Blinded-Reader Comparison of Magnetic Resonance Angiography and Duplex Ultrasonography for Carotid Artery Bifurcation Stenosis

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Background and Purpose We compared two-dimensional time-of-flight magnetic resonance angiography (MRA) and duplex ultrasonography with arteriography for the detection of 70% to 99% stenoses at the carotid artery bifurcation (ie, surgical disease according to findings of the North American Carotid Endarterectomy Trial).

Methods Three blinded readers independently measured stenoses on MRA in 73 vessels from 38 patients. Duplex ultrasonography was available in 66 vessels from 35 of these patients, and blinded reading was performed by one reader. Comparison was made to arteriography.

Results Magnetic resonance angiography demonstrated a sensitivity of 92.4%, specificity of 74.5%, and negative predictive value of 95.8% for 70% to 99% stenoses. Interobserver agreement was high ($k=0.91$). Absence of signal at stenoses with evidence of distal flow usually, but not always, corresponded to surgical disease. Duplex ultrasonography demonstrated a sensitivity of 81.0%, specificity of 82.2%, and negative predictive value of 90.2% for surgical disease. There was no significant difference between MRA and duplex ultrasonography for the sensitivity or specificity in detecting 70% to 99% stenoses ($P>.1$, exact form of the McNemar test). MRA had no false positives or false negatives for complete occlusions of the carotid artery, whereas duplex ultrasonography missed one occlusion and falsely called two patent vessels occluded. In seven cases, both MRA and duplex ultrasonography overestimated stenoses to misclassify them as surgical disease.

Conclusions Although the sensitivity and specificity of MRA and duplex ultrasonography are not significantly different for distinguishing surgical and nonsurgical degrees of stenosis at the carotid bifurcation, MRA has some advantages that may make it the screening test of choice. Concordant MRA and duplex ultrasonography for surgical disease does not necessarily obviate the need for catheter arteriography.

Key Words • carotid artery diseases • diagnostic imaging • ultrasonics

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) reported significant reduction in morbidity and mortality for patients with symptomatic carotid bifurcation stenoses of 70% to 99% who underwent carotid endarterectomy compared with medical therapy alone.

A European multicenter trial has reported similar benefit for endarterectomy in symptomatic patients. No benefit has been shown for symptomatic patients with less than 30% stenosis, and the NASCET study is continuing for patients with 30% to 69% carotid stenoses.

Duplex ultrasonography (DUS), aided by the color Doppler technique, is widely used to screen patients with suspected carotid artery disease. It has been validated by many studies that demonstrate high sensitivity and specificity for distinguishing stenoses at thresholds ranging from 50% to 80%. However, it is also well known that DUS has several pitfalls, including inability to visualize intracranial vessels, difficulties in distinguishing near total occlusion ("trickle flow") from total occlusion, artifacts from calcified plaque, and, perhaps most importantly, operator dependence. Magnetic resonance angiography (MRA) has been examined as a potential alternative to DUS, and earlier studies have shown accuracies comparable to DUS using two-dimensional (2D) time-of-flight (TOF) and three-dimensional (3D) TOF MRA techniques.

The NASCET study also emphasizes the importance of standardizing the measurement of carotid bifurcation stenoses. They compared the diameter at maximal stenosis to the diameter of the internal carotid artery (ICA) well beyond the carotid bulb. Unfortunately, most widely used duplex criteria either are based on comparison of residual carotid lumen diameter to estimated carotid bulb diameter, thus overestimating the stenosis as determined by the NASCET method, or do not explicitly describe how carotid stenoses were measured.

We compared 2D TOF MRA with DUS for evaluation of carotid bifurcation stenosis to identify "surgical disease" as defined by the NASCET study (70% to 99% stenosis). Newly published criteria that allow categorization of stenoses on DUS into a 70% to 99% category were used. This enabled us to directly compare the...
accuracy of both techniques for the detection of the same range of surgically relevant disease. We used multiple blinded readers for evaluation of the MRAs, and we measured rather than estimated stenoses directly on the arteriograms and MRAs.

Subjects and Methods

Thirty-eight patients (20 men, 18 women; mean age, 66 years [range, 48 to 80 years]) with clinically suspected atherosclerotic carotid artery disease were identified for whom both MRA and catheter arteriograms were available. Both studies were available for 73 carotid arteries. DUS was available for 66 vessels in 35 of these patients. Indications for imaging evaluation were the following: transient ischemic attack or amaurosis fugax in 20, cerebral infarct in 8, asymptomatic bruit in 9, and subclavian steal in 1.

