2 kHz, field of view 26–27 cm, and 30 partitions, each 2.2 mm thick. The acquisition time was 26 seconds for each 3D volume of MRA data. The scan was repeated at least twice to obtain arterial and venous phases.

RESULTS

Reliable ultrasound contrast arrival determinations were made in the aorta, carotids, internal jugular vein, common femoral artery, and popliteal artery. The effect of the bubbles on the ultrasound signal disappeared in 3–4 minutes so repetition of the measurement was not degraded by a prior injection. In general, if it was difficult to find the vessel of interest for the first measurement, it became very easy to find during the equilibrium phase of the bubbles, making a repeat measurement easier to perform.

MRA based on these ultrasound test bolus timing measurements produced perfect arterial phase images in the most recent patients (Figs. 4, 5). However, in the initial patients, a number of difficulties were encountered, as described below.

Arm Position

For peripheral MRA, the contrast travel time determination was performed with the arm at the patient's side, but MRA was performed initially with the arm elevated over the patient's head. In one patient, late arrival of the gadolinium was hypothesized to have been caused by the elevated arm pinching and obstructing the axillary/subclavian vein and slowing down the bolus compared to when it was measured by ultrasound. In subsequent patients we have had the patient keep the arms crossed over the abdomen and used a larger field of view instead of placing the arms overhead, to avoid arm wraparound artifact.

Injector Failure

In two patients, our mechanical injector stopped prematurely, once because of an inadequate battery charge and a second time because of sensing excessive resis-

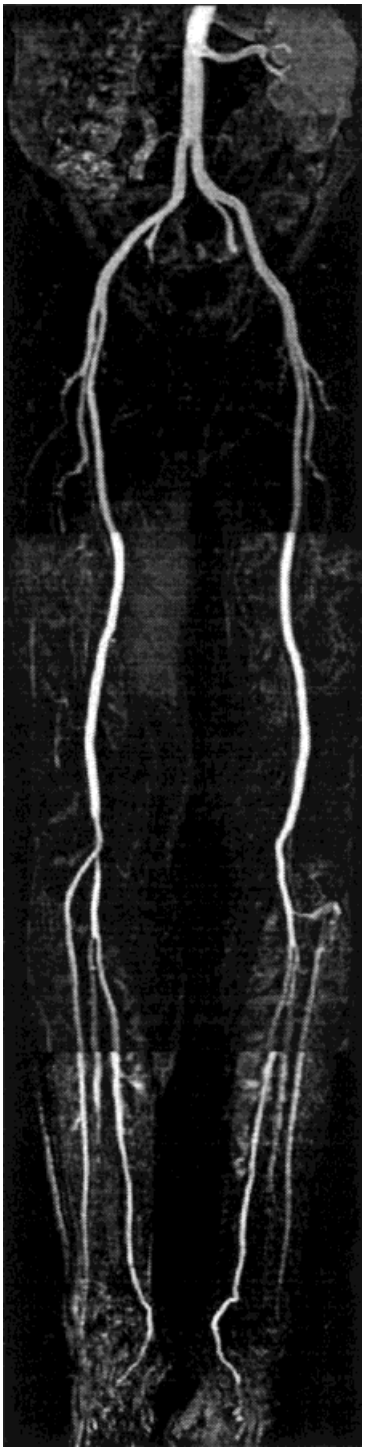

Figure 4. Bolus-chase peripheral MRA obtained with an 11 second scan delay, 58 second bolus duration, 0.7 ml/sec Gd injection rate for a Gd dose of 40 ml and a scan time of 30 seconds per station. These parameters were based on ultrasound bolus timing measurements of aorta peak time = 26 seconds, femoral artery time = 33 seconds, and popliteal artery time = 38 seconds. Note the optimum arterial phase of the bolus at all three stations.

tance. In a third patient, we forgot to account for the dead space in the IV tubing. This caused an additional delay between activating the injector and when contrast actually began entering the arm vein. Switching to hand injection with a standardized IV tubing set (SmartSet, Topspins Inc., Ann Arbor, MI) eliminated these injector problems. With hand injection, a 20-gauge angiocatheter was necessary for carotid MRA to make it easy to inject at 2 ml/sec. For peripheral vascular bolus-chase MRA, a 22-gauge angiocatheter seemed to provided the optimal resistance to make a slower, 1-ml/sec infusion rate easy to perform.

