JACC: CARDIOVASCULAR IMAGING VOL. 5, NO. 4, 2012

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC. DOI:10.1016/j.jcmg.2012.01.012

Prevalence of Nonstenosing, Complicated Atherosclerotic Plaques in Cryptogenic Stroke

Tobias M. Freilinger, MD,*† Andreas Schindler, BSc,§ Caroline Schmidt, MD,*
Jochen Grimm, MD,§ Clemens Cyran, MD,§ Florian Schwarz, MD,§
Fabian Bamberg, MD,§ Jennifer Linn, MD,‖ Maximilian Reiser, MD,§ Chun Yuan, PhD,‡
Konstantin Nikolaou, MD,§ Martin Dichgans, MD,† Tobias Saam, MD§

Munich, Germany; and Seattle, Washington

OBJECTIVES Our goal was to assess the prevalence of complicated American Heart Association (AHA) lesion type VI plaques in the carotid arteries of patients with cryptogenic stroke.

BACKGROUND In up to 40% of ischemic stroke patients, no definite cause can be established despite extensive workup (i.e., cryptogenic stroke). To test the hypothesis if nonstenosing complicated carotid plaques may be the underlying etiology in some of these patients, we used high-resolution black-blood carotid magnetic resonance imaging (MRI), which can quantitatively assess plaque composition and morphology with good correlation to histopathology. Specifically, we focused on AHA type VI plaques, which are characterized by hemorrhage, thrombus, or fibrous cap rupture.

METHODS Thirty-two consecutive patients (22 male; mean age 71.7 ± 11.9 years) with cryptogenic stroke and nonstenosing (<50%) eccentric carotid plaques were recruited from a single stroke unit. All patients underwent extensive clinical workup (brain MRI, duplex sonography, electrocardiography and Holter monitoring, transthoracic and transesophageal echocardiography, and laboratory investigations) to exclude other causes of stroke. All patients received a black-blood carotid MRI at 3-T with fat-saturated pre- and post-contrast T-1–, proton density–, and T-2–weighted and time-of-flight images using surface coils and parallel imaging techniques. Prevalence of AHA type VI plaque was determined in both carotid arteries on the basis of previously published MRI criteria.

RESULTS AHA type VI plaques were found in 12 of 32 arteries (37.5%) ipsilateral to the stroke, whereas there were no AHA type VI plaques contralateral to the stroke ($p = 0.001$). The most common diagnostic feature of AHA type VI plaques was intraplaque hemorrhage (75%), followed by fibrous plaque rupture (50%) and luminal thrombus (33%).

CONCLUSIONS This pilot study suggests that arterio-arterial embolism from complicated, nonstenosing carotid atherosclerotic plaques may play a role in a subgroup of patients previously diagnosed with cryptogenic stroke. To further evaluate the significance of AHA type VI plaques in cryptogenic stroke, future studies will have to analyze both clinical and imaging follow-up data, including event rates for secondary strokes. (J Am Coll Cardiol Img 2012;5:397–405) © 2012 by the American College of Cardiology Foundation

From the *Department of Neurology, Ludwig-Maximilians-University Munich, Klinikum Großhadern, Munich, Germany; †Institute for Stroke and Dementia Research, Ludwig-Maximilians-University Munich, Munich, Germany; ‡Department of Radiology, University of Washington, Seattle, Washington; §Institute of Clinical Radiology, Ludwig-Maximilians-University Munich, Munich, Germany; and the ‖Department of Neuroradiology, Ludwig-Maximilians-University Munich, Munich, Germany. Dr. Bamberg has received a speakers fee from Siemens Healthcare, Forchheim, Germany. Dr. Reiser serves on the editorial board of Der Radiologe (Zeitschrift für diagnostische und interventionelle Radiologie, Radioonkologie, Nuklearmedizin). Dr. Yuan has been a consultant to Pfizer, Merck, Bristol Myers Squibb, and ImagePace, and has received grant support from Philips and VP Diagnostics. Dr. Nikolaou has served on a scientific advisory board for Bayer Schering Pharma; serves as Cardiac Section Editor for *European Radiology*; receives royalties from the publication of *Multislice CT, Third Edition* (Springer, 