Contrast material–enhanced MRA overestimates severity of carotid stenosis, compared with 3D time-of-flight MRA

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Objective: **Non–contrast-enhanced magnetic resonance angiography (MRA) carotid imaging with the time-of-flight (TOF) technique compares favorably with angiography, ultrasound, and excised plaques. However, gadolinium contrast-enhanced MRA (CE-MRA) has almost universally replaced TOF-MRA, because it reduces imaging time (25 seconds vs 10 minutes) and improves signal-to-noise ratio. In our practice we found alarming discrepancies between CE-MRA and TOF-MRA, which was the impetus for this study.**

Study design: **To compare the two techniques, we measured stenosis, demonstrated on three-dimensional images obtained at TOF and CE-MRA, in 107 carotid arteries in 58 male patients. The measurements were made on a Cemax workstation equipped with enlargement and measurement tools. Measurements to 0.1 mm were made at 90 degrees to the flow channel at the area of maximal stenosis and distal to the bulb where the borders of the internal carotid artery lumen were judged to be parallel (North American Symptomatic Carotid Endarterectomy Trial criteria). Experiments with carotid phantoms were done to test the comtribution of imaging software to image quality.**

Results: **Twelve arteries were occluded. In the remaining 95 arteries, compared with TOF-MRA, CE-MRA demonstrated a greater degree of stenosis in 42 arteries, a lesser degree of stenosis in 14 arteries, and similar (±5%) stenosis in 39 arteries ($P = .02$, χ^2 analysis). The largest discrepancies were arteries with 0% to 70% stenosis. In those arteries in which CE-MRA identified a greater degree of stenosis than shown with TOF-MRA, mean increase was 21% for 0% to 29% stenosis, 36% for 30% to 49% stenosis, and 38% for of 50% to 69% stenosis. The carotid phantom experiments showed that the imaging parameters of CE-MRA, particularly the plane on which frequency encoding gradients were applied, reduced signal acquisition at the area of stenosis.**

Conclusions: **Collectively these data demonstrate that CE-MRA parameters must be retooled if the method is to be considered reliable for determination of severity of carotid artery stenosis. CE-MRA is an excellent screening technique, but only TOF-MRA should be used to determine degree of carotid artery stenosis. (J Vasc Surg 2003;38:36-40.)**

In contrast material–enhanced magnetic resonance angiography (CE-MRA) a highly concentrated bolus of Gd-DTPA (gadolinium-diethylene-triamine-pentaacetic acid) is injected through an arm vein and a hyperintense signal is visualized within vessels as a result of shortened T1-time of blood. This produces vascular images that closely approximate the classic x-ray angiographic standard. However, CE-MRA must be performed during the first pass of the contrast bolus, limiting the time for data acquisition to 14 to 25 seconds in most cerebrovascular studies.

Because of more rapid imaging time, reduced patient movement, and increased image definition with CE-MRA, this method has largely displaced the older technique of time-of-flight magnetic resonance angiography (TOF-MRA).[1,2] In TOF-MRA imaging, data are acquired in a series of overlapping thin sections that span a volumetric region of interest. These images are then processed with a maximum intensity projection algorithm, in which the brightest pixels, representing blood flow, are extracted from the data set to create the image. Three-dimensional (3D) images are produced by a combination of very thin contiguous sections, requiring several minutes to complete a study. For cerebrovascular studies, data acquisition with TOF-MRA studies may require 5 to 20 minutes to produce a high-resolution image.

At our institution we have continued to perform both TOF-MRA and CE-MRA for evaluation of carotid artery stenosis. We have noted that in certain cases CE-MRA exaggerated the degree of stenosis, compared with TOF-MRA (Fig 1). A review of the literature revealed that a rigorous comparison of CE-MRA and 3D TOF-MRA across a range of stenosis severity has not been done. We began a comparison of these two technologies, which established that on CE-MRA images vessel size was reduced and degree of stenosis was amplified. To determine the source of this error, a series of experiments were conducted with a flow phantom model. The results of our review and the experimental data are reported here.

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Competition of interest: none.

Presented at the Seventeenth Annual Meeting of the Western Vascular Society, Newport Beach, Calif, Sep 22-25, 2002.

