Mild Carotid Artery Atherosclerosis
Assessment by 3-Dimensional Time-of-Flight Magnetic Resonance Angiography, With Reference to Intravascular Ultrasound Imaging and Contrast Angiography

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Background and Purpose—Our aim was to evaluate the usefulness of 3-dimensional time-of-flight magnetic resonance angiography (3-D TOF MRA) in detection and quantification of mild atherosclerotic changes of carotid arteries with reference to intravascular ultrasound (IVUS) and contrast angiography.

Methods—TOF MRA at 1.5 T, IVUS, and selective digital subtraction angiography were performed on 31 extracranial carotid arteries of 27 patients (mean age, 52 years; age range, 17 to 75 years) undergoing neuroendovascular interventions. The atherosclerotic lesions were registered, and quantitative measurements of plaque thickness, luminal diameters, and diameter stenosis were independently performed for the imaging modalities.

Results—Among 170 arterial segments analyzed, IVUS revealed a total of 48 atherosclerotic lesions (mean diameter stenosis, 17%; range, 4% to 40%), only 25 of which were depicted on digital subtraction angiography. Analysis of the axial source images of TOF MRA resulted in sensitivity of 77% to 83% and specificity of 71% to 80% in lesion depiction for the 2 readers with reference to IVUS. The values of diameter stenosis measured from MRA and IVUS were closely interrelated (r=0.53 to 0.61, P<0.001).

Conclusions—Three-dimensional TOF MRA is feasible and moderately accurate for evaluation of mild atherosclerotic changes of carotid arteries. (Stroke. 1999;30:827-833.)

Key Words: angiography ■ carotid artery diseases ■ magnetic resonance angiography ■ ultrasonography, interventional

T rials verifying efficacy of medical treatment of atherosclerosis require accurate imaging that facilitates both correct identification of even minor atherosclerotic lesions and quantitative determination of incipient changes; a reliable and reproducible noninvasive imaging tool is required both for the initial diagnostic workup and for the follow-up phase after different conservative treatment interventions and epidemiological follow-up studies.

Despite its well-known limitations, contrast angiography is widely preferred as the standard method in evaluating the severity of atherosclerotic carotid stenosis. Angiography offers only indirect information on atherosclerotic lesions as a change in the luminal wall profile but provides no further information on composition of plaque material unless ulcerated or heavily calcified. Because of compensatory enlargement of the vessel, mild atherosclerotic plaques do not encroach on the lumen until the lesion occupies up to 40% of the combined arterial wall and lumen volume.1,2

Intravascular ultrasound (IVUS) is currently verified as the standard of reference for imaging normal and atherosclerotic coronary and peripheral vessel wall morphology.3-5 The utility of IVUS in carotid artery imaging in vivo has recently been reported.6 However, in addition to its limited availability and some technical disadvantages, IVUS is invasive, and there is a definite need for low-risk noninvasive imaging.

Three-dimensional time-of-flight magnetic resonance angiography (3-D TOF MRA) is widely available and a commonly used method to determine the severity of atherosclerotic stenosis of the carotid artery. MRA has proven to be accurate in assessing degree of stenosis,7-10 and promising preliminary results in characterization of heavy atherosclerotic lesions have been published.11 The utility of 3-D TOF MRA in direct visualization of mild atherosclerotic lesions and intraplaque morphology is still not well known.

The purpose of this study was to evaluate the usefulness of 3-D TOF MRA in detection and quantification of mild atherosclerotic changes of carotid arteries, with reference to IVUS imaging and contrast angiography.
Subjects and Methods

Patients
Three-dimensional TOF MRA and IVUS imaging were performed on 31 carotid arteries of 27 voluntary patients after informed consent was obtained (15 males, 12 females; mean age, 52 years; age range, 17 to 75 years). IVUS imaging was performed in connection with various intracranial and extracranial endovascular interventions, including embolization of cerebral artery aneurysms (n = 7), arteriovenous malformations (n = 14) or tumors (n = 1), balloon angioplasty of the middle cerebral artery (n = 3), and test occlusions (n = 2). The patients had no history of ischemic cerebrovascular events. The study protocol was approved by the ethical committee of the hospital.

