Semiautomated Magnetic Resonance Imaging Assessment of Carotid Plaque Lipid Content

Karolina Skagen, MD,*† Kristin Evensen, MD,*‡ Helge Scott, MD, PhD,§ Kirsten Krohg-Sørensen, MD, PhD,‖ Svein Are Vatnehol, MSc,¶ Per Kristian Hol, MD, PhD,†¶ Mona Skjelland, MD, PhD,* and David Russell, MD, PhD*†

Background: The composition of a carotid plaque is important for plaque vulnerability and stroke risk. The main aim of this study was to assess the potential of semiautomated segmentation of carotid plaque magnetic resonance imaging (MRI) in the assessment of the size of the lipid-rich necrotic core (LRNC). *Methods:* Thirty-four consecutive patients with carotid stenosis of 70% or higher, who were scheduled for carotid endarterectomy, underwent a clinical neurological examination, Color duplex ultrasound, 3-T MRI with an 8-channel carotid coil, and blood tests. All examinations were performed less than 24 hours prior to surgery and plaques were assessed histologically immediately following endarterectomy. Plaques were defined as symptomatic when associated with ipsilateral cerebral ischemic symptoms within 30 days prior to inclusion. The level of agreement between the size of the LRNC and calcification on MRI to the histological estimation of the same tissue components, plaque echolucency on ultrasound, and symptoms was assessed. *Results:* The size of the LRNC on MRI was significantly correlated to the percentage amount of lipid per plaque on histological assessment ($P = .010$, $r = .5$), and to echogenicity on ultrasound with echolucent plaques having larger LRNC than echogenic plaques ($P = .001$, $r = –.7$). *Conclusions:* In this study, we found that semiautomated MRI assessments of the percentage LRNC in carotid plaques were significantly correlated to the percentage LRNC per plaque on histological assessment, and to echogenicity on ultrasound with echolucent plaques having larger LRNC than echogenic plaques. **Key Words:** Carotid stenosis—carotid magnetic resonance imaging—ischemic stroke—carotid ultrasound.

From the *Department of Neurology, Oslo University Hospital, Norway; †Institute of Clinical Medicine, University of Oslo, Norway; ‡Vestre Viken, Drammen Hospital, Norway; §Department of Pathology, Oslo University Hospital, Norway; ‖Department of Thoracic and cardiovascular surgery, Oslo University Hospital, Norway; and ¶The Intervention Centre, Oslo University Hospital, Norway.

Received August 28, 2015; revision received December 16, 2015; accepted January 29, 2016.

Source of funding: This work was supported by The Norwegian Health Association (6.2009.567).

Address correspondence to Karolina Skagen, MD, Department of Neurology, Oslo University Hospital, 0424 Oslo, Norway. E-mail: kskagen@ous-hf.no.

1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2016.01.043

Introduction

A significant proportion of thromboembolic strokes are caused by emboli from an atherosclerotic plaque at the carotid bifurcation. Two major randomized trials and additional analyses have shown that for patients with plaques causing 70%-99% stenosis in the carotid artery, thromboembolic strokes are effectively preventable by carotid endarterectomy (CEA).[1-3] Based on results from these trials, selection for revascularization in clinical practice today primarily involves assessment of the severity of luminal artery stenosis. It has, however, become increasingly clear that the degree of luminal stenosis alone is not the best predictor of stroke risk. Strokes may occur as a result of

nonstenotic carotid disease, and conversely, a non-negligible proportion of patients with significant carotid stenosis may remain completely asymptomatic throughout their lifetime. Developing new tools to identify patients at risk of stroke is therefore warranted.

Recent developments in magnetic resonance imaging (MRI) technology have shown promise regarding the identification of these high-risk plaque characteristics and the accurate discrimination between the specific histological subtypes of carotid plaques as proposed by the American Heart Association,[4-8] all of which include a lipid-rich necrotic core (LRNC) as a feature of plaque instability. Furthermore, with particular reference to LRNC, studies have shown that carotid plaques with larger LRNC at baseline are associated with both a significantly higher risk of plaque surface disruption and symptoms.[9,10] MRI of plaque composition is a relatively new technique, and studies to date have shown a high diversity in findings that may be due to the fact that different MRI protocols and techniques for the histological assessments have been used.[6,7] The majority of MRI studies of atherosclerotic plaques have relied on visual assessments of images with different contrast weighting. Visual plaque segmentation on MRI requires expertise, is time consuming, and produces results that are subject to interobserver variability.[11] Software allowing the automated MRI classification of plaque components may provide a less time-consuming, more objective, and reliable tool for the assessment of plaque content.[12,13] Replacing the visual segmentation with automated segmentation has therefore been a long-time goal.