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0741-5214/2003/$30.00 + 0
doi:10.1016/S0741-5214(03)00332-X

METHODS

Patients. Studies for 58 patients were reviewed. All had at least one measurable stenosis at TOF-MRA and underwent both TOF-MRA and CE-MRA. All patients were men, ages 56 to 83 years, and underwent imaging between July 2001 and January 2002. Nine of 116 arteries were excluded because either TOF-MRA or CE-MRA studies were unilateral, leaving 107 carotid bifurcations for evaluation. The experimental protocol was approved by the Committee on Human Research of the University of California, San Francisco, and all patients gave informed consent.

MRA parameters. Studies were performed with a 1.5 T scanner (Symphony; Siemens, Erkengen, Germany) with a custom-made receive-only coil applied to the patient's neck.

TOF-MRA. Three-slab multiple overlapping thin slab acquisition was performed with the following parameters: field of view, 130 mm; TR/TE/flip angle, 40/7/20°. A 256 × 192 matrix was used, giving in-plane resolution of 0.7 mm × 0.5 mm with partition thickness of 1 mm. Total acquisition time was 10 minutes 45 seconds.

CE-MRA. A 30 mL bolus injection of Gd-DTPA was injected over 12 seconds. A timing run was performed to determine transit time between injection and arrival at the target area, with elliptic-centric acquisition. Imaging parameters were as follows: field of view, 128 mm; TR/TE/flip angle, 6/2/25°. A 256 × 192 matrix was used, giving in-plane resolution of 0.7 mm × 0.5 mm with partition thickness of 1.6 mm. Total acquisition time was 23 seconds.

Arterial measurements from MRA studies. Both TOF-MRA and CE-MRA studies were displayed on a Cemax workstation equipped with enlargement and measurement tools. Arterial images were rotated to determine the maximal diameter at the point of measurement. Cross-sectional measurements to 0.1 mm were made at 90 degrees to the flow channel at the area of maximal stenosis and at the distal internal carotid artery, where the walls were judged to be parallel for at least 1 cm. There was no statistical difference between readers' measurements.

Phantom studies. A silicone (Silastic) model lumen with 80% stenosis was used for the phantom studies. This phantom was created by first obtaining an acrylic model of the lumen with laser polymerization from a data set consisting of a high-resolution (200 μm^3) magnetic resonance image of a carotid plaque excised en bloc. With lost wax casting technique, a silicone negative mold was created around a wax reproduction of the acrylic lumen.

The phantom was perfused with a glycerol and water mixture to give the viscosity of blood. To this mixture gadolinium was added to a concentration of 1:100, the approximate concentration of gadolinium in its first pass through the carotid bifurcation in vivo. This was imaged with the scanner with TOF-MRA and CE-MRA parameters described for the in vivo studies, followed by adjustments to CE-MRA parameters in an attempt to improve image quality.

Fig 1. Magnetic resonance angiograms (MRA) of same carotid artery in vivo. Contrast-enhanced MRA *(left)* shows flow void; time-of-flight MRA *(right)* does not.

RESULTS

Comparison of TOF-MRA and CE-MRA. CE-MRA images were judged to be of high quality. Image quality of TOF-MRA studies varied because of patient motion, as evidenced by soft tissue signal ghosting outside the true anatomy and decreased clarity of tissue interfaces. Vessel blurring in regions distal to tight stenosis was also more pronounced on TOF-MRA images compared with CE-MRA images.

Twelve arteries were occluded in this group of patients with vascular disorders. Compared with TOF-MRA images, CE-MRA images demonstrated a greater degree of stenosis in 42 arteries, a lesser degree of stenosis in 14 arteries, and a similar degree (within 5%) of stenosis in 39 arteries ($P = .02$, χ^2 analysis; Table). The greatest increase in stenosis representation was in the mild to moderate range, ie, stenosis of 30% to 70% at TOF-MRA. CE-MRA images demonstrated substantial apparent increases in severity of stenosis. In the range of 30% to 49% stenosis at TOF-MRA, CE-MRA depicted greater stenosis in 7 of 14

Comparison of degree of stenosis with CE-MRA and TOF-MRA

TOF stenosis (%)	*0–29*	*30–49*	*50–69*	*70–99*
CE > TOF	20	7	10	5
CE < TOF	2	3	5	4
CE = TOF	15	4	3	17
Amount CE > TOF* (%)	21 ± 9	36 ± 17	38 ± 11	21 ± 6

CE-MRA, Contrast-enhanced magnetic resonance angiography; *TOF-MRA,* time-of-flight magnetic resonance-angiography.
*Mean of absolute percentage difference in cases in which CE-MRA depicted greater stenosis than TOF-MRA did.