Percutaneous catheter arteriograms were obtained in all patients and served as the "gold standard" for determining the degree of carotid stenosis. At least two-view or, in the majority of cases, four-view blipune selective common carotid arteriograms evaluated 70 vessels, and a nonselective aortic arch injection was performed for the other three vessels. One vessel only was evaluated in 2 of the 38 patients, and one side was excluded in another patient because of prior endarterectomy, yielding a total of 73 vessels examined. High-resolution digital subtraction imaging (1024 x 1024 matrix) was used in 23 patients, cut film subtraction in 14 patients, and both techniques were used in 1 patient. The arteriograms were interpreted in a consensus manner by two neuroradiologists with extensive angiography experience (H.I.G., M.M.M.). The readers were blinded to the MRA and DUS results and the clinical information. Direct measurements of the maximum stenoses in the carotid bifurcation region (distal common carotid artery [CCA] and proximal ICA) were made using a hand-held magnifier marked in 1-mm increments. The percent stenosis was determined by comparison with the diameter of the normal-appearing ICA distal to the bifurcation using the technique described for the NASCET study.22,23

The MRA examinations were performed on a 1.5-T system (GE Signa) using an anterior-posterior neck coil (Medical Advances). The 2D TOF MRA technique has been described elsewhere.20 We obtained 110 1.5-mm axial partitions covering the region from the aortic arch to the carotid siphon. A 20-cm field of view was used with a 128 x 256 matrix. The flip angle was 60 degrees in all cases. The repetition time varied between 45 milliseconds (24 cases) and 50 milliseconds (14 cases), depending on the field of view was used with a 128x256 matrix. The flip angle was 60 degrees in all cases. The repetition time varied between 45 milliseconds (24 cases) and 50 milliseconds (14 cases), depending on the spatial resolution desired. Each carotid artery bifurcation was segmented individually, yielding 12 projections at 30-degree increments around the cephalocaudal axis. Interpretation of the MRAs was performed in an independent and blinded manner by three neuroradiologists (S.W.A., H.I.G., M.M.M.). Direct measurements of the most stenotic point at the carotid artery bifurcation region and of the normal-appearing distal ICA as described for the NASCET study were made using the hand-held magnifier marked with 1-mm increments. Individual axial partitions were not presented for analysis.

The 2D TOF MRA technique has been described previously.20 The data was analyzed in the following ways: (1) sensitivity, specificity, and positive and negative predictive values of MRA with catheter arteriography as proof; (2) sensitivity, specificity, and positive and negative predictive values of DUS with catheter arteriography as proof; and (3) MRA versus DUS with catheter arteriography as proof. We focused our attention on the group that benefited from endarterectomy in the NASCET study, ie, 70% to 99% stenoses. Carotid stenoses were determined on arteriography and postprocessed MRA images by direct measurement. For the assessment of stenoses relative to the known clinically relevant categories, each study was classified into one of the following categories: 0% to 29%, 30% to 69%, 70% to 99%, and 100% (occluded). When comparison was made with DUS, the following categories were used for data analysis: 0% to 69%, 70% to 99%, and 100% (duplex criteria did not allow distinction between those with more or less than 30% stenosis). Vessels in which a signal void on MRA was accompanied by evidence of flow in the ICA distal to the bifurcation were considered patent25 and predefined as 70% to 99% stenoses. Prior studies also classified such findings as high-grade stenoses.23,25,26

Spearman rank correlation coefficients were used to determine the degree of relatedness of stenoses measured by MRA versus arteriography and DUS versus arteriography. Interobserver variability was assessed with κ, in which the degree of agreement between different readers was defined by the scale of Landis and Koch:27 less than 0.00, poor; 0.00 to 0.20, slight; 0.21 to 0.40, fair; 0.41 to 0.60, moderate; 0.61 to 0.80, substantial; and 0.81 to 1.0, almost perfect. The sensitivity and specificity of DUS and the average of the MRA measurements were compared with the exact form of the McNemar test.28

Results

Magnetic Resonance Angiography Versus Arteriography

Comparisons of the MRA interpretations with the arteriographic findings in 73 vessels were analyzed for each of the blinded readers. Table 1 contains the pooled data for all three readers. The Spearman rank correlation coefficient for the categories used for reader 1 was .83, for reader 2 was .86, for reader 3 was .88, and for the pooled data was .86. These were true negative-positive and false-negative readings of vessels with complete (100%) occlusion. Interobserver reliability for the presence of surgical disease was almost perfect as measured by κ, with a value of 0.91.