The main aim of the present study was therefore to assess the level of agreement between the size of carotid plaque LRNCs using semiautomated MRI and histological assessments of the plaques immediately following endarterectomy. We also assessed the correlation between the size of the LRNC and carotid plaque ultrasound echogenicity and symptoms.

Materials and Methods

Patients

Thirty-four consecutive patients with internal carotid artery stenosis of 70% or higher, who were scheduled for CEA because of symptomatic carotid stenosis or as a stroke preventative measure prior to thoracic surgery, were included in the study. MRI was carried out within 24 hours of CEA and close to the last symptom (median 19 days, range 2-54 days). Plaques were defined as symptomatic when associated with ipsilateral cerebral symptoms (minor strokes, transitory ischemic attack, or amaurosis fugax) within 30 days prior to inclusion. Exclusion criteria were prior CEA or carotid stenting, carotid occlusion, vasculitis, malignancy, prior radiation therapy to the neck, treatment with immunomodulating drugs, and oncological disease.

All patients underwent a clinical neurological examination and registration of the following cardiovascular risk factors: cholesterol values, hypertension, diabetes, and coronary artery disease. The Regional Committee for Medical and Health Research Ethics approved the study and informed written consent was obtained from all patients.

MRI

All carotid arteries were imaged using a 3-T whole-body scanner (Achieva; Philips Healthcare, Best, The Netherlands) equipped with an 8-channel carotid coil (Philips/Shanghai Chenguang Medical Technologies, Shanghai, China). For each scan, the location of the carotid bifurcation was located using a 3D time-of-flight angiographic sequence, followed by 8 continuous slices using 2D turbo spin echo, proton density, T1 and T2 weighting, and fast field echo high-resolution 3D time-of-flight. The T1-weighted images were obtained before and after the injection of .2 mL/kg contrast agent (Dotarem; Guerbet, Paris, France). The imaging parameters were as follows: field of view, 160×160 mm; matrix, 268×260; image resolution, $.6 \times .6$; 2-mm slice thickness; and time to repetition/time to echo of 850/10, 3584/50, and 4600/20 ms for T1, T2, and proton density-weighted sequences, respectively. The total scan time per patient was 17-20 minutes.

Custom software (MRI-Plaque View; VP Diagnostics, Seattle, WA) was used for the automatic analysis of the MRI examinations for plaque content. The boundaries of the lumen, the outer vessel wall, and the different plaque components were automatically detected by the software using an automated classifier (morphology-enhanced probabilistic plaque segmentation algorithm).[12,14,15] This was followed by alignment of the other contrast weightings to the T1TW images before manual corrections were applied by a reader blinded to the results of other imaging modalities and clinical information. The software then calculated the absolute (in cubic millimeter) and relative (in percentage) volumes of the different plaque components. Plaque composition from 1.5-T cerebral magnetic resonance images derived using this software has been validated to correlate with histology[16] and results on 1.5 T have been shown to correlate highly with 3-T imaging.[12,14]

Necrotic core, calcification, hemorrhage, and fibrous tissue in each slice were summarized to give total plaque component volumes. The percentage plaque lipid content (LRNC), plaque calcification content, and intraplaque hemorrhage (IPH) were included.