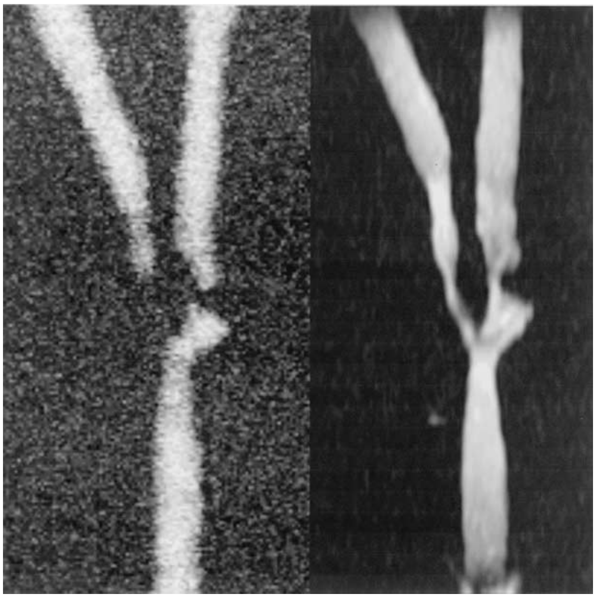

Fig 2. Silicone phantom of a carotid bifurcation with 80% internal carotid artery stenosis imaged with both contrast-enhanced magnetic resonance angiography (CE-MRA; *left*) and time-of-flight MRA *(right)*. CE-MRA demonstrates flow void in both internal and external carotid arteries at areas of stenosis.

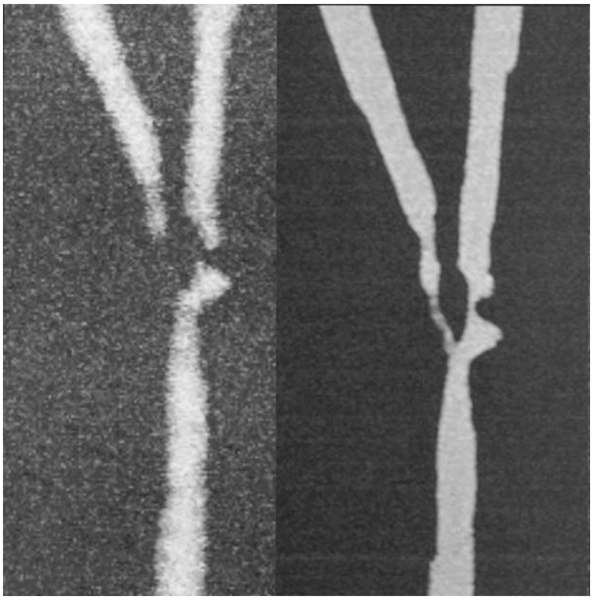

Fig 3. Contrast-enhanced magnetic resonance angiograms of phantom with flow *(left)* and without flow *(right)* through the phantom show excellent resolution of the phantom without flow but loss of signal with flowing medium.

arteries. In 2 of these, CE-MRA images depicted the stenosis as in the 50% to 69% range, and in 3 arteries the stenosis was represented as greater than 80%. In the 18 arteries in which TOF-MRA demonstrated 50% to 69% stenosis, CE-MRA exhibited 9 arteries with greater than 70% stenosis and 5 arteries with greater than 90% stenosis.

In 6 arteries in this series CE-MRA images depicted lesser degrees of stenosis, 20% or more, compared with TOF-MRA images.

Experimental data obtained at TOF-MRA and CE-MRA with the carotid bifurcation phantom. The phantom was imaged with both TOF-MRA and CE-MRA. In our initial study, TOF-MRA gave excellent images of the lumen, whereas a flow void was seen on CE-MRA images (Fig 2). When the phantom was evaluated with CE-MRA without flow, the lumen appeared (Fig 3), demonstrating that signal loss at the area of stenosis is not a problem of resolution but is created by flow.