Magnetic Resonance Angiography
MRA (1.5 T, Siemens Magneton SP4000 and Vision) was performed with a neck coil within 2 days of the endovascular procedure. Axial 3-D TOF MRA sequences (repetition time 33 ms, echo time 8.0 ms, flip angle 20°, effective slice thickness 0.8 to 1.5 mm, field of view 200 mm, 256 × 512 matrix) were performed covering both the carotid bifurcations for a segment extending ≥30 mm cranially and caudally from the flow divider. Acquisition time for TOF MRA was 9 minutes. Multiplanar-reformatted (MPR) and maximum-intensity-projection images through the carotid bifurcation were routinely obtained, but only the axial source images were used for the evaluation of the present study. Theoretical in-plane resolution was 0.78 × 0.39 mm.

IVUS and Contrast Angiography
We performed IVUS with a 3.5-F, 30-MHz imaging catheter (Sonos; Hewlett Packard) using a mechanical transducer (Medi-tech/Boston Scientific) through a 7F multipurpose or right coronary guiding catheter. By the use of digital road mapping control, the IVUS catheter was introduced into the internal carotid artery (ICA) over a 0.018-inch guide wire. Imaging was registered on a super-VHS tape while the catheter was slowly pulled backward manually from the ICA to the proximal part of the common carotid artery (CCA). Gentle manipulation of the catheter was applied to keep the probe positioned as centrally as possible. To register the exact location of the probe within the artery, 7 to 10 single x-ray exposures were obtained in the same projection during the imaging, and the corresponding time points were marked with annotations in the IVUS equipment software; for MRA axial source images and for DSA, the MRA source images were accomplished in these defined levels.

Image Reading
The DSA images and the single x-ray exposures were first read to determine the longitudinal position of the individual axial levels of IVUS. All IVUS videotapes were interpreted by 2 vascular radiologists with prior experience of peripheral and coronary artery IVUS. Stenotic lesions were registered, and focal areas with very low signal intensity were interpreted as calcification. A detailed description of IVUS reading is presented elsewhere. One of the radiologists also read the DSA films 6 months later, measured the diameter stenosis, and registered calcifications of the lesions. The MRA studies were registered, and focal areas with very low signal intensity were interpreted as calcification.

To determine the intraobserver reproducibility, one radiologist read the MRA axial source images twice with an interval of 3 months. The image quality for both IVUS and MRA was graded as good, satisfactory, or poor, and the reason for this, if evident, was defined.

Measurements
The imaged portion of the extracranial carotid artery was divided into 4 segments: (1) the ICA above the bulb area, ie, the distal ICA; (2) the ICA bulb, while in cases without unequivocal anatomic bulb widening, the ICA bulb was defined as covering a segment 0 to 20 mm above the flow divider; (3) the carotid bifurcation 0 to 10 mm below the flow divider; and (4) the CCA 10 to 50 mm below the flow divider. Image analysis and the measurements for each artery were routinely performed at 1 or 2 axial levels within each segment.

The exact longitudinal position of the IVUS probe was determined by calculating the distance of the probe from the upper edge of the carotid bifurcation (flow divider) in the single x-ray image. The corresponding axial levels of MRA source images were identified on the basis of the distance from the position of the flow divider within error limits of 0.9 mm. Quantitative measurements of IVUS and MRA source images were accomplished in these defined levels.

Luminal diameters and thickness of the plaques were measured on IVUS during the systolic phase at a single freeze video image. The luminal caliber was defined as the mean value of 2 perpendicular inner diameters, and the plaque thickness was gauged at the thickest site of the lesion on both IVUS and MRA images. The smallest bisecting luminal diameter at the site of tightest stenosis and the reference diameter from the outer edge of the arterial wall at the same site were measured. For IVUS, measurement of the percent stenosis and the thickness of plaques was performed with the equipment software; for MRA axial source images and for DSA, measurement was performed with a digital micrometer at a conventional view box. For DSA, the stenosis was measured according to the European Carotid Surgery Trial criteria, analogous to the IVUS and MRA measurements.