Carotid Ultrasound

Color duplex ultrasound was performed with a General Electric Vivid 7 (General Electric, Horten, Norway) using a M12L probe (14 MHz) on both carotid arteries. The degree of stenosis was determined using peak systolic veloci-

ties according to the consensus criteria of the Society of Radiologists in Ultrasound.[17] Plaque echogenicity was assessed with the vessel lumen as the reference structure for defining echolucency, and the bright echo zone produced by the media–adventitia interface as the reference for defining echogenicity.[18-20] Echogenicity was classified as echolucent or echogenic by an experienced ultrasound examiner (K.S.) who was blinded to the results of MRI and histological findings.[18]

Carotid Plaque Processing and Histological Analysis

The plaques were removed at CEA en bloc (intact), fixed in 4% formaldehyde, decalcified in EDTA, and cut into 2- to 3-mm slices. After dehydration, the slices were embedded in paraffin and 5-µm histological slices were cut and stained with hematoxylin and eosin. The plaques were assessed by a pathologist and a research physician blinded to the clinical, MRI, and ultrasound findings. Each slice was evaluated with 120× magnification. Percentage lipid per slice was estimated and then added for all slices to give a total percentage lipid per plaque. The same estimation was done for calcification and fibrous tissue. Histological assessments were made on 16 slices from 4 plaques on 2 occasions more than 2 months apart to assess the reproducibility of findings. For this analysis, the amount of each tissue type was classified into 10 categories of 10% from 0%-10% up to 90%-100%. The results were assessed using kappa statistics.

Statistical Analysis

SPSS for Windows statistical software (version 18.0; SPSS Inc., Chicago, IL) was used for all data analyses. Student *t*-test or Mann-Whitney *U* test was used depending on the distribution of data. The chi-square test was used for analyzing contingency data. LRNC, calcification and hemorrhage on MRI, and the percentages of these tissue types on histological analysis were unequally distributed, and the coefficients of correlation were therefore calculated using the Spearman rank test. All statistical results were considered significant when the *P* value was less than .05.

Results

Baseline Patient Characteristics

Six patients were excluded because the MRI was suboptimal, leaving 28 patients for analysis. There were 19 males (67.6 ± 7 years) and 9 females (66.7 ± 8 years). Fourteen patients were symptomatic and 14 were asymptomatic according to the predefined cutoff of 30 days. There were no statistically significant differences between the symptomatic and asymptomatic patients with respect to age. There were significantly more males in the symptomatic group (12 patients) compared to the asymptomatic group (7 patients, $P = .05$). For symptomatic patients (n = 14), the mean time from last symptom to MRI was 14 days (ranging from 2 to 27 days) compared to 37.8 (range 32-54) days in the asymptomatic group. Patients in the asymptomatic group had significantly higher high-density lipoprotein cholesterol levels at 1.55 mmol/L compared to 1.17 mmol/L in the symptomatic group ($P = .03$). Plasma levels of leucocytes, C-reactive protein, total cholesterol, low-density lipoprotein cholesterol, and glucose were similar in the 2 groups. The clinical characteristics of the patients are shown in Table 1.

LRNC on MRI and Correlation to Histological Assessments

For the group as a whole, the percentage LRNC per plaque on MRI, which ranged from 0% to 46% (median 8.0%), was significantly correlated to the percentage LRNC on the histological specimens, which ranged from 8.30% to 83.33% (median 20.48%, $P = .01$, $r = .5$; Figs 1, 2).

The correlation between the percentage calcification per plaque on MRI (median 12.0%, range 1.80%-29.50%) and calcification on the histological assessments (median 5.1%, 0%-24.20%) did not reach statistical significance ($P = .073$).

When the histopathological assessments were repeated on 2 occasions more than 2 months apart, we found that the amount of lipid was in the same 10% category at both assessments for 11 of the 16 slices (69%, kappa = .69), and calcification was in the same 10% category at both assessments for 14 of 16 slices (87.5%, kappa = .88).

Plaque Composition on MRI and Correlation to Ultrasound Plaque Echogenicity

There was a significant correlation between the percentage LRNC in the plaques as measured by MRI and ultrasound plaque echogenicity. Plaques that were echolucent on ultrasound had larger LRNCs on MRI (median 24.6%, range 5.6%-46%) than echogenic plaques (median 4.5%, range 0%-18.3%, $P = .001$, $r = -.7$; Fig 3).

Plaque echolucency was also inversely correlated to increasing percentage hemorrhage on MRI with echolucent plaques having increased amounts of hemorrhage on MRI ($P = .034$, $r = -.4$).

