Reproducibility of Fibrous Cap Status Assessment of Carotid Artery Plaques by Contrast-Enhanced MRI

Robert M. Kwee, MD; Jos M.A. van Engelshoven, MD; Werner H. Mess, MD; Johannes W.M. ter Berg, MD; Floris H.B.M. Schreuder, MD; Cees L. Franke, MD; Arthur G.G.C. Korten, MD; Bé J. Meems, MD; Robert J. van Oostenbrugge, MD; Joachim E. Wildberger, MD; Marianne E. Kooi, PhD

Background and Purpose—Reproducibility in identifying the fibrous cap (FC) of carotid artery plaques by noncontrast-enhanced MRI has been shown to be poor. The objective of this study was to assess the reproducibility of multisequence MRI, including contrast-enhanced images, in assessing FC status.

Methods—Forty-five symptomatic patients with 30% to 69% carotid artery stenosis underwent a multisequence MRI protocol, which included contrast-enhanced images. FC status (ie, discrimination between fibrotic and/or calcified plaques, plaques with a lipid-rich necrotic core and an intact and thick FC, and plaques with a lipid-rich necrotic core and a thin and/or ruptured FC) was independently assessed by 3 observers of which one also scored all images on a different occasion. Linear weighted kappa coefficients (κ) were calculated as indicators of inter- and intraobserver agreement.

Results—On a per-slice basis, interobserver agreement was good (κ=0.60, 0.64, and 0.71), whereas intraobserver agreement was very good (κ=0.86). On a per-plaque basis, interobserver agreement was good (κ=0.64, 0.69, and 0.78), whereas intraobserver agreement was very good (κ=0.96).

Conclusion—This study found good interobserver and very good intraobserver agreement in assessing FC status of carotid artery plaques. Future studies are warranted to determine the predictive value of FC status assessment by multisequence MRI, including contrast-enhanced images, on the occurrence of (recurrent) cerebral ischemic events. (Stroke. 2009;40:3017-3021.)

Key Words: carotid plaque ■ fibrous cap ■ magnetic resonance imaging ■ stroke

The fibrous cap (FC) is a layer of connective tissue separating the lipid-rich necrotic core (LRNC) of the atherosclerotic plaque from the carotid artery lumen. Rupture of the FC exposes the thrombogenic LRNC to flowing blood, which may result in arterial thrombus formation and/or cerebral embolization.1 Assessment of FC status may identify patients at risk for stroke, which may lead to better patient selection for surgical intervention. There is therefore a need for a reliable method to assess FC status in vivo. Reproducibility in identifying FCs by non–contrast-enhanced (CE) MRI has been shown to be poor.2 Reproducibility may be improved by using CE MRI, because the FC of carotid plaques enhances with gadolinium-based contrast agents.3 Therefore, the objective of this study was to assess reproducibility of multisequence MRI, including CE images, in assessing FC status in vivo.

Methods

Patients
Forty-five patients (27 male; mean age, 70.8±9.7 years), who were diagnosed by a neurologist as having amaurosis fugax, transient ischemic attack, or minor stroke within 3 months before inclusion, and an ipsilateral 30% to 69% carotid artery stenosis, as determined with duplex ultrasonography, were included. This study was approved by the local medical ethics committee and all patients gave written informed consent.

MRI Protocol
All MRI examinations were performed on a 1.5-T whole-body imager (Intera 11.1.4.4; Philips Healthcare, Best, The Netherlands). For optimal imaging results, patients were positioned in a head holder. A dedicated radiofrequency surface coil with a diameter of 47 mm (Philips Healthcare) was used for unilateral carotid plaque imaging on the symptomatic side. Four MR pulse sequences (Table 1) were obtained around the carotid bifurcation so that the plaque...
was imaged within 9 transverse slices. All images were obtained shortly after each other. Before obtaining the postcontrast T1-weighted turbo spin-echo (TSE) images, all patients were intravenously injected with 0.1 mmol/kg body weight of gadopentate dimeglumine (Magnevist; Bayer Schering Pharma AG, Berlin, Germany).

