Noninvasive Detection of Steno-Occlusive Disease of the Supra-Aortic Arteries With Three-Dimensional Contrast-Enhanced Magnetic Resonance Angiography
A Prospective, Intra-Individual Comparative Analysis With Digital Subtraction Angiography

Winfried A. Willinek, MD; Marcus von Falkenhausen, MD; Markus Born, MD; Jürgen Gieseke, PhD, MD; Tobias Höller, MSc; Thomas Klockgether, MD; Hans J. Textor, MD; Hans H. Schild, MD; Horst Urbach, MD

Background and Purpose—Concomitant disease of the supra-aortic arteries can influence the outcome of surgical treatment of carotid artery stenosis. However, sensitivity and specificity data of noninvasive contrast-enhanced 3-dimensional (3D) magnetic resonance angiography (CE MRA) for the detection of steno-occlusive disease of the entire supra-aortic arteries including the circle of Willis remain unclear. We aimed to intra-individually compare high-spatial-resolution CE 3D MRA and digital subtraction angiography (DSA) for the assessment of steno-occlusive vascular disease of the supra-aortic arteries.

Methods—CE MRA and DSA of the supra-aortic arteries were prospectively performed in 50 consecutive patients. Intra-individual comparison of CE MRA and DSA was available in 833 arteries. High-spatial-resolution CE MRA comprised a measured voxel size of 0.81 mm × 0.81 mm × 1 mm (0.66 mm³). Steno-occlusive vascular disease of the 833 arteries was assessed independently by 2 radiologists according to the NASCET criteria.

Results—CE MRA had a sensitivity of 100% (73/73), a specificity of 99.3% (760/765), a positive predictive value of 93.6% (73/78), and a negative predictive value of 100% (760/760) by using a 70% to 99% threshold of arterial diameter stenosis. For detection of occlusion, sensitivity, specificity, PPV, and NPV value of CE MRA were 100%, respectively.

Conclusions—Noninvasive high-spatial-resolution CE MRA is suited to replace diagnostic DSA for the detection of steno-occlusive disease of the supra-aortic arteries. (Stroke. 2005;36:38-43.)

Key Words: carotid stenosis ■ comparative study ■ magnetic resonance angiography ■ magnetic resonance imaging ■ supra-aortic arteries

Arterial steno-occlusive disease of supra-aortic vessels, particularly of the carotid arteries, is frequent in the general population with the potential risk of thrombo-embolic and hemodynamic cerebral infarctions and fatal stroke. Carotid endarterectomy may prevent stroke in symptomatic persons with >70% stenosis, or even with stances of 50% to 69%, and in asymptomatic persons with at least 60% stenosis.1–5 For effective surgical treatment, correct classification of atherothrombotic lesions is essential.

Three-dimensional contrast-enhanced magnetic resonance angiography (MRA) has gained increasing importance as a non-invasive test in the preoperative work-up of carotid artery stenosis.6,7 Even with highly advanced techniques, MR evaluation of the entire supra-aortic arteries covering the aortic arch up to the circle of Willis still meets challenges such as prevention of venous overlay and acquisition of both sufficient spatial resolution and imaging coverage.8,9 Because concomitant disease of the supra-aortic arteries can influence the outcome of surgical treatment, visualization of the entire brain supplying arteries is required if MRA wants to compete with conventional angiography. However, to our knowledge, the role of MRA for the detection of steno-occlusive disease of the entire supra-aortic arteries still remains unclear. Thus, the purpose of this study was to determine the sensitivity and specificity of supra-aortic MRA as compared with digital subtraction angiography (DSA).