Statistical Analysis
For statistical comparison of the continuous MRA and IVUS variables, the Pearson correlation coefficient was calculated. To test intraobserver and interobserver consistency of interpretation, the mean difference of the paired observations was calculated. To assess the diagnostic performance of MRA, sensitivity, specificity, and overall accuracy of the dichotomized stenosis measurements were calculated with IVUS used as a standard. The correspondence between MRA and IVUS classifications with nominal scale variables was given as percent agreement.

Results
IVUS examinations were successfully completed in all 27 patients without complications or side effects. A total of 170
TABLE 1. Findings on IVUS and MRA of 170 Analyzed Levels in 31 Carotid Arteries

<table>
<thead>
<tr>
<th>Finding</th>
<th>IVUS</th>
<th>Reader 1</th>
<th>Reader 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>122</td>
<td>94</td>
<td>108</td>
</tr>
<tr>
<td>Atherosclerotic lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>76</td>
<td>62</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA, above bulb</td>
<td>6</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>ICA, bulb</td>
<td>19</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>Bifurcation</td>
<td>22</td>
<td>26</td>
<td>25</td>
</tr>
<tr>
<td>CCA</td>
<td>1</td>
<td>10</td>
<td>8</td>
</tr>
</tbody>
</table>

Atherosclerotic Findings on IVUS and DSA
Of 170 levels analyzed in the 31 carotid arteries, a total of 48 atherosclerotic lesions were recognized on IVUS (Table 1). In 7 patients, no atherosclerotic changes were registered. Forty-three of the lesions were eccentric, and 5 were concentric. The mean diameter stenosis of the atherosclerotic lesions was 17% (range, 4% to 40%). Thirteen of the lesions caused stenosis <10%, and 14 lesions caused stenosis >20%.

DSA revealed 25 atherosclerotic lesions with mean diameter stenosis of 17% (range, 10% to 32%).

Image Quality
The overall image quality of IVUS was good in all patients except in one case of compromised quality due to technical reasons. In 7 arteries there was difficulty in visualization of the fading opposite side of the arterial wall at the level of carotid bifurcation, causing some uncertainty in the assessment of arterial wall morphology. There was no specific artifact that degraded study analysis. The flow divider was accurately identified at IVUS in every carotid artery.

The quality of 3-D TOF MRA axial source images was assessed as good in 64% (109/170), satisfactory in 22% (38/170), and poor in 14% (23/170) of the images. The poor quality was caused by signal loss and inhomogeneity in slices located at the periphery of the imaging slab (13/23), by motion artifacts (8/23), or by turbulent flow (2/23). All the images were included in the study.

Reproducibility of MRA Image Reading
MRA diameter stenosis measurements (n=170) performed by 2 readers correlated closely (r=0.61, P<0.001). The mean difference between the measured diameter stenosis by the 2 readers was 2.9% (SD, 9.0%). Two repeated readings of the diameter stenosis on MRA by the same radiologist denoted similar correlation (r=0.58, P<0.001), with a mean difference of 4.1% (SD, 9.4%). The plaque thickness measured by the 2 readers also correlated statistically very significantly (r=0.55), with a mean difference of 0.07 mm (SD, 0.86 mm)

between the results of the 2 observers. The readers agreed in regard to 65% of the lesions for the presence of calcification.

Correlation Between MRA, DSA, and IVUS Measurements
All stenoses detected by DSA were also diagnosed on MRA. Pearson correlation coefficients between DSA and MRA for these lesions were 0.38 and 0.37 (P<0.001) for the 2 readers.

Measurements of the luminal diameters on MRA and IVUS (n=170) correlated closely (r=0.91, P<0.001), and the mean lumen diameters obtained by the 2 modalities were almost equal (mean±SD difference, 0.01±0.7 mm). The correlations did not differ remarkably at the various arterial segments. Measurements of plaque thickness from MRA and IVUS also correlated statistically very significantly: correlation coefficients for the 2 readers were 0.28 to 0.64 (P<0.001) (Table 2).