Plaque Composition on MRI and Correlation to Symptoms

There was a trend toward a larger percentage of LRNC per plaque on MRI in symptomatic compared to asymptomatic patients, although this was not statistically significant ($P = .109$). The median percentage LRNC in plaques from symptomatic patients was 14.9% (range 1.3%-46.0%) compared to the median of 6.5% (range 0%-36.9%) in asymptomatic patients (Fig 4).

Table 1. *Patient clinical characteristics (n = 28)*

Characteristics	Symptomatic	Asymptomatic	*P*
Age (years)	68.6 ± 8	66.7 ± 6	.52
Sex, male*	12 (85.7)	7 (50)	.05
Days from symptoms to MRI†	14 (2-27)	37.8 (32-54)	
Statin treatment*	13 (92.8)	14 (100)	.33
Antihypertensive medication*	8 (57.1)	10 (71.4)	.60
Coronary artery disease*	6 (42.9)	5 (35.7)	.71
Diabetes*	3 (21.4)	2 (14.3)	.64
Leukocytes (10 × 9/L)			
CRP (mg/L)	8.2 ± 1.8	8.3 ± 2.3	.77
Cholesterol (mmol/L)	10.1 ± 28	11 ± 24	.89
LDL (mmol/L)	4.0 ± 1.37	4.6 ± .87	.41
HDL (mmol/L)	2.53 ± 1.34	2.6 ± 1.5	.92
Glucose (mmol/L)	1.17 ± .27	1.55 ± 1.3	.03
	6.17 ± .92	5.7 ± .32	.09

Abbreviations: CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MRI, magnetic resonance imaging; SD, standard deviation.

Values are given as mean ± SD.

*Number (percentage).

†Mean (range).

The percentage calcification and percentage hemorrhage per plaque on MRI were similar in symptomatic and asymptomatic patients. The median percentage calcification on MRI was 12.1% (range 1.90%-29.5%) in symptomatic compared to the median of 12.0% (range 1.8%-28.6%) in asymptomatic patients ($P = .22$). The median percentage hemorrhage on MRI was 4.75% (range 0%-24.2%) in symptomatic compared to the median of 3.25% (range 0%-16.9%) in asymptomatic patients ($P = .215$).

Discussion

In the present study, we investigated the potential of semiautomated MRI for the assessment of carotid plaque content. The main finding was that the algorithm used was accurate and can be potentially time saving in the MRI assessment of carotid plaques. We found that there was a good level of agreement between the percentage LRNC per plaque on semiautomated MRI and the

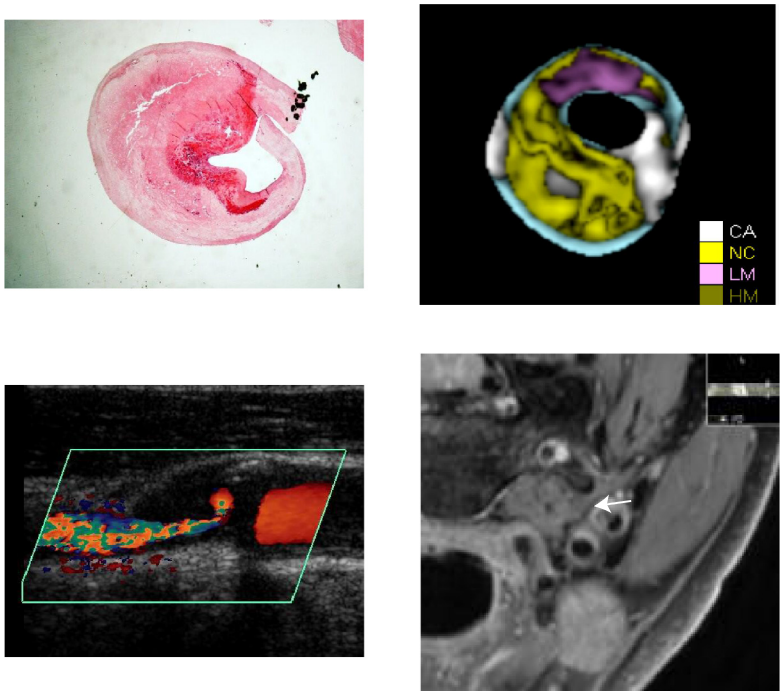

Figure 1. *Contrast enhanced axial T1-weighted magnetic resonance image with plaque in the internal carotid artery (arrow), segmented image, carotid ultrasound image, and histological slice of the plaque demonstrating the different plaque components. The segmented image shows different plaque components. Abbreviations: CA, calcium; HM, hemorrhage; LM, loose matrix; NC, necrotic core.*