Materials and Methods

Patient Studies
A prospective, intra-individual comparative study was performed between March 2002 and June 2003 in a total of 50 consecutive

Received June 29, 2004; accepted October 1, 2004.
From the Department of Radiology (W.A.W., M.v.F., M.B., J.G., H.J.T., H.H.S., H.U.), Institute of Medical Biometrics, Informatics, and Epidemiology (T.H.), and the Department of Neurology (T.K.), University of Bonn, Germany.
Presented in part at the 89th Scientific Assembly and Annual Meeting of the RSNA 2003, Chicago, Ill.
Correspondence to Dr W. A. Willinek, Department of Radiology, University of Bonn, Sigmund-Freud-Strasse 25, D-53105 Bonn, Germany. E-mail winfried.willinek@ukb.uni-bonn.de
© 2004 American Heart Association, Inc.
Stroke is available at http://www.strokeaha.org DOI: 10.1161/01.STR.0000149616.41312.00

38
patients with suspected cerebrovascular disease (38 men, 12 women; age range, 38 to 80 years; mean age [SD]: 60 ± 12 years). Patients who were scheduled for conventional catheter angiography because of suspected steno-occlusive disease were included in the study. All patients underwent MRA and conventional angiography within 5 days. Although attempts were made to randomize the order in which the studies were performed, in most cases conventional angiography was performed the day before MRA. The study protocol was approved by our institutional review board and written informed consent was obtained from all patients.

MR Imaging

Contrast-enhanced MRA was performed on a 1.5-T MR scanner (Intera; Philips Medical Systems; gradient amplitude, 30 mT/m; rise time, 0.2 ms; slew rate, 150 T/m per second) equipped with a commercially available phased-array coil (Synergy head neck coil; Philips Medical Systems). That covers the regions of the upper chest, neck, and head. A standardized, automatic bolus injection (Spectris MR Injection System; Medrad Europe) of 0.2 mmol/kg body weight of gadopentetate dimeglumine (Magnevist) was used at a flow rate of 3.0 mL/sec, followed by a saline solution flush of 30 mL. Two-dimensional (2D) real-time fluoroscopy in the coronal plane was performed to trigger MRA. MRA included first coronal 2D phase-contrast scout imaging (repetition time [TR]/echo time [TE], 10.3 ms/5.0 ms; acquisition time, 45 sec) and second fast axial 2D time-of-flight imaging (TR/TE, 16.4 ms/6.9 ms; acquisition time, 62 sec). Finally, 3-dimensional (3D) contrast-enhanced MRA was performed using randomly segmented k-space ordering,10 and the following acquisition parameters: 3D gradient echo-sequence with TR/TE/flip angle (FA), 4.8 ms/1.48 msec per 40°; slab thickness, 60 mm; sections, 60; and acquisition time, 58 seconds with a breath hold of 15 to 20 seconds at the beginning of the acquisition. An image matrix of 432 × 432 on a 350-field of view with 1-mm slice thickness yielded a measured voxel volume of 0.66 mm³ (0.81 mm × 0.81 mm × 1.0 mm).

Catheter Angiography

DSA was performed on a biplane Integris V 5000 (Philips Medical Systems, Best, the Netherlands). A 5-French pigtail catheter was navigated into the ascending aorta via the femoral route in 48 of 50 and the transbrachial route in 2 of 50 patients. The aortic arch and the proximal parts of the supra-aortic arteries were displayed in anterior-posterior projection at 3 frames per second after automatic injection of 35 mL of iopromide (Ultravist) at 17 mL per second. After the aortic arch injection, a 5-French vertebral or sidewinder catheter was navigated into both common carotid arteries, the prominent vertebral, and the contralateral subclavian artery. The carotid bifurcation and the intracranial arteries were displayed separately in at least 2 projections each by manual injections of 5 to 7 mL of contrast material.