Table 2 lists the sensitivities, specificities, and predictive values of each of the readers for identifying the presence of surgical disease (70% to 99% stenosis).
TABLE 1. Magnetic Resonance Angiography vs Arteriography: Pooled Data (n=3×73)

<table>
<thead>
<tr>
<th>Arteriographic Stenosis, %</th>
<th>MRA Stenosis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-29</td>
<td>30-69</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>0-29</td>
<td>51</td>
</tr>
<tr>
<td>30-69</td>
<td>5</td>
</tr>
<tr>
<td>70-99</td>
<td>1</td>
</tr>
<tr>
<td>100</td>
<td>...</td>
</tr>
</tbody>
</table>

Spearman ρ=.86

MRA indicates magnetic resonance angiography.

MRA tended to overestimate but rarely underestimate stenoses as reflected by its high sensitivity and negative predictive value but lower specificity.

Cases With Signal Loss and Distal Patency on Magnetic Resonance Angiography

Some vessels on MRA demonstrated a signal void at the carotid bifurcation and distal flow in the ICA (Fig 1). These were classified as 70% to 99% MRA stenoses for the purposes of analysis. The number of cases read as showing signal dropout by each reader is listed in Table 3 and compared with the arteriographic findings in these vessels. The majority of these cases corresponded to 70% to 99% stenosis at arteriography for each reader (72.7% of vessels for readers 1 and 2, 66.7% of vessels for reader 3). None corresponded to less than a 35% arteriographic stenosis. Of the 22 vessels with 70% to 99% arteriographic stenosis, 16 (72.7% of vessels) were correctly classified as 70% to 99% MRA stenoses for each reader, MRA and DUS agreed with each other for reader 2, and 50 cases for reader 3. In seven vessels for each reader, MRA and DUS agreed with each other but incorrectly classified stenoses as 70% to 99% (all were measured as 50% to 69% stenoses at arteriography). There were no cases for any reader in which both modalities concurred but incorrectly underestimated arteriographically proven surgical stenosis. In the remainder of the cases for each reader, the two modalities were discordant for the presence or absence of surgical disease.

In those cases in which MRA incorrectly overestimated stenoses (based on arteriography) as surgical disease and for which DUS was available, the DUS correctly classified the vessel as having nonsurgical disease (less than 70% stenosis) in 13% to 46% of cases (see Table 6).

Because some investigators have proposed that concordant DUS and MRA results demonstrating the presence of surgical disease may be sufficient to forgo arteriography before surgery, we examined all cases in which the two modalities were in agreement for the presence or absence of 70% to 99% stenoses. Both modalities agreed by correctly classifying stenoses as surgical or nonsurgical in 46 cases for reader 1, 47 cases for reader 2, and 30 cases for reader 3. In seven vessels for each reader, MRA and DUS agreed with each other but incorrectly classified stenoses as 70% to 99% (all were measured as 50% to 69% stenoses at arteriography). There were no cases for any reader in which both modalities concurred but incorrectly underestimated arteriographically proven surgical stenosis. In the remainder of the cases for each reader, the two modalities were discordant for the presence or absence of surgical disease.

TABLE 2. Magnetic Resonance Angiography vs Arteriography for 70%-99% Stenoses

<table>
<thead>
<tr>
<th>Reader</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>95.5</td>
<td>70.6</td>
<td>58.3</td>
<td>97.3</td>
</tr>
<tr>
<td>2</td>
<td>90.9</td>
<td>74.5</td>
<td>60.6</td>
<td>95.0</td>
</tr>
<tr>
<td>3</td>
<td>90.9</td>
<td>78.4</td>
<td>64.5</td>
<td>95.2</td>
</tr>
<tr>
<td>Pooled data</td>
<td>92.4</td>
<td>74.5</td>
<td>59.2</td>
<td>95.8</td>
</tr>
</tbody>
</table>

PPV indicates positive predictive value; NPV, negative predictive value.

Discussion

The purpose of this study was to evaluate and compare 2D TOF MRA and DUS as screening tests for the detection of surgical and nonsurgical carotid bifurcation stenoses. The recent NASCET study demonstrated definite benefit for patients with 70% to 99% carotid stenoses who underwent endarterectomy compared with those treated medically. Our data show that both modalities are very sensitive for clinically relevant stenoses (ie, 70% to 99%) of the carotid bifurcation. Although there was a trend toward higher sensitivity...
and higher negative predictive values for MRA, the specificity of DUS trended higher. Comparison of the two modalities using the McNemar test shows no statistical difference in overall accuracy. Advantages of this study compared with others that assessed the 2D TOF technique include use of clinically relevant stenosis categories, multiple blinded readers, large numbers of vessels with disease, and advanced postprocessing techniques to overcome limitations of the standard MIP technique.