The phantom was then imaged with CE-MRA with increased through-plane resolution (Fig 4). There was overall deterioration in signal-to-noise ratio, with minimal improvement in signal acquisition from the area of stenosis. The phantom was then imaged with CE-MRA with flow compensation software installed (Fig 5). Flow compensation is part of the TOF-MRA program, but is not used during CE-MRA. The resulting image had slightly improved resolution at the area of stenosis, but continued to demonstrate some signal dropout. The phantom was then imaged after altering the orientation of the planes of signal acquisition (Fig 6). In this study the frequency encoding gradient was changed from an axis in line with the flow to an axis perpendicular to the direction of flow, ie, in a plane traverse to the lumen. With this modification the definition at the area of stenosis was markedly improved. These observations are consistent with a compromise in signal acquisition fidelity along the frequency encoding axis, because it is where the duration of gradient application is most extended and therefore most sensitive to flow velocity.

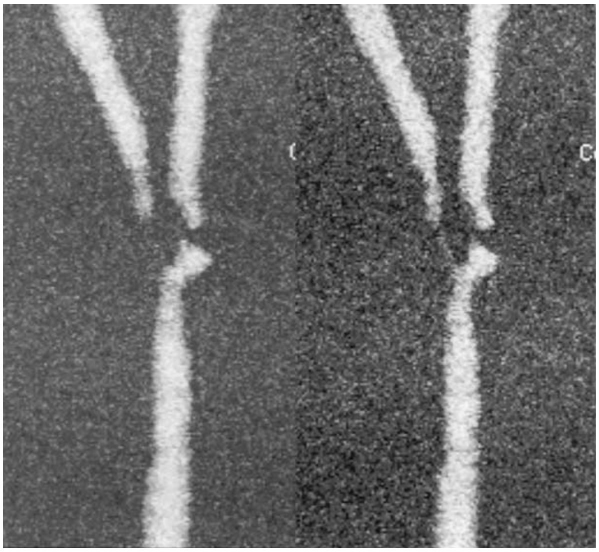

Fig 4. Contrast-enhanced magnetic resonance angiograms of phantom with standard *(left)* and increased in-plane resolution *(right)*.

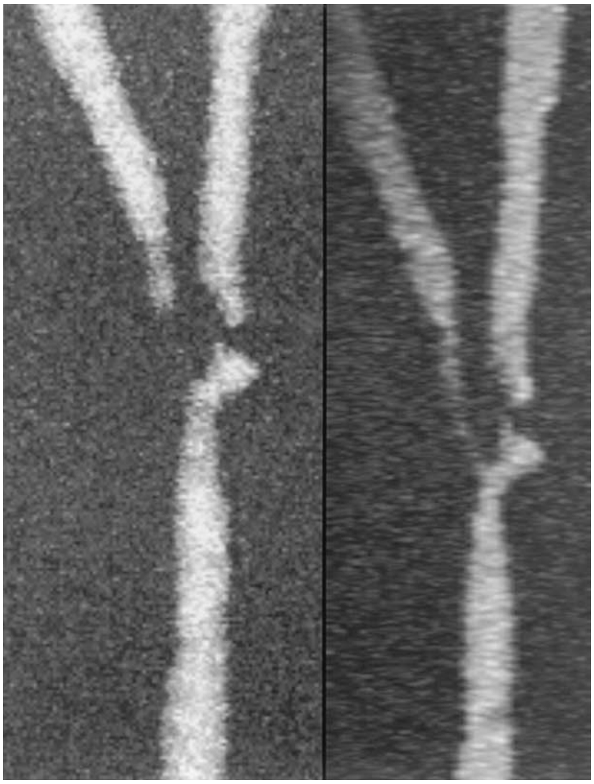

Fig 5. Contrast-enhanced magnetic resonance angiograms of phantom without *(left)* and with *(right)* flow compensation.