Image Evaluation

Images were evaluated on hard copy images using identical projections (anterior-posterior and oblique); axial views were only available for MRA. Both DSA and MRA were independently reviewed at different times by 2 experienced readers in a randomized order. The readers were blinded to the patient’s name, the clinical history of the patients, and results of other diagnostic procedures. In 12 of 50 cases, DSA was performed by 1 of the 2 readers, but the image interpretation took place up to 12 weeks after the DSA procedure to minimize the level of familiarity. In each case, 18 vascular segments were assessed: proximal subclavian arteries, brachiocephalic trunk/innominate artery, common carotid arteries (CCA), external and internal carotid arteries (ECA, ICA), vertebral arteries (VA), basilar artery, middle cerebral arteries (MCA), and anterior and posterior cerebral arteries (ACA and PCA). As DSA was performed according to the clinical presentation of the patients, DSA did not selectively image all arteries in each patient. As a consequence, 833 arteries were available for direct comparison with DSA and were included for statistical analysis (99 subclavian arteries, 50 LA, 100 CCA, 97 ICA, 49 ECA, 88 VA, 50 basilar arteries, 100 MCA, 100 ACA, 100 PCA). The readers were asked to review the angiograms to identify vascular disease. The final percentage of artery stenosis was determined by using the NASCET measurement criteria.11 The percentage of diameter stenosis was defined as the mean of the 2 independent measurements. Subsequently, the radiologists were asked to evaluate the presence of plaque ulceration or irregularity by consensus. A plaque was classified as ulcerated if it fulfilled the radiographic criteria of an ulcer niche, seen in profile as a crater penetrating into a stenotic plaque.

A near-occlusion with string sign on either the MRA or the conventional angiogram was defined as 99% stenosis. If stenosis and occlusion occurred in the same vessel, ie, stenosis of the proximal and occlusion of the distal segment, the artery was defined as “occluded” according to the hemodynamic relevance for the appending vessel tree.

Statistical Analysis

For MRA and DSA sensitivity, specificity and positive and negative predictive values were calculated. Thresholds for diameter stenosis were set at 70% to 99% and occlusion (100%). A 2-sided 95% confidence interval was calculated for these thresholds. Linear regression analysis was used to compare the different imaging modalities. To estimate inter-observer variability, the intraclass coefficient was calculated. Statistical analyses were performed using SAS statistical software (SAS version 8.02, SAS Institute Inc).

Results

Vascular Disease

Vascular disease was detected by DSA in the 106 of 833 arteries with the following localizations: 6 of 106 SA, 4 of 106 CCA, 8 of 106 ECA, 54 of 106 ICA, 23 of 106 VA, 1 of 106 basilar arteries, 5 of 106 MCA, 3 of 106 ACA, 1 of 106 PCA, and 1 of 106 innominate artery. Occlusion was diagnosed based on the DSA images in 35 of 833 (4.2%), stenosis ≥70% in 37 of 833 (4.4%) and stenosis <70% in 34 of 833 (4.1%).

Vascular disease was diagnosed in 103 of 106 (97.2%) by MRA, resulting in a total of 3 false-negative results: 1 50% stenosis of the ECA, 1 30% stenosis of the ICA, and 1 40% stenosis of the VA were missed by MRA. MRA revealed occlusion in 35 of 833 (4.2%) and stenosis ≥70% in 42 of 833 (5.0%). Seventy-two of 72 (100%) of stenosis ≥70%, as well as occlusions, were correctly identified by MRA, yielding no false-negative test results. With the threshold of stenosis ≥70%, MRA had 5 false-positive test results, but MRA and DSA findings matched in 72 of 77 (93.5%) (Figures 1, 2 and 3). In the 5 false-positive cases, MRA versus DSA showed a trend of overestimating the grade of stenosis. A 55% right ICA stenosis was overestimated as 75% by MRA; in this patient, DSA revealed a thrombus causing the obstruction. Retrospectively, the thrombus could be identified also on the MRA (Figure 4). A 65% right ICA stenosis was overestimated as 75% stenosis by MRA. A 55% right VA stenosis was overestimated as 70% by MRA. A 65% right VA stenosis was overestimated as 70% by MRA. In 1 case, fenestration of the basilar artery detected by DSA was misdiagnosed as 90% stenosis by MRA. Retrospectively, on the enlarged MIP image, the correct diagnosis was made (Figure 5). Concordance of MRA and DSA diagnoses included multisegmental VA stenosis of 90% in 2 cases, as well as
a 90% stenosis with a 40% tandem stenosis and a 99% stenosis with a 50% tandem stenosis at the ICA bifurcation and at the clinoid segment, respectively. Intraclass correlation coefficients between the 2 readers to identify vascular disease were 0.996 and 0.994 for MRA and DSA, respectively.