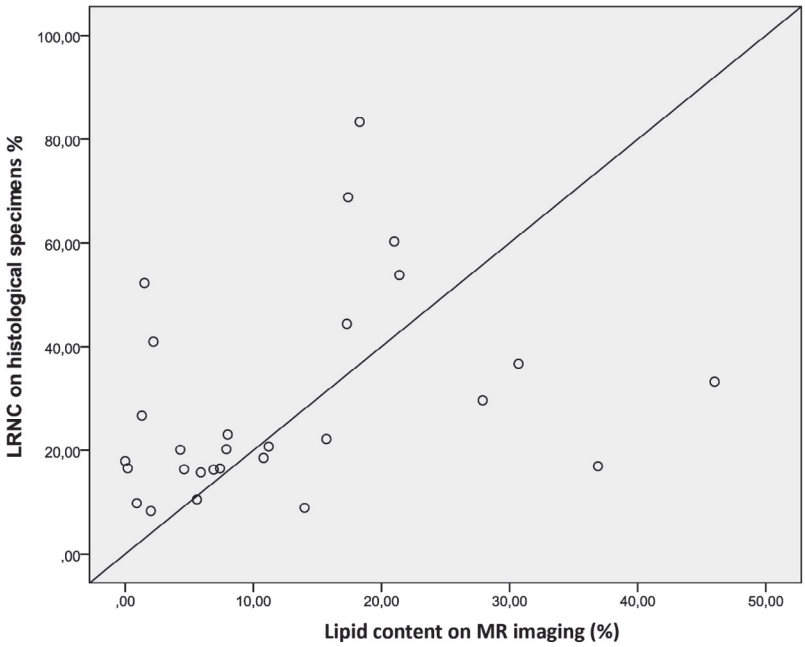

Figure 2. *Correlation between percentage area of LRNC on MRI and percentage LRNC on histological assessment* (P = .001). *Abbreviations: LRNC, lipid-rich necrotic core; MR, magnetic resonance.*

percentage LRNC per plaque on histological assessments. The percentage LRNC on MRI was also strongly correlated to plaque echogenicity on carotid ultrasound with echolucent plaques having larger LRNCs than echogenic plaques.

Previous studies have shown that semiautomated MRI assessments of carotid plaque content are possible, but these have lacked either validation of the MRI findings with histological plaque assessments[21] or information regarding the temporal relationship from symptoms to MRI.[22] Van't Klooster et al compared automatic and visual MRI assessments of carotid plaques in 40 patients and concluded that the volumes of different plaque components, obtained visually and automatically, were reasonably consistent for both hemorrhage and lipids but not for calcium.[23] Van't Klooster et al did not, however, include a comparison with histological findings. In the current study, we included a histological validation of the MRI findings and imaging was carried out within 24 hours of endarterectomy, which reduced the possibility that plaque composition could have changed in the interval between the 2 investigations.

In the current study, increased amounts of LRNC detected by MRI and histology had a strong, significant