Diameter stenosis measured from IVUS and MRA axial source images correlated closely (r=0.53 to 0.61, P<0.001) for the 2 readers. The diagnostic performance of MRA is shown in Table 3, in which we calculated sensitivity, specificity, and overall accuracy for stenosis detection using various cutoff points and using IVUS as a standard. Table 3 indicates that up to 100% sensitivity was reached by 1 reader for detection of stenoses >20% on IVUS at the expense of an increasing number of false-positive findings. Analysis of the false-positive findings on MRA showed that these were primarily due to artifacts caused by turbulent flow near the arterial wall (Figure 2).

Assessment of Plaque Calcification
Altogether 29 lesions with calcification were registered on IVUS, none of which were detected on DSA. Specificity of the false-positive findings on MRA showed that these were primarily due to artifacts caused by turbulent flow near the arterial wall (Figure 2).

TABLE 2. Pearson Correlation Coefficient Between MRA and IVUS of Measurements from Arterial Segments (n=170) and Interobserver Correlation for MRA Reading

<table>
<thead>
<tr>
<th>Analyzed</th>
<th>Reader 1</th>
<th>Reader 2</th>
<th>Interobserver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal diameter</td>
<td>0.91</td>
<td>0.61</td>
<td>0.61</td>
</tr>
<tr>
<td>Diameter stenosis</td>
<td>0.61</td>
<td>0.53</td>
<td>0.61</td>
</tr>
<tr>
<td>Plaque thickness</td>
<td>0.64</td>
<td>0.28</td>
<td>0.55</td>
</tr>
</tbody>
</table>

P<0.001.

TABLE 3. Diagnostic Performance of 3-D TOF MRA for Detection of Mild Atherosclerotic Lesions With Reference to IVUS Using Various Values of Diameter Stenosis as Cutoff Point Between Normal and Abnormal Finding

<table>
<thead>
<tr>
<th>Cutoff Point</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0% vs &gt;0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reader 1</td>
<td>83% (40/48)</td>
<td>71% (87/122)</td>
<td>74% (127/170)</td>
</tr>
<tr>
<td>Reader 2</td>
<td>77% (37/48)</td>
<td>80% (97/122)</td>
<td>79% (134/170)</td>
</tr>
<tr>
<td>&lt;10% vs ≥10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reader 1</td>
<td>86% (31/36)</td>
<td>67% (90/134)</td>
<td>71% (121/170)</td>
</tr>
<tr>
<td>Reader 2</td>
<td>83% (30/36)</td>
<td>76% (102/134)</td>
<td>78% (132/170)</td>
</tr>
<tr>
<td>&lt;20% vs ≥20%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reader 1</td>
<td>93% (13/14)</td>
<td>60% (94/156)</td>
<td>63% (107/170)</td>
</tr>
<tr>
<td>Reader 2</td>
<td>100% (14/14)</td>
<td>69% (108/156)</td>
<td>72% (122/170)</td>
</tr>
</tbody>
</table>
MRA for detection of calcifications with reference to IVUS was high (79% to 95%) for the 2 readers, but sensitivity was poor (17% to 52%). The platelike, heavy calcifications were constantly detected on TOF MRA axial source images, while the smaller, disseminated lesions were frequently missed (Figures 1, 3, 4, and 5).

