Noninvasive Detection of Vertebral Artery Stenosis
A Comparison of Contrast-Enhanced MR Angiography, CT Angiography, and Ultrasound

Sofia Khan, MRCP; Philip Rich, FRCR; Andrew Clifton, FRCR; Hugh S. Markus, FRCP

Background and Purpose—Vertebral stenosis is associated with a high risk of recurrent stroke, but noninvasive imaging techniques to identify it have lacked sensitivity. Contrast-enhanced MR angiography and CT angiography have been recently developed and appear to have better sensitivity. However, no prospective studies have compared both of these techniques with ultrasound against the gold standard of intra-arterial angiography in the same group of patients.

Methods—Forty-six patients were prospectively recruited in whom intra-arterial angiography was being performed. Contrast-enhanced MR angiography, CT angiography, and duplex ultrasound were also performed. Angiographic images were analyzed blinded to patient identity by 2 experienced neuroradiologists.

Results—Contrast-enhanced MR angiography had the highest sensitivity and specificity (Radiologist 1, 0.83 and 0.91, respectively; Radiologist 2, 0.89 and 0.87) for detecting ≥50% stenosis. CT angiography had good sensitivity (Radiologist 1, 0.68; Radiologist 2, 0.58) and excellent specificity (Radiologist 1, 0.92; Radiologist 2, 0.93), whereas duplex had low sensitivity (0.44) but excellent specificity (0.95). For vertebral origin stenosis ≥50%, sensitivities were similar for contrast-enhanced MR angiography (Radiologist 1, 0.91; Radiologist 2, 0.82) but relatively higher for CT angiography (Radiologist 1, 0.82; Radiologist 2, 0.82) and duplex (0.67).

Conclusions—Contrast-enhanced MR angiography is the most sensitive noninvasive technique to detect vertebral artery stenosis and also has high specificity. CT angiography has good sensitivity and high specificity. In contrast, ultrasound has low sensitivity and will miss many vertebral stenoses. (Stroke. 2009;40:3499-3503.)

Key Words: CT ■ diagnostic methods ■ MR angiography ■ vertebrobasilar

One fifth of all ischemic strokes occur in the posterior circulation. Emerging data suggest they have a similar high early recurrence rate as that for symptomatic carotid artery stenosis. A meta-analysis of all available data showed that patients with acute posterior circulation stroke and transient ischemic attack (TIA) have a similar, or perhaps even higher, rate of recurrence compared with patients with anterior circulation stroke. A recent prospective study of patients presenting with TIA and stroke in the posterior circulation has confirmed these findings. These data highlight the need for effective secondary prevention. One fourth of patients with posterior circulation ischemic stroke are thought to have vertebral artery stenosis with artery-to-artery embolism being the likely mechanism. Vertebral artery stenosis is amenable to revascularization through stenting techniques, although randomized, controlled trials are necessary to definitively prove their role. Accurate noninvasive diagnosis of vertebral stenosis is essential if more intensive management approaches are to be developed.

Intra-arterial angiography (IAA) is the current gold standard but is invasive and carries a 1% to 2% risk of iatrogenic stroke. Older noninvasive methods had significant limitations. Duplex ultrasound allows only limited visualization of the vertebral artery. Noncontrast MR angiography (MRA) methods often do not provide complete vessel visualization, particularly of the vertebral origins. The newer methods of contrast-enhanced MRA (CE-MRA) and contrast CT angiography (CTA) appear to provide better vessel visualization (Figure). Considerable evidence has shown they have good sensitivity and specificity in the diagnosis of carotid stenosis. There is much less data evaluating them in vertebral stenosis. A recent systematic review identified only 13 studies that compared the accuracy of these noninvasive techniques with IAA. Three studies examined duplex without color, 2 duplex with color, 2 time-of-flight MRA, 5 CE-MRA, and one CTA. The review suggested that CE-MRA, and possibly CTA, are the best imaging modalities for vertebral stenosis. However, most studies were of varied sample size and methodological quality, making it difficult to draw definitive conclusions. Notably, there were no studies that compared the accuracy of all 3 noninvasive imaging techniques with IAA in the same patient cohort.
In this prospective study, we compared the sensitivity and specificity of duplex, CE-MRA, and CTA with the gold standard of IAA to determine the most accurate noninvasive imaging modality for diagnosing vertebral artery stenosis.