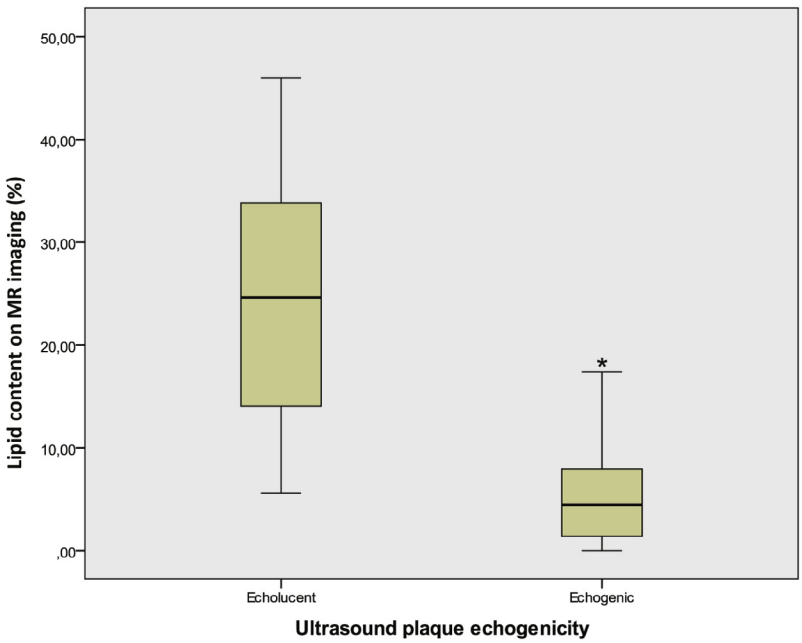

Figure 3. *Correlation of percentage LRNC on MRI and plaque echogenicity on carotid ultrasound* (P = .001). *Box plot shows the distribution of lipid content in patients with echogenic and echolucent plaques. The bottom and the top boxes represent the first and third quartiles. Horizontal lines in boxes represent the median (second quartile) and the whiskers the range limit. Median lipid content was 24.6% (range 5.6%-46%) in echolucent plaques compared to 4.5% (range 0%-18.3%) in echogenic plaques* (P = .001). *The* P *value is from a Mann–Whitney* U*-test. Abbreviations: LRNC, lipid-rich necrotic core; MR, magnetic resonance.*

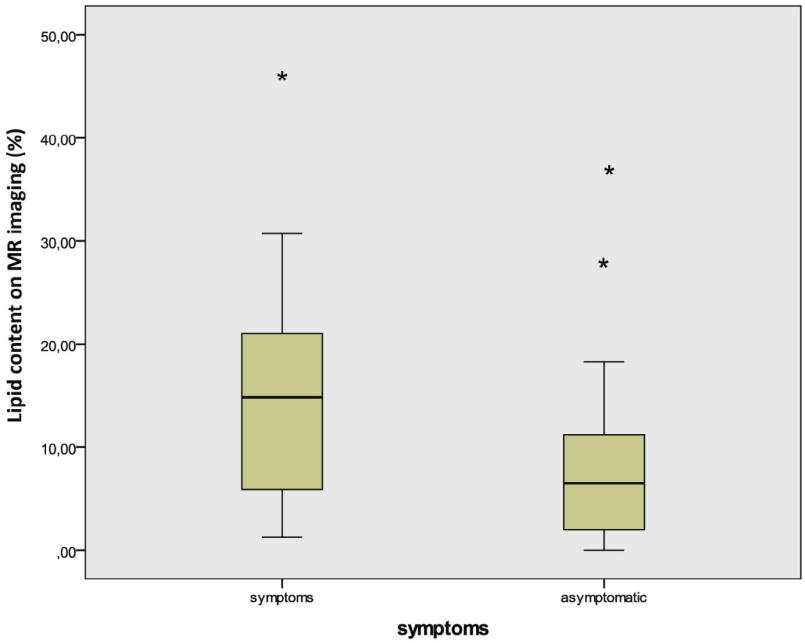

Figure 4. *Comparison of percentage LRNC on MRI in symptomatic and asymptomatic patients. Box plot shows the distribution of lipid content in symptomatic and asymptomatic patients. The bottom and the top boxes represent the first and third quartiles. Horizontal lines in boxes represent the median (second quartile) and the whiskers the range limit. Median LRNC on MRI was 14.9% (range 1.3%-46%) in symptomatic patients compared to 6.5% (range 0%-36.9%) in asymptomatic patients (P = .109). Abbreviations: LRNC, lipid-rich necrotic core; MR, magnetic resonance.*

correlation to plaque echolucency on carotid ultrasound, which is in agreement with previous studies.[18,24]

We found a poor correlation between plaque calcium content on MRI and histological assessments of calcium content, which has also been the case in other studies.[13,25] This lack of correlation of MRI and histology may be due to the fact that in some MRI sequences (time of flight), calcification can be difficult to separate from other plaque components such as the fibrous cap because they share the same signal intensity characteristics.[11,26] The use of postcontrast T1-weighted image sequence may improve calcium detection.[22] The prognostic value of plaque calcification for embolic risk is unclear, as only a few studies have shown a correlation between the amount of carotid plaque calcification and patient outcome.[27]

In the current study, we found that it was not possible histologically to distinguish actual IPH from hemorrhage caused by the surgical removal of the plaque. Correlation of IPH assessed by MRI and histology was therefore not possible.