Sensitivity and Specificity
By using the threshold of 70% to 99% of diameter stenosis, sensitivity and specificity of MRA was 100% (73/73) and 99.3% (760/765), respectively. Results for sensitivity and specificity are listed in Table. Five of 833 cases with plaque ulceration and wall irregularities were concordantly depicted in 5 of 5 by MRA and DSA. Overall correlation between MRA and DSA in the 833 arteries was $r=0.98126$ ($P<0.0001$).

Discussion
We assessed the diagnostic accuracy of contrast-enhanced MRA for the detection of steno-occlusive disease of the supra-aortic arteries. As compared with DSA, sensitivity and specificity were 100% (33/33) and 100% (800/800) for detection of occlusion and 100% (73/73) and 99.3% (760/765) for detecting stenosis of 70% to 99%. Wutke et al reported sensitivity and specificity in the range of 90% to 100% for MRA. In their study, however, evaluability of 51
vessel segments (proximal CCA [at its origin in the aortic arch], distal ICA, and intracranial MCA and ACA) was graded uncertain or not possible. One explanation for the improved evaluability of all 833 of 833 vessels in our study might be the higher spatial resolution. We used a measured voxel size of $0.81 \times 0.81 \times 1.0$ mm$^3$, whereas in the study conducted by Wutke et al the measured voxel size was $1.2 \times 0.6 \times 1.3$ mm$^3$. The effect of decreased voxel size on image quality has been demonstrated; decreased voxel size improves the delineation of cervical carotid and vertebral arteries in MR angiograms. In recent publications of MRA studies, voxel sizes for carotid artery imaging range between 0.90 and 2.4 mm$^3$. To our knowledge, these are the first data of diagnostic accuracy for the supra-aortic arteries based on a MRI protocol at a spatial resolution of 0.66 mm$^3$.

For a noninvasive test that selects candidates for surgery or intervention, it is mandatory to provide high sensitivity and specificity. A false-negative test result means that a patient who would benefit from treatment is not correctly classified as having disease. In our study, no false-negative result was found.

### Comparison of CE MRA and Digital Subtraction Angiography for the Detection of Steno-Occlusive Disease of the Supra-Aortic Arteries

<table>
<thead>
<tr>
<th>Arterial Stenosis</th>
<th>Diameter</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Negative Predictive Value</th>
<th>Positive Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>70%–99%</td>
<td>100%</td>
<td>99.3%</td>
<td>100%</td>
<td>(95.1–100)</td>
<td>(85.7–97.9)</td>
</tr>
<tr>
<td></td>
<td>(95.1–100)</td>
<td>(98.5–99.8)</td>
<td>(95.1–100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>(99.5–100)</td>
<td>(89.7–100)</td>
</tr>
<tr>
<td></td>
<td>(99.5–100)</td>
<td>(99.5–100)</td>
<td>(99.5–100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>100%</td>
<td>96.5%</td>
<td>100%</td>
<td>(93.5–100)</td>
<td>(83.4–99.4)</td>
</tr>
<tr>
<td>70%–99%</td>
<td>(87.9–99.6)</td>
<td>(91.2–100)</td>
<td>(93.5–100)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data in parentheses are 95% CI and percentages. ICA indicates internal carotid artery.
found, i.e., all patients with relevant disease were classified as “patients.” However, misclassification with false-positive results may result in patients undergoing treatment without presenting disease. With regard to artery occlusion, no false-positive result was observed in our study. This is an important finding, because a misclassified occlusion would result in nontreated patients who may benefit from treatment. With an underlying threshold of stenosis 70% to 99%, we had in a total of 97 ICAs 2 false-positive test results in 2 different patients. Grade of stenosis in these patients ranged between 55% and 75%. In the first case, a thrombus in the ICA was misinterpreted by MRA as an atherosclerotic plaque, whereas DSA and duplex ultrasound displayed the thrombus. Respectively, the thrombus was identified on MRA, but not as clear as on the catheter angiography film. Therefore, we conclude that a thrombus might be a limitation for MRA. Because duplex ultrasound, the recommended screening method, should display the thrombus even before both MRA and DSA studies are conducted, this misinterpretation would not have happened outside the study setting with knowledge of clinical history and duplex test result. In the second case, a 55% ICA stenosis was overestimated as 70% in asymptomatic patients. Based on the recommendations from the endarterectomy trials, i.e., considering 60% ICA stenosis in asymptomatic patients and >50% ICA stenosis in symptomatic patients, the cutoff point from which the patients may benefit from surgical therapy, this misclassification would not necessarily have meant a change in the clinical management for this patient.14