Two-dimensional TOF MRA is basically a functional technique in which signal is related to flow physiology and is produced within a vessel lumen by laminar flow of blood into an axially acquired slice. This differs from catheter arteriography, which gives a morphological picture of the lumen of a vessel filled by contrast media. Acquisition of multiple contiguous axial slices through a vessel lumen (ie, carotid artery) allows computer manipulation of the data set to produce a 2D projection image that is analogous to an arteriographic image. Signal loss may be produced on MRA within a patent vessel at sites of nonlaminar flow (vortex and turbulent flow) due to intravoxel phase dispersion or at sites of extremely slow flow. On the other hand, the 2D TOF technique should be very sensitive to small amounts of laminar flow and therefore very useful at distinguishing trickle flow from complete occlusion. The 2D TOF technique is probably the MRA technique most sensitive to slow flow. This property of 2D TOF MRA has recently been shown to be clinically important in evaluating slow flow in arteriographically occult runoff vessels of the leg.30

These phenomena are reflected in our experience with 2D TOF MRA of the carotid arteries. Review of

<p>| TABLE 4. Comparison of Duplex Ultrasonography and Arteriography (n=66) and Comparison of Magnetic Resonance Angiography and Arteriography in the 66 Vessels for Which Duplex Ultrasound Data Are Available (Pooled Readings) (n=3×66) |</p>
<table>
<thead>
<tr>
<th>Arteriographic Stenosis, %</th>
<th>DUS stenosis, %</th>
<th>MRA stenosis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-69</td>
<td>70-99</td>
</tr>
<tr>
<td>0-69</td>
<td>31</td>
<td>3</td>
</tr>
<tr>
<td>70-99</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>100</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Spearman ρ=.71

<p>| TABLE 5. Evaluation of 70%-99% Stenoses by Duplex Ultrasonography and Magnetic Resonance Angiography in 66 Vessels Examined by Both Techniques |</p>
<table>
<thead>
<tr>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>DUS</td>
<td>81.0</td>
<td>82.2</td>
<td>68.0</td>
</tr>
<tr>
<td>MRA</td>
<td>92.1</td>
<td>75.6</td>
<td>83.7</td>
</tr>
</tbody>
</table>

DUS indicates duplex ultrasonography; MRA, magnetic resonance angiography. PPV indicates positive predictive value; NPV, negative predictive value; DUS, duplex ultrasonography; and MRA, magnetic resonance angiography.
Table 1 reveals a tendency of MRA to overestimate stenoses, whereas it rarely underestimated stenoses. This is related to the effect of nonlaminar flow at and just distal to stenoses, which creates loss of signal with DUS, even with color-assisted Doppler. This is related to the effect of nonlaminar flow at and just distal to stenoses, which creates loss of signal with DUS, even with color-assisted Doppler.

Table 6. Comparison of Cases in Which Magnetic Resonance Angiography Overestimated Stenoses of <70% With Duplex Ultrasonography

<table>
<thead>
<tr>
<th>Reader</th>
<th>No. of False-Positive MRA Cases for 70%-99%</th>
<th>No. Correctly Categorized by DUS</th>
<th>No. Incorrectly Categorized by DUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>

MRA indicates magnetic resonance angiography; DUS, duplex ultrasonography. Each of the vessels that readers 2 and 3 overestimated was contained within the set of vessels that were also incorrectly classified by reader 1’s measurements, but they had fewer vessels overall that were overestimated than reader 1.

Based on arteriography.

The sensitivity of 2D TOF MRA to trickle flow probably accounts for its perfect performance in this study for distinguishing subtotal from complete occlusion, with no false positives or false negatives. We recognize that our study contained few cases with complete occlusion, however. DUS in our study correctly classified most vessels but missed one complete occlusion and classified two vessels as occluded that were actually patent. This emphasizes the well-described difficulties in identifying occluded ICAs with DUS, even with color-assisted Doppler. Many previous studies using the 2D TOF MRA technique have reported 100% sensitivity and specificity for complete occlusion.