There was a nonsignificant trend toward increased carotid plaque LRNC on MRI in symptomatic compared to asymptomatic patients (median percentage LRNC 14.9% in symptomatic versus 6.5% in the asymptomatic patients). Confirmation of such an association would require a larger patient population. Classification systems on LRNC size have not given a definite quantitative cutoff for a lipid core size for defining unstable plaques. However, plaques wherein the core occupies more than 25% of the total plaque volume have been considered unstable.[28-30] Interestingly, 2 patients labeled as asymptomatic in the present study had a plaque LRNC content higher than 25% at 27.9% and 36.9%, respectively. These 2 plaques were both echolucent on ultrasound and one of them had reported symptoms just outside the 30-day cutoff for being defined as symptomatic (at 32 days).

In the present study, we found that rapid automated carotid plaque analyses were accurate for the quantification of LRNC when compared to histology. The implementation of this automatic method into clinical practice would decrease both imaging time and the time used for postprocessing analysis.

The main limitation of the present study is the small sample size and our findings require validation by larger, prospective studies. Furthermore, the definition of symptoms used in the current study is based on patient history with the possibility of missing silent cerebral infarction. Further studies correlating MRI carotid plaque findings and symptoms should therefore include cerebral MRI. The main strengths of the study are the short time from last symptom to MRI and ultrasound, the fact that these investigations were performed within 48 hours of endarterectomy, and the histological assessments.

Conclusions

The present study provides evidence that semiautomated segmentation of carotid MRI can accurately measure LRNC size, which may be of help in assessing carotid plaque vulnerability and stroke risk. The validation of automated MRI methods for atherosclerotic plaque segmentation by large-scale studies would significantly reduce processing time and eliminate interobserver variability. This possibility would facilitate better pretherapeutic assessments of carotid atherosclerosis.

Acknowledgment: The authors thank Are Hugo Pripp, Department for Medical statistics, University of Oslo.