Multiple Intravenous Lines

In one patient with multiple IV lines, a contrast bolus timing error was attributed to using different IV sites for the ultrasound bolus timing measurement and subsequent gadolinium injection for MRA.

Claustrophobic Patient

One patient could not tolerate being inside the bore of the magnet for more than a few minutes at a time. During the confusion of pulling her out of the magnet every 1–2 minutes, we inadvertently started her peripheral MRA at the middle station (thigh) instead of the abdomen/pelvis. Bolus timing optimized for the abdomen/pelvis did not work for the thigh.

Difference Between Arrival and Peak

The ultrasound was so sensitive to the bubbles that it was easy to identify the leading edge of the bolus but more difficult to identify the bolus peak. This was because the ultrasound signal quickly became fully saturated. However, for MRA, the time to the peak of the test bolus was more important than its arrival time. To make it easier to identify the peak, it was helpful to reduce the scanner gain. Reduced gain increased the dynamic range, thereby reducing the problem of saturation and making it easier to identify the peak of the

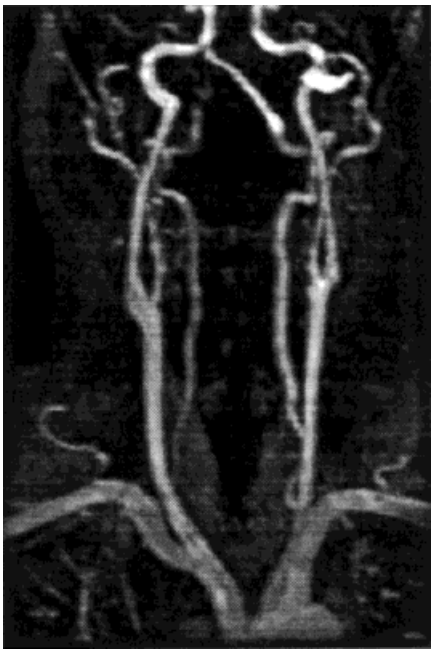

Figure 5. Arterial phase carotid MRA obtained during a 28 second breath-hold with injection of 40 ml gadolinium timed based upon ultrasound measurement of the contrast travel time.

bolus. However, in spite of adjusting the gain, saturation always occurred at these doses of ultrasound contrast agent. We wanted to determine contrast bolus duration, but this proved elusive. Ultrasound was so sensitive that the duration was tens of seconds for every injection.

DISCUSSION

Optimizing contrast bolus timing has been a particularly challenging aspect of 3D contrast-enhanced MRA. Considerable effort has gone into developing techniques whereby the scanner can precisely determine the contrast travel time to the vessel of interest. These data demonstrate a method using ultrasound contrast that can be performed prior to bringing the patient into the magnet. It can also be repeated multiple times at multiple different locations without accumulating gadolinium contrast in the background tissues. Although there were errors in the initial patients, subsequent refinements allowed this technique to time contrast infusions reliably for MRA.

MRA is not the only type of examination that might benefit from using ultrasound to measure contrast travel times. Computed tomography angiography could also benefit from this technique, especially with ultrafast, multidetector scanners that can do the chest, abdomen, and pelvis in a single breath-hold. It would be useful to know the time to reach aortic arch, suprarenal abdominal aorta, and infrarenal abdominal aorta to avoid having a fast scanner get ahead of the bolus. This might be especially important in patients who have slow flow such as those with aneurysmal disease or a history of congestive heart failure. Liver, breast, pelvis, and functional MRI may also benefit from knowing the contrast travel time before beginning the examination. To obtain abdominal arterial and portal venous phases, it may be helpful to use the time to aorta and time to portal vein to help decide how short to make the arterial phase acquisition so it is still possible to catch the portal venous phase.

Cost may be a problem with using ultrasound contrast agents because they tend to be expensive. The agent used in this study costs $110 per 3-ml vial. However, a vial has enough agent for 10 measurements, so if there were several patients in a row this may be economical. Another possibility is to use carbon dioxide bubbles. Even air can be mixed with saline to form bubbles that are safe for intravenous injection. However, these bubbles may only be useful for measurements up to the pulmonary circulation because they tend to be dissipated in the lungs.

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