The sensitivity of 2D TOF MRA for trickle flow is one of its advantages over DUS. Other potential advantages include the high interobserver agreement in interpretation of MRA of the carotid bifurcation we demonstrated. MRA is less operator dependent than DUS when standardized protocols are used. It also allows evaluation of the entire carotid artery in the neck from its origin to the carotid siphon, whereas DUS is limited by its inability to assess the high cervical and intracranial carotid artery segments to rule out tandem stenoses. Conventional MR imaging of the brain can also be performed at the same session as MRA evaluation of the neck and may be supplemented by MRA of the circle of Willis and its branches. MRA may have a potential advantage over conventional arteriography through the ability to view vessels from almost any projection, as opposed to the limited number of projections obtained in a standard arteriographic evaluation.

Specific advantages of this study over previous studies using similar techniques include the use of clinically relevant NASCET stenosis categories and standardized measurement of stenoses for all imaging modalities (including DUS). Most previous 2D TOF MRA studies used categories that are clinically less relevant such as 50% to 99%, 75% to 99%, or 80% to 99%. No study to our knowledge has classified vessels evaluated by MRA, DUS, and arteriography into a 70% to 99% stenosis category for comparison in the same cohort of patients. This is because almost no published DUS criteria for evaluating carotid stenoses allow classification of stenoses into a 70% to 99% category but rather have categories that cover the ranges of 75% to 99% or 80% to 99%. We used recently published ultrasound criteria that allow classification into this category.

To measure the percent stenoses of arteriograms and MRAs, we used the method employed in the NASCET study, namely, measurement of maximal stenosis and comparison with the diameter of the normal-appearing proximal ICA beyond the carotid bulb to determine the percent stenosis. The ultrasound criteria we used were also based on this measurement technique for their reference arteriograms. Many other published ultrasound criteria were either based on arteriograms in which the maximal stenotic region was compared with the estimated carotid bulb diameter (thus overestimating stenosis) or do not clearly state the method used in determining the arteriographic stenosis.

We avoided some of the recognized artifacts related to the widely used MIP postprocessing technique. Because of de facto thresholding of MIP images, the apparent vessel diameter in MIP images is reduced. We used TRAP, a previously reported sophisticated ray-tracing technique that enables vessel diameters to be represented more truly and images to be generated with 3D depth cueing, allowing more accurate assessment of complex overlapping anatomy.

We sought to overcome the shortcomings from which other studies of the 2D TOF technique suffer. A number of other studies evaluating the 2D TOF technique failed to use multiple independent blinded readers. Many also did not explicitly use direct measurement of MRA and arteriographic stenoses, which can potentially lead to misclassification of stenoses as greater or less than 70% in a significant proportion of cases. One study evaluated a small proportion of vessels with disease of 73 vessels, fewer than 10 had surgical disease (defined as 76% to 99% stenosis). This study does not suffer from these shortcomings because we used three blinded readers in assessing the MRAs, directly measured stenoses on MRA and arteriography,
and had a wide range of vessel stenoses, with 22 of 73 vessels demonstrating surgical (70% to 99%) stenoses on arteriography.

Our data do not support the notion proposed by some investigators that conventional arteriography is unnecessary for cases in which the MRA and DUS data are concordant for the presence or absence of surgical disease. In seven of 66 vessels the MRA and DUS findings were concordant but incorrect in categorizing the stenoses as 70% to 99% when they were actually less than 70% by arteriography.

In summary, MRA and DUS are comparable as screening examinations for atherosclerotic stenoses at the carotid bifurcation. MRA has advantages as a screening modality that include less operator dependence, high interobserver agreement, ability to visualize vessels from the aortic arch to the intracranial circulation, and a high sensitivity to trickle flow. These advantages may outweigh the higher cost of magnetic resonance imaging. Use of a high-resolution 3D TOF MRA technique to supplement the 2D TOF examination may yield less overestimation of stenoses because of its ability to attain smaller voxel sizes and thus mitigate the effects of turbulent flow at stenoses. Our preliminary experience, in fact, suggests that this may be the case (Fig 2). Ultrasound evaluation of carotid stenosis can also be improved with the use of transcranial Doppler studies and oculoplethysmography. Our data also suggest that combined MRA/DUS evaluation is not adequate to forgo arteriography because both modalities may overestimate and, less commonly, under estimate stenoses. As MRA hardware and software continue to evolve, however, conventional catheter angiography may indeed be replaced by MRA for evaluation of extracranial carotid artery narrowing, with the caveat that the accuracy of MRA for concomitant intracranial disease is not well documented.

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