References

1. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet 1998;351:1379-1387.
2. Barnett HJ, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1998;339:1415-1425.
3. Rothwell PM, Eliasziw M, Gutnikov SA, et al. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. Lancet 2003;361:107-116.
4. Stary HC, Chandler AB, Dinsmore RE, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Arterioscler Thromb Vasc Biol 1995;15:1512-1531.
5. Parmar JP, Rogers WJ, Mugler JP 3rd, et al. Magnetic resonance imaging of carotid atherosclerotic plaque in clinically suspected acute transient ischemic attack and acute ischemic stroke. Circulation 2010;122:2031-2038.
6. Gupta A, Baradaran H, Schweitzer AD, et al. Carotid plaque MRI and stroke risk: a systematic review and meta-analysis. Stroke 2013;44:3071-3077.
7. den Hartog AG, Bovens SM, Koning W, et al. Current status of clinical magnetic resonance imaging for plaque characterisation in patients with carotid artery stenosis. Eur J Vasc Endovasc Surg 2013;45:7-21.
8. Cai JM, Hatsukami TS, Ferguson MS, et al. Classification of human carotid atherosclerotic lesions with in vivo multicontrast magnetic resonance imaging. Circulation 2002;106:1368-1373.
9. Takaya N, Yuan C, Chu B, et al. Association between carotid plaque and subsequent ischemic cerebrovascular events: a prospective assessment with MRI. Stroke 2006;37:818-823.
10. Underhill HR, Yuan C, Yarnykh VL, et al. Predictors of surface disruption with MR imaging in asymptomatic carotid artery stenosis. AJNR Am J Neuroradiol 2010;31:487-493.
11. Touze E, Toussaint JF, Coste J, et al. Reproducibility of high-resolution MRI for the identification and the quantification of carotid atherosclerotic plaque components: consequences for prognosis studies and therapeutic trials. Stroke 2007;38:1812-1819.
12. Kerwin WS, Liu F, Yarnykh V, et al. Signal features of the atherosclerotic plaque at 3.0 Tesla versus 1.5 Tesla: impact on automatic classification. J Magn Reson Imaging 2008;28:987-995.
13. Hofman JM, Branderhorst WJ, ten Eikelder HM, et al. Quantification of atherosclerotic plaque components using in vivo MRI and supervised classifiers. Magn Reson Med 2006;55:790-799.
14. Yarnykh VL, Terashima M, Hayes CE, et al. Multicontrast black-blood MRI of carotid arteries: comparison between 1.5 and 3 tesla magnetic field strengths. J Magn Reson Imaging 2006;23:691-698.
15. Yuan C, Mitsumori LM, Ferguson MS, et al. In vivo accuracy of multispectral magnetic resonance imaging for identifying lipid-rich necrotic cores and intraplaque hemorrhage in advanced human carotid plaques. Circulation 2001;104:2051-2056.
16. Cai J, Hatsukami TS, Ferguson MS, et al. In vivo quantitative measurement of intact fibrous cap and lipid-rich necrotic core size in atherosclerotic carotid plaque: comparison of high-resolution, contrast-enhanced magnetic resonance imaging and histology. Circulation 2005;112:3437-3444.
17. Grant EG, Benson CB, Moneta GL, et al. Carotid artery stenosis: gray-scale and Doppler US diagnosis—Society of Radiologists in Ultrasound Consensus Conference. Radiology 2003;229:340-346.
18. Mathiesen EB, Bonaa KH, Joakimsen O. Echolucent plaques are associated with high risk of ischemic cerebrovascular events in carotid stenosis: the tromsø study. Circulation 2001;103:2171-2175.
19. Nordestgaard BG, Gronholdt ML, Sillesen H. Echolucent rupture-prone plaques. Curr Opin Lipidol 2003;14:505-512.
20. Carotid artery plaque composition—relationship to clinical presentation and ultrasound B-mode imaging. European Carotid Plaque Study Group. Eur J Vasc Endovasc Surg 1995;10:23-30.
21. Adame IM, van der Geest RJ, Wasserman BA, et al. Automatic segmentation and plaque characterization in atherosclerotic carotid artery MR images. MAGMA 2004;16:227-234.
22. Liu F, Xu D, Ferguson MS, et al. Automated in vivo segmentation of carotid plaque MRI with morphology-enhanced probability maps. Magn Reson Med 2006;55:659-668.
23. van't Klooster R, Naggara O, Marsico R, et al. Automated versus manual in vivo segementation of carotid plaque MRI. AJNR Am J Neuroradiol 2012;33:1621-1627.
24. Gronholdt ML, Nordestgaard BG, Bentzon J, et al. Macrophages are associated with lipid-rich carotid artery plaques, echolucency on B-mode imaging, and elevated plasma lipid levels. J Vasc Surg 2002;35:137-145.
25. North American Symptomatic Carotid Endarterectomy Trial. Methods, patient characteristics, and progress. Stroke 1991;22:711-720.
26. Yuan C, Mitsumori LM, Beach KW, et al. Carotid atherosclerotic plaque: noninvasive MR characterization and identification of vulnerable lesions. Radiology 2001;221:285-299.
27. Hunt JL, Fairman R, Mitchell ME, et al. Bone formation in carotid plaques: a clinicopathological study. Stroke 2002;33:1214-1219.
28. Plasschaert H, Heeneman S, Daemen MJ. Progression in atherosclerosis: histological features and pathophysiology of atherosclerotic lesions. Top Magn Reson Imaging 2009;20:227-237.
29. Redgrave JN, Lovett JK, Gallagher PJ, et al. Histological assessment of 526 symptomatic carotid plaques in relation to the nature and timing of ischemic symptoms: the Oxford plaque study. Circulation 2006;113:2320-2328.
30. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: part II. Circulation 2003;108:1772-1778.