Table 1. Relevant Parameters of the 4 MR Pulse Sequences

<table>
<thead>
<tr>
<th>Scan Parameters</th>
<th>3-Dimensional T1-Weighted TFE</th>
<th>3-Dimensional Time-of-Flight</th>
<th>Pre- and Postcontrast*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TR/TE, ms</td>
<td>10.3/4.4</td>
<td>23/3.9</td>
<td>1 heartbeat/18</td>
</tr>
<tr>
<td>Inversion prepulse</td>
<td>Yes</td>
<td>No</td>
<td>Double inversion-recovery</td>
</tr>
<tr>
<td>T1, ms</td>
<td>900</td>
<td>Not applicable</td>
<td>1</td>
</tr>
<tr>
<td>Flip angle</td>
<td>15°</td>
<td>25°</td>
<td>90°</td>
</tr>
<tr>
<td>NSA</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Profile order</td>
<td>Linear</td>
<td>Not applicable</td>
<td>Linear</td>
</tr>
<tr>
<td>Fat suppression</td>
<td>No</td>
<td>No</td>
<td>Spectral selection-attenuated inversion recovery</td>
</tr>
<tr>
<td>Field of view, mm</td>
<td>100×80</td>
<td>100×80</td>
<td>100×80</td>
</tr>
<tr>
<td>Matrix size</td>
<td>256×163</td>
<td>256×205</td>
<td>256×205</td>
</tr>
<tr>
<td>In-plane resolution, mm</td>
<td>0.39×0.49</td>
<td>0.39×0.39</td>
<td>0.39×0.39</td>
</tr>
<tr>
<td>Slice thickness, gap, mm</td>
<td>3.0, 0</td>
<td>3.0, 0</td>
<td>2.5, 0.5</td>
</tr>
<tr>
<td>Other</td>
<td>Shot interval time 3000 ms, TFE factor 163</td>
<td>Echo train length 9</td>
<td></td>
</tr>
</tbody>
</table>

NSA indicates number of signal averages; TFE, turbo field-echo.

*The postcontrast T1-weighted TSE sequence was obtained 7 to 8 minutes after intravenous administration of 0.1 mmol/kg body wt of gadopentate dimeglumine (Magnevist; Bayer Schering Pharma AG, Berlin, Germany).

†T1 was adjusted according to heart rate and postcontrast T1 relaxation time of blood.

Image quality was assessed by one observer (R.M.K.) using a 4-point scale (excellent, good, average, poor) based on signal-to-noise quality and presence or absence of artifacts. Images of poor quality were also excluded from analysis. Three observers (R.M.K., J.M.A.v.E., M.E.K.) with 2, 8, and 8 years of experience in carotid plaque analysis by MRI, respectively, independently evaluated the data sets. Two months after the first reading, one observer (R.M.K.) re-evaluated all MR images in random order blinded to the results of the first reading session. The algorithm used for the assessment of LRNC and FC status was based on previous studies and is presented in Figure 1. First, presence or absence of LRNC (including possible intraplaque hemorrhage) was assessed. On the T1-weighted turbo field-echo (TFE) image, LRNC was defined as an area of high signal intensity in the bulk of the plaque using signal intensity of the adjacent sternocleidomastoid muscle as reference.

**Image Review**

Coregistered MR images were evaluated using dedicated software for vessel wall analysis (VesselMASS; Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands). In a few cases, slices were manually repositioned to achieve optimal coregistration in the in-plane and longitudinal direction using the position of the carotid artery, internal jugular vein, sternocleidoid muscle, and carotid bifurcation as landmarks. Slices of which the MRI sequences did not coregistrate were excluded from analysis.

**Figure 1. Algorithm used to assess FC status.** *Regions of dense calcification might also demonstrate little enhancement, but these were identified as areas with hypointense signals (relative to the signal of the adjacent sternocleidomastoid muscle) on ≥2 MRI sequences.*
Statistical Analysis

Degree of inter- and intrarobserver agreement for distinguishing among (in rank order) (1) fibrotic and/or calcified tissue; (2) LRNC with an intact and thick FC; and (3) LRNC with a thin and/or ruptured FC was calculated by using linear weighted kappa ($\kappa$) statistics $^6$ both on a per-slice and on a per-plaque basis. The linear weighted $\kappa$ reflects the degree of agreement between observers and can range from 0 (no agreement) to 1.00 (perfect agreement). $\kappa$ values 0.20, 0.21 to 0.40, 0.41 to 0.60, 0.61 to 0.80, and 0.81 to 1.00 were considered to indicate poor, fair, moderate, good, and very good agreement, respectively. $^7$ Statistical analyses were executed using dedicated software (SPSS, Version 12.0, SPSS Inc, Chicago, Ill).

Results

Forty-seven consecutive patients underwent the MRI protocol. Two patients were excluded, because all their MR images could not be used for analysis due to poor image quality and incomplete MRI examination, respectively. Eventually, 45 patients (27 male; mean age, 70.8 $\pm$ 9.7 years) were included, resulting in $45 \times 9 = 405$ slices. Fourteen slices of 6 patients that had poor image quality and 9 slices of 7 patients of which either corresponding T1-weighted TFE, time-of-flight, pre- or postcontrast T1 TSE images did not coregistrate were excluded from analysis (5.7% of all slices). Frequencies of MRI findings for each observer, on a per-slice and on a per-plaque basis, are displayed in Table 2. On a per-slice basis, interobserver agreement in FC status assessment was good ($\kappa=0.60 [95\% CI, 0.52 to 0.69], 0.64 [95\% CI, 0.56 to 0.72], and 0.71 [95\% CI, 0.64 to 0.79]$), whereas intraobserver agreement was very good ($\kappa=0.86 [95\% CI, 0.80 to 0.92]$). On a per-plaque basis, interobserver agreement was good ($\kappa=0.64 [95\% CI, 0.43 to 0.85], 0.69 [95\% CI, 0.49 to 0.90], and 0.74 [95\% CI, 0.57 to 0.91]$), whereas intraobserver agreement was very good ($\kappa=0.96 [95\% CI, 0.87 to 1.00]$).