**Discussion**

The rapid development of imaging modalities for atherosclerotic disease has recently shown promise in characterizing intraluminal morphology of carotid artery stenosis.\(^6\)\(^{,16}\) Color-coded Doppler ultrasound (as well as power Doppler) is the most widely used technique to screen atherosclerosis. It is very useful in noninvasive determination of the degree of stenosis and also evaluates plaque characteristics in routine clinical use.\(^17\) Unfortunately, calcification of lesions may seriously disturb this evaluation and diminish the value of percutaneous ultrasound examination.\(^18\)\(^{–20}\) Furthermore, high extracranial lesions are out of range of conventional US. Spiral CT facilitates accurate diagnosis of carotid artery stenosis and is very sensitive for detection of calcifications, but it does not provide sufficient contrast to depict other intraluminal morphology.\(^21\)\(^^{,22}\) In preliminary studies, MRI with spin-echo sequences allows identification of collagenous cap lesion with lipid core,\(^16\)\(^{,23}\)\(^{,24}\) but MRI by itself relieves limited spatial resolution, and adjunctive MRA is almost invariably needed.

Benefits of 3-D TOF MRA techniques in the extracranial carotid imaging include simultaneous ability to assess the degree and the extension of the stenosis and to gain information about the arterial wall. On the other hand, its sensitivity to motion artifacts and progressive in-plane spin saturation artifacts occasionally degrades image quality.\(^25\) Despite these limitations, good diagnostic performance of 3-D TOF MR angiography with the use of longitudinal MPR and maximum-intensity-projection reconstructions in the diagnosis of stenotic lesions of carotid arteries has been reported in several studies.\(^7\)\(^{–10}\) In epidemiological studies, MRA may offer better postprocessing facilities and better observer-related repeatability than conventional US, especially since the anatomic location of the lesion is more accurately defined on MR than on external US imaging. In clinical practice, 3-D
TOF MRA is also very useful as a complementary technique for gadolinium-enhanced MRA of carotid arteries. 26 IVUS is widely used in coronary and peripheral arteries for diagnosis and characterization of atherosclerotic lesions. In a recent study, 6 IVUS of the carotid arteries provided good intraobserver and interobserver repeatability; 2 readers disagreed in their assessment of atherosclerotic changes in 9%, and intraobserver variation was found in 7%. The 2 readers disagreed about 28% of the segments in the assessment of IVUS morphology of the lesions, correspondingly. Histopathologic and IVUS classifications of the plaque were in agreement in the majority of plaques (82%), and IVUS reliably depicted histopathologic “fibrous cap” lesions (Figures 3, 5, and 6). It has also been firmly established by several studies, in both coronary and peripheral arteries, that IVUS frequently reveals atherosclerotic changes in angiographically normal segments. 3,6,27 The present study showed that IVUS is feasible and safe in carotid arteries with mild atherosclerosis, which confirms previous results. 6 Further evidence of safety is mandatory before it is routinely used in severely atherosclerotic carotid arteries.

Three-Dimensional TOF in Quantification of Carotid Atherosclerosis

While most of the MRA literature evaluates the accuracy of identification of severely stenosed carotid arteries, the present study concentrates on identification of incipient atherosclerotic lesions. Diameter stenosis was <20% in more than two thirds (34/48) of the lesions, and only 52% (25/48) of the lesions were detected on DSA. We selected axial source images of 3-D TOF MR angiography for the principal analysis of these mild atherosclerotic changes instead of image reconstructions to maximize sensitivity and to facilitate comparison with IVUS, which provides basically 2-dimensional axial data.

Three-dimensional TOF MRA depicted all stenotic lesions of the carotid arteries evident on DSA. Moreover, analysis of the axial source images revealed several additional changes not seen on DSA. Sensitivity of 3-D TOF MRA in the diagnosis of even the mildest atherosclerotic changes with reference to IVUS was good: 86% and 83% for the 2 readers for detection of lesions of ≥10% diameter stenosis. The usefulness of MRA suffered from an excess of false-positive findings (40% to 49%). This was mostly due to flowing artifacts next to the luminal wall, which were mistaken for arterial wall thickening. These phenomena usually appeared eccentrically at the outer curve of the vessel wall and frequently had a relatively high signal intensity. The most severe misinterpretation due to flow artifact in MRA was as high as 40% and 31% for the 2 readers in the same ICA, where no stenosis was detected on IVUS. A meticulous analysis of MPR reconstructions can occasionally reveal the artifactual nature of this kind of finding (Figure 2).

Three-Dimensional TOF MRA in Characterization of Morphology of Atherosclerotic Lesions

Few previous studies provide information about the morphological classification of atherosclerotic plaques in TOF MRA, especially with correlation to histopathologic analysis. Wildy et al 13 used 3-D TOF MRA to analyze plaque composition of severely diseased arteries before endarterectomy by using contrast-to-noise ratios (CNRs), in which the signal intensity of sternocleidomastoid muscle and the signal intensity of air were given as references in the equation. The histological
findings of postendarterectomy plaque composition were compared with CNR values with the result, although with a certain amount of disagreement, that heterogeneous plaques (mixed plaques) had the same signal intensity as surrounding muscle tissue (CNR value of zero). Furthermore, tissues having negative CNR values, such as calcium, were hypointense, and those with positive CNR values, such as intraplaque hemorrhage, were hyperintense. Wildy et al noted that these 3 types of plaque contents—calcification, hemorrhage, and mixed composition—and flowing blood all had distinct ranges of CNR that had no overlap.

In a preliminary analysis of the present study, we compared plaque characterization of MRA with reference to IVUS. Classification of intraplaque morphology was based on knowledge of MRA axial source images and T1-weighted spin-echo images, and analysis of IVUS was based on criteria established by several authors. In our experience, visual analysis of MRA source images provided poor and inconsistent differentiation of fibrotic and soft constituents of mild atherosclerotic lesions with reference to IVUS. In our previous study we found ≈82% agreement in morphology of carotid plaques between IVUS and histopathology, and in the absence of absolute histopathologic reference in the present study we restrained from further detailed evaluation of plaque characterization by 3-D TOF MRA.

It is firmly established that IVUS reliably detects macroscopic intraplaque calcifications with reference to histopathologic findings. In our study, MRA diagnosed very specifically (79% to 95%) intraplaque calcifications with reference to IVUS, but at the expense of a large count of missed ones. While IVUS is sensitive even for punctate calcifications, small calcifications were missed on MRA because of the more limited spatial resolution. On the other hand, none of the calcifications was detected on DSA.

We found that some fibrous intimal thickening seen on IVUS were very hypointense on MRA and were mistakenly interpreted as calcifications. According to the preliminary studies of von Ingersleben et al on MRI, a fibrous plaque appeared darker on T1-weighted and proton-density–weighted images when the cells had a layered appearance. This might suggest a similar explanation for the varying signal intensity on TOF MRA. On the other hand, the identification of calcified and fibrous plaques on TOF MRA might be as valuable because they probably are more stable. O’Holleran et al used external US and found no strokes in patients with calcified plaques that resulted in stenosis of the carotid bifurcation to <75% in diameter, whereas the risk for stroke was 10% if the plaque was soft.

Two of the patients with intracranial arteriovenous malformations died within a short period after imaging. Carotid arteries of these patients were excised and available for histopathologic studies. Histopathologic findings of arterial wall appearance and plaque morphology were equal to in vivo IVUS findings. However, MRA images were more demonstrative at the carotid bifurcation than IVUS images, where the whole arterial wall circumference is not always totally gained in a single freeze image (Figure 5).

In addition to use in epidemiologic follow-up studies and for verification of the efficacy of different conservative treatment interventions, a potential application of 3-D TOF MRA might be the observation of patients with calcified but only mildly or moderately stenosed carotid arteries. Extensive draping calcification often jeopardizes evaluation of accompanying plaque formation and impairs reliability of stenosis determination on Doppler US imaging. In contrast, macroscopic calcification of an atherosclerotic lesion offers a good landmark for TOF MRA for serial imaging, without impairing accurate measurements of the plaque burden.

To summarize, quantitative analysis of axial source images of 3-D TOF MRA seems accurate and reproducible enough to facilitate serial follow-up of mild atherosclerotic changes of human carotid arteries in vivo. Visual analysis may suggest the presence of intraplaque calcifications, but the ability of the imaging modality to characterize other intraplastral morphology requires further studies with histopathologic correlation.

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