DISCUSSION

TOF-MRA compares favorably with both ultrasound and angiography in depicting carotid stenosis when compared with endarterectomy specimens excised en bloc.[3] Other studies[4-7] have found good agreement between TOF-MRA, Doppler ultrasound scanning, and digital subtraction angiography. However, there has been no rigorous comparison of TOF-MRA and CE-MRA to determine whether this apparent advance in magnetic resonance technology similarly represents in vivo vascular anatomy. A review of the literature found only two studies that comparing CE-MRA with 3D TOF-MRA. Sardanelli et al[8] demonstrated that gadolinium-enhanced CE-MRA yielded 100% sensitivity and specificity for evaluation of carotid artery stenosis greater than 70%, compared with 100% sensitivity and 80% to 85% specificity with 3D TOF-MRA. Johnson et al[9] demonstrated that CE-MRA yielded 94% sensitivity and 95% specificity when compared with traditional contrast-enhanced angiography, whereas 3D TOF-MRA yielded 82% sensitivity and 100% specificity. Both studies primarily examined lesions with greater than 70% stenosis, a range in which our data suggest a reasonable correlation between these two techniques.

Fig 6. Contrast-enhanced magnetic resonance angiograms of phantom with frequency encoding gradients aligned along vessel axis *(left)* and at 90 degrees to the vessel axis *(right)*.

This series represents a wide range of carotid stenosis. Only 26 of 95 vessels evaluated had stenosis of 70% or more at TOF-MRA. When TOF-MRA images showed stenosis less than 70%, CE-MRA images demonstrated a greater degree of stenosis than TOF-MRA in more than half of the cases. This increase in stenosis, by North American Symptomatic Carotid Endarterectomy Trial criteria, occurred even while the reference distal internal carotid artery diameter was also reduced in most of these studies. If CE-MRA were the only imaging method used to measure these lesions, fully 1 in 5 arteries would have been depicted as having stenosis of sufficient severity to warrant intervention, whereas TOF-MRA depicted these lesions as only mild or moderate. TOF-MRA is the more rigorously tested technique, and our phantom experiments indicate image acquisition problems with CE-MRA. Therefore the conclusion seems clear: contrast-enhanced MRA, as currently used, cannot be relied on to accurately determine degree of carotid artery stenosis. We suggest that when CE-MRA is used, TOF-MRA also must be performed to determine degree of stenosis, with reliance on the cross-sectional source images as the ultimate arbitrator of luminal narrowing.[10]

The problem with results from a single institution is that they may not be representative of technology as practiced elsewhere. Perhaps the timing of our imaging can be improved. CE-MRA of the carotid artery depends on timing the imaging with movement of a contrast bolus through the carotid bifurcation. Our experimental data show that, while timing does affect the quality of the scan, it is more dramatically affected by the orientation of frequency encoding, an inherent limitation of the CE-MRA software package. There are potential corrections for this. The orientation of the frequency encoding gradient could be aligned at right angles to the axial plane, as shown in Fig 6. This orientation would substantially lengthen scanning time and cause jugular enhancement, which would obscure the carotid artery. To minimize the effect of jugular enhancement, elliptic centric image acquisition would be required. An additional improvement could be provided with gadolinium-based contrast agents, which remain within the intravascular space and are currently in clinical trials. However, even with these alterations CE-MRA will need to undergo a rigorous trial against TOF-MRA and an accepted standard, either angiography or excised plaque, to demonstrate that it is a reliable clinical tool.

Although disappointed with these results, as a group we continue to be positive regarding the eventual usefulness of CE-MRA in evaluation of carotid artery stenosis. CE-MRA has great potential to enable identification of ulcerations and clarification of lumen anatomy in areas of low flow, but the application of this technology needs to be modified to minimize signal dropout in areas of high flow velocity. For now, TOF-MRA remains an excellent imaging method, and when used in conjunction with Doppler ultrasound scanning it obviates the need for angiography in most cases.[7] In addition, new advances in magnetic resonance hardware with receiver coils applied directly to the neck are producing images of carotid plaque that have sufficient resolution to enable identification of individual plaque components. This may usher in a new era when the biologic behavior of an atherosclerotic plaque may be determined with examination of the plaque itself rather than inferred by examination of the residual lumen.[11]

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Submitted Sep 30, 2002; accepted Jan 23, 2003.