Discussion

The present study shows that, by using multisequence MRI, including CE images, FC status of carotid artery plaques can be assessed with good inter- and very good intraobserver agreement both on a per-slice and per-plaque basis.

Cai et al $^3$ showed the capability of CE MRI in quantitatively measuring the dimensions of the intact FC; they found a moderate to good correlation between FC area and length measurements of in vivo CE MRI and matched histological sections. They also found excellent inter- and intraobserver reproducibility in FC area and length measurements by using CE MRI. However, in their study, only locations with an intact FC at histology were evaluated. Locations with FC rupture or without LRNCs at histology were excluded from analysis. Reproducibility of FC status assessment (ie, discrimination between fibrotic and/or calcified plaques, plaques with a LRNC and an intact and thick FC, and plaques with a LRNC and a thin and/or ruptured FC) was not investigated by Cai et al. $^3$ Before applying CE MRI for FC status assessment in plaque imaging studies, its reproducibility should be investigated in all patients with carotid atherosclerosis regardless of final histological findings. The results of the present study indicate that reproducibility is good.

Observer variability in assessment of FC status may be declared by variation in degree of FC enhancement $^3$ and the
use of implicit thresholds. The use of new MRI sequences, which increase contrast between LRNC and the FC, may further improve reproducibility. MRI at higher field strengths may also improve reproducibility due to increased signal-to-noise ratio. In addition, improvement in signal-to-noise ratio at higher magnetic field strength can also be traded for increased spatial resolution, which could permit FC thickness measurements. The development of software that can (semi) automatically assess FC status may further enhance reproducibility. However, such methods also need to be validated with histology to investigate their accuracy.

Redgrave et al recently defined a quantitative histopathological measure of a ruptured FC for carotid plaques; they suggested a combination of a minimum FC thickness of <0.20 mm and a representative cap thickness of <0.50 mm as cutoff values. Because the spatial resolution on cross-sectional CE MR images was 0.39×0.39 mm in the present study, and because of partial volume effects and possible variation in degree of FC enhancement, we could not reliably apply these cutoff values. However, it still remains to be determined which threshold predicts the occurrence of ipsilateral cerebral ischemic events. Another shortcoming is that we did not have histological confirmation. This was not possible because the included patients were not operated on (because the benefit of CEA was unclear). However, particularly in patients with a moderate symptomatic carotid stenosis, in vivo assessment of FC status may be helpful in identifying vulnerable plaques.

Other imaging modalities that may be used to noninvasively assess FC status in vivo include ultrasonography (US) and CT. Devuyst et al found a good correlation between semiautomatic FC thickness measurements by US and those of corresponding carotid endarterectomy specimens. However, correlation between minimum FC thickness measurements and histology was lower than that of mean and maximum FC thickness, which could be caused by the resolution limits of the US probe, which was used in that study (in-plane resolution 0.30×0.40 mm). In addition, FC thickness measurements by US may be limited when there are plaque calcifications causing acoustic shadowing. Furthermore, although Devuyst et al reported good inter- and intraobserver agreement in their subset of 20 patients, it is well known that the acquisition and interpretation of US images remains observer-dependent. Wintemark et al recently showed the potential of CT to evaluate FC thickness; in their study of 8 symptomatic patients, they found a good correlation between automatic minimal FC thickness measurements on in vivo CT images (in-plane resolution 0.50×0.50 mm) and corresponding carotid endarterectomy sections. However, a potential limitation was that the automatic software they used was validated in the same patients in whom the thresholds were defined, which may have biased their results. In addition, FC thickness was defined as the radial distance to the most superficial core of nonconnective tissue, which also included calcifications. It is questionable whether this definition of FC thickness is correct; Redgrave et al, who performed the largest ever histological study of carotid endarterectomy specimens from symptomatic patients, defined the FC as a layer of connective tissue separating (only) LRNC from the lumen. Future studies should further explore which imaging modality (MRI, US, or CT), which acquisition methods, and which assessment methods achieve highest accuracy (using histology as reference standard) and reproducibility in assessing FC status in vivo. Subsequently, it should be investigated by prospective longitudinal studies which imaging modality is most effective in predicting cerebral ischemic events.

In conclusion, in the present study, we found good interobserver and very good intraobserver agreement in distinguishing between fibrotic and/or calcified plaques, plaques with a LRNC and an intact and thick FC, and plaques with a LRNC and a thin and/or ruptured FC. Future studies are warranted to determine the predictive value of FC status assessment by multisequence MRI, including CE images, on the occurrence of (recurrent) cerebral ischemic events.

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Disclosures
None.

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