One limitation of our study is the small number of patients with pathologies in the main branches of the circle of Willis: 5 occlusions or stenosis ≥70% in the MCA, 3 in the ACA, and 1 in the PCA. As a consequence, exact sensitivity and specificity for the MCA, PCA, and ACA would not be representative. However, 9 of 9 stenoses or occlusions of the circle of Willis were correctly identified by MRA, and no false-positive result was documented in these territories. In our opinion, this may reflect the ability of the technique to reliably visualize the entire brain-supplying arteries, including the main branches of the circle of Willis.

There are 2 possible explanations for the lower specificity as compared with the sensitivity in our study: underestimation of stenosis by DSA or overestimation by MRA. The latter is a well-known phenomenon of MRA, occurring especially in noncontrast-enhanced techniques such as time-of-flight MRA.12,13,15,16 However, one has to bear in mind that DSA also has limitations despite being an invasive procedure that still harbors a neurologic complication rate of 1.3%, including permanent disability.17 X-ray angiography is known to identify less high-grade stenosis if compared with rotational x-ray angiography and 3D MRA because of the limited number of projections.15 Furthermore, it might be possible that DSA tends to underestimate stenosis in some cases.19 It is also important to note that MRA reading should ideally be made on a workstation with access to the source data rather than on a MIP film as source images can improve the specificity of MIP alone.13

Recently, pooled sensitivity and specificity of MRA for discriminating <70% and ≥70% carotid artery stenosis were 95% and 90%16 compared with 100% and 99.3% in our study. One explanation for the higher discriminating power is that we used a very-high-spatial-resolution protocol and advanced MR technique, whereas Nederkoorn included data from 1994 to 2001, when these MR techniques were not yet available.16 In addition, in their analysis, only 4 studies conducted contrast-enhanced MRA. On the basis of the results of Nederkoorn et al, Forsting and Wanke stated in an editorial comment in a recent issue of Stroke that “we do not need diagnostic DSA in patients with carotid artery stenosis” anymore.20 This is still subject of discussion, especially in patients with >50% and <70% stenosis by MRA.21,22

In conclusion, in the present study noninvasive high-spatial-resolution contrast-enhanced MRA demonstrated high sensitivity and specificity of 100% and 99.3% for detecting steno-occlusive disease of the supra-aortic arteries with stenosis ≥70% to 99%. Although further studies are needed to estimate the exact diagnostic accuracy of MRA in the circle of Willis, contrast-enhanced MRA appears to be adequate to replace DSA in the diagnostic assessment of steno-occlusive lesions of the supra-aortic arteries in most patients, thus justifying diagnostic DSA only in equivocal cases. Moreover, reliable MRA may be considered as a method for screening and follow-up, and also to select candidates for intervention therapy. If the patient is scheduled for endovascular therapy, the diagnostic assessment is verified immediately before intervention.

References
Noninvasive Detection of Steno-Occlusive Disease of the Supra-Aortic Arteries With Three-Dimensional Contrast-Enhanced Magnetic Resonance Angiography: A Prospective, Intra-Individual Comparative Analysis With Digital Subtraction Angiography

Winfried A. Willinek, Marcus von Falkenhausen, Markus Born, Jürgen Gieseke, Tobias Höller, Thomas Klockgether, Hans J. Textor, Hans H. Schild and Horst Urbach

Stroke. 2005;36:38-43; originally published online November 29, 2004;
doi: 10.1161/01.STR.0000149616.41312.00

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/36/1/38

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/