Methods

Patients

Patients undergoing IAA in a regional neurosciences center were prospectively recruited and consented to undergo all of duplex, CE-MRA, and CTA. Consecutive patients with posterior circulation stroke/TIA (n=31), anterior circulation stroke/TIA (n=7), and, in addition, nonconsecutive patients with likely normal vessels (n=8) were recruited to include patients with varying degrees of stenosis. The indications for IAA in patients with “normal” vertebral arteries were: routine check angiography postcoiling of an aneurysm (n=3), coiling of an aneurysm (n=2), vasculitis (n=1), carotocavernous fistula (n=1), and previous intracerebral hemorrhage (n=1). The demographic details are shown in Table 1. All patients gave written informed consent and the study was approved by the local ethics committee. All imaging was performed within a time period of 1 month and usually within 1 week.

Imaging Acquisition

Intra-arterial digital subtraction catheter angiography (Advantx bi-plane; General Electric) was performed using standard techniques through a 4- or 5-French common femoral artery sheath and up to 150 mL of Omnipaque 300 contrast medium. First, a test injection using 10 mL of neat contrast (Omnipaque 300) was given into each vessel origin could be seen and the presence and site of stenosis. Where possible, peak systolic velocity measurements were taken at the origins of the vertebral arteries (with 7 to 10 mL of diluted contrast, 60% contrast 40% heparinized saline). Repeated contrast injections with lateral, anteroposterior, or lateral oblique imaging projections were acquired as necessary to illustrate the vertebral arteries and any stenoses using a frame rate of 2 to 3 per second, a 25- to 30-cm field of view, and a 1024x1024 matrix.

CTA was performed using General Electric Lightspeed 16-slice scanner. One hundred milliliters of iohexol (Omnipaque; General Electric) 300 was administered intravenously at an infusion rate of 4 mL/s. Anteroposterior and lateral scout views were obtained to enable planning of the axial series. Imaging was obtained from the aortic arch to the vertex spirally in 1.25-mm cuts and 1.375 pitch. Postprocessing was performed on a General Electric Advantage Windows workstation.

Three-dimensional CE-MRA was performed using a 1.5-T Philips Intera scanner with a volume Philips head and neck coil. First scout views were obtained to assess the 3-plane position and localize the vessels. Then a region-of-interest box was placed to include the top of the aortic arch to the circle of Willis. Gadodiamide (Omniscan; General Electric) contrast medium was injected through intravenous pump injection at a rate of 2.5 mL/s followed by a 25-mL bolus of normal saline solution and source imaging obtained. Maximum intensity projections images were routinely produced on the scanner console.

Standard prescanning safety questionnaires and precautions were used for all modalities according to local clinical protocols.

Ultrasound was performed in by trained vascular technicians using either a Phillips IU22 machine with a linear L8-4-MHz probe or a Philips HDI 5000 with a linear L7-4 MHz probe. The technician imaged the carotid and vertebral arteries and recorded whether the vessel origin could be seen and the presence and site of stenosis. Where possible, peak systolic velocity measurements were taken before the stenosis and at the site of stenosis, and a >2.5-fold increase was taken to indicate >50% stenosis. B-mode information was also considered where contributory.

Table 1. Demographic and Stroke Risk Factors of Patients

<table>
<thead>
<tr>
<th>Ischemic Stroke/TIA Group</th>
<th>Posterior Circulation</th>
<th>Anterior Circulation</th>
<th>‘Normal’ Vessels</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>31</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>25 (81)</td>
<td>6 (86)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Mean (SD) age, years</td>
<td>62.1 (11.9)</td>
<td>62.1 (14.4)</td>
<td>48.9 (8.1)</td>
</tr>
<tr>
<td>Hypertension (%)*</td>
<td>25 (81)</td>
<td>5 (71)</td>
<td>1 (13)</td>
</tr>
<tr>
<td>Diabetes (%)*</td>
<td>6 (19)</td>
<td>2 (29)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)*</td>
<td>21 (68)</td>
<td>7 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>2 (6)</td>
<td>3 (43)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Exsmokers (%)</td>
<td>14 (45)</td>
<td>1 (14)</td>
<td>4 (50)</td>
</tr>
<tr>
<td>History of VB stroke/TIA (%)</td>
<td>31 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>History of carotid stroke/TIA (%)</td>
<td>3 (10)</td>
<td>6 (86)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Hypertension: persistently elevated blood pressure >140 mm Hg systolic or diastolic blood pressure >90 mm Hg or on treatment. Diabetes: random glucose >11.1 mmol/L or fasting blood glucose >7.0 mmol/L or on treatment. Hypercholesterolemia: total serum cholesterol >5.2 mmol/L or on treatment.
Image Analysis

All angiographic images (IAA, CTA, and CE-MRA) were analyzed independently by 2 experienced consultant neuroradiologists. Images were transferred onto CD and anonymized and CTA, CE-MRA, and IAA were analyzed at separate time points. Radiologist 1 repeated all image analysis at a second time point over 1 month after the first analysis to determine intraobserver reproducibility. Information was collected on the size of the vertebral artery and how well the artery and its origin could be visualized. Stenosis was graded into 4 categories (<50%, 50% to 69%, 70% to 99%, and 100%). A method similar to the North American Symptomatic Carotid Endarterectomy Trial method of measuring carotid stenosis and to the Warfarin–Aspirin Symptomatic Intracranial Disease method of measuring intracranial verteobasilar stenosis was used for IAA, CTA, and CE-MRA. Comparison was made of the diameter of the vessel at the site of stenosis (D stenosis) with the normal diameter of the vessel just distal to the stenosis (D distal) using the following formula: % stenosis = (1 − [D stenosis/D distal]) × 100%. Localization of the stenosis in the vertebral arteries was defined according to the structural anatomic subdivision: V1 (extracranial preforaminal artery), V2 (extracranial foraminal artery), and V3 (extracranial postforaminal artery). The V4 section forms the intracranial vertebral artery.

CTA imaging was analyzed using a combination of multiplane reformats, maximum intensity projections, and 3-dimensional reconstructions as required for each case. CTA images were reviewed using both multiplane reformats and maximum intensity projections. Three-dimensional reconstructions were used at the discretion of the neuroradiologist when required to help clarify anatomy. If a stenosis was detected, then source imaging was also reviewed. Duplex imaging data were assessed by the ultrasonographer performing the scan; this included whether the vertebral artery origin could be seen and whether stenosis (categorized as 50% to 100%) was present.

Statistical Analysis

Sensitivity and specificity values and their 95% CIs were calculated. Analysis was repeated for both ≥50% and ≥70% stenosis, except for ultrasound in which only ≥50% was performed because differentiating degrees of stenosis for the vertebral artery is unreliable on ultrasound. Sensitivity, specificity, and 95% CIs were calculated using clinical calculator software (http://faculty.vassar.edu/lowry/clin1.html).

Results

Of the 46 patients, 41 patients had IAA imaging of the right vertebral artery and 45 had IAA imaging of the left vertebral artery. Of these 86 vessels, 2 had vertebral artery origin stenosis and were excluded. Therefore, 84 were included in the analysis.

The image quality of IAA was excellent in all the vessels imaged. Twenty-one vessels had ≥50% stenosis on IAA. Of these, 15 were 50% to 69%, 4 70% to 99%, and 2 100%. Of the ≥50% stenoses, 13 were V1 (all origin), 4 V2, one V3, and 3 V4. There was both IAA and CTA data for 78 arteries in 43 patients, both CE-MRA and IAA data for 72 arteries in 40 patients, and both duplex ultrasound and IAA data for 88 arteries in 44 patients. Intraobserver and interobserver agreement in identification of ≥50% stenosis is shown in Table 2.

Of the 46 patients, 43 had CTA (3 patients refused to consent to it), 40 had CE-MRA (one was claustrophobic, one had a pacemaker, 4 refused to consent), and 44 had duplex imaging.

The sensitivity and specificity of each noninvasive technique for detecting both ≥50% and ≥70% stenosis are shown in Table 3.

For detection of ≥50% stenoses, CE-MRA had the highest sensitivity (0.83 and 0.89 for Neuroradiologists 1 and 2, respectively), CTA the next highest sensitivity (0.68 and 0.58), and ultrasound the lowest sensitivity (0.44). For detection of ≥70% stenosis, the sensitivity of CTA (0.80, 0.80) improved almost to the level of CE-MRA (0.80, 1.00), which remained high. All 3 techniques had similarly high specificity of the order of ≥0.9 (Table 3). The number of false-positives and -negatives for each comparison are given in Table 4. For CTA, approximately equal numbers of stenoses were underestimated and overestimated, but for CE-MRA, there was a tendency to overestimate stenoses compared with IAA.

Analysis was repeated for vertebral origin stenoses alone and sensitivity and specificity values for both ≥50% and ≥70% stenosis are shown in Table 4. Both CE-MRA and CTA had similar, and high, levels of specificity. The sensitivity of ultrasound to detect ≥50% stenosis improved to 0.67 but was still lower than that of CE-MRA and CTA. Again, specificity for all techniques was high.

Similar levels of sensitivity and specificity were obtained when Radiologist 1 repeated the analysis with the exception of CTA for ≥50% stenoses for which sensitivity improved on the second analysis (Table 3).

Discussion

In this prospective study, we compared CE-MRA, CTA, and duplex ultrasound with the gold standard of IAA. Both CE-MRA and CTA had a high sensitivity for detecting both moderate and tight stenosis with CE-MRA having a slightly higher sensitivity than CTA. In contrast, duplex ultrasound had a much lower sensitivity.

A recent meta-analysis found little good-quality data evaluating the sensitivity and specificity of both CE-MRA and CTA against IAA in vertebral artery disease. Only 5 studies with CE-MRA and one with CTA were identified and no study compared all techniques in the same subjects. Studies were of varied sample size and methodological quality. However, the review suggested that CE-MRA and CTA were the best imaging modalities for detecting vertebral stenosis, and this prospective study would support that finding. This study is the first prospective study in which both modalities as well as ultrasound have been compared against the gold standard in the same patients.

All techniques had high specificity. Ultrasound had a low sensitivity of 0.44 but a similarly high specificity. Therefore,
if an abnormality is detected on duplex ultrasound, it is likely to indicate a stenosis, but many stenoses will be missed using this technique. Contrast ultrasound may produce higher sensitivities, although it was not tested in this study.

Many vertebral stenoses are at the vertebral origins. Stenoses at this site can often be directly visualized by ultrasound, but have been less well imaged using noncontrast MRA techniques. Therefore, we carried out a separate analysis for stenoses at this site. Ultrasound showed a higher sensitivity at this site (0.67 versus 0.44) and CTA also had a higher sensitivity for detection of origin of stenoses.

Our results have important clinical implications. Recent data have shown the risk of recurrent stroke after vertebrobasilar TIA and minor stroke is as high as that for carotid territory stroke.³,⁴ In addition, recent prospective studies have shown that the presence of vertebral stenosis identifies a group of patients with vertebrobasilar TIA and minor stroke who have a particularly high risk of recurrent stroke, as high as 30% in the first month.⁴,¹¹ This group of patients may benefit from more intensive antiplatelet therapy or intervention with stenting. Uncontrolled studies suggest stenting may be associated with a reduced risk of stroke, although data from randomized trials are awaited. In the past, identifying these high-risk patients with vertebral stenosis has been difficult. Due to its low sensitivity, ultrasound will miss many stenoses. Noncontrast MRA often provides incomplete vis-

### Table 3. Sensitivity and Specificity Analysis for Whole Vertebral Artery

<table>
<thead>
<tr>
<th></th>
<th>Radiologist 1</th>
<th></th>
<th>Radiologist 2</th>
<th></th>
<th>Radiologist 1 Repeat Analysis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>FP/FN</td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>FP/FN</td>
</tr>
<tr>
<td>≥50% versus &lt;50% stenosis</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>IAA versus CTA</td>
<td>0.68 (0.43–0.86)</td>
<td>0.92 (0.81–0.97)</td>
<td>5/6</td>
<td>0.58 (0.34–0.79)</td>
<td>0.93 (0.83–0.98)</td>
<td>4/8</td>
</tr>
<tr>
<td>IAA versus MRA</td>
<td>0.83 (0.58–0.96)</td>
<td>0.91 (0.79–0.97)</td>
<td>5/3</td>
<td>0.89 (0.64–0.99)</td>
<td>0.87 (0.74–0.94)</td>
<td>7/2</td>
</tr>
<tr>
<td>IAA versus IAA</td>
<td>0.95 (0.77–0.99)</td>
<td>0.98 (0.92–1.00)</td>
<td>1/1</td>
<td>1.00 (0.81–1.00)</td>
<td>1.00 (0.93–1.00)</td>
<td>0/0</td>
</tr>
<tr>
<td>IAA versus duplex</td>
<td>0.44 (0.23–0.67)</td>
<td>0.95 (0.86–0.98)</td>
<td>1/9</td>
<td></td>
<td></td>
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</tbody>
</table>

 FP indicates false-positive; FN, false-negative.

### Table 4. Sensitivity and Specificity Analysis for Vertebral Artery Origin

<table>
<thead>
<tr>
<th></th>
<th>Radiologist 1</th>
<th></th>
<th>Radiologist 2</th>
<th></th>
<th>Radiologist 1 Repeat Analysis</th>
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<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
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<td>FP/FN</td>
<td>Sensitivity</td>
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<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>IAA versus CTA</td>
<td>0.80 (0.30–0.99)</td>
<td>0.99 (0.92–0.99)</td>
<td>1/1</td>
<td>0.80 (0.30–0.99)</td>
<td>0.95 (0.86–0.98)</td>
<td>4/1</td>
</tr>
<tr>
<td>IAA versus MRA</td>
<td>0.80 (0.30–0.99)</td>
<td>0.91 (0.81–0.96)</td>
<td>6/1</td>
<td>1.00 (0.46–1.00)</td>
<td>0.82 (0.70–0.90)</td>
<td>12/0</td>
</tr>
<tr>
<td>IAA versus IAA</td>
<td>1.00 (0.61–1.00)</td>
<td>0.91 (0.83–0.96)</td>
<td>7/0</td>
<td>0.83 (0.36–0.99)</td>
<td>0.99 (0.92–1.00)</td>
<td>1/1</td>
</tr>
</tbody>
</table>

 FP indicates false-positive; FN, false-negative.
alization of the posterior circulation and vertebral origins are not always well visualized. CE-MRA and CTA now provide sensitive and specific techniques that can be applied noninvasively to identify patients with vertebral stenosis for specific interventions.

The high sensitivity and specificity of CE-MRA and CTA is similar to that reported for carotid stenosis, for which much more data are available. Here, however, the stenosis is usually at the bifurcation and this is usually well visualized by duplex ultrasound. A large meta-analysis of studies in carotid disease noted few studies in which all techniques were compared in the same group of patients, as has been performed in this study.

Our study design has a number of strengths. Patients were prospectively recruited and patients were imaged with all 3 noninvasive imaging modalities as well as IAA. A small number did not receive one or other imaging modality due to contraindications or failure to consent, but this was a small minority. All images were analyzed blinded to clinical details and separately from other images from the same patient performed using different modalities. Analyses were performed by 2 experienced neuroradiologists and these demonstrated similar results. Intraobserver reproducibility studies were also performed for one of these. We studied a variety of patients, some with suspected stenoses and others with suspected normal vessels. This allowed assessment of sensitivity across a range of degrees of stenosis. A limitation is that there were few patients with ≥70% stenosis and therefore the results are less robust for this degree of stenosis compared with ≥50% stenosis.

In conclusion, this prospective study demonstrates that CE-MRA has a high sensitivity and specificity for detecting vertebral stenoses. CTA also has a high sensitivity and specificity, although perhaps slightly less than CE-MRA. In contrast, duplex ultrasound has a low sensitivity although a high specificity. CE-MRA and CTA are the best techniques for noninvasive imaging of the vertebral arteries, although in some cases, a combination of different noninvasive techniques may be necessary.

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Disclosures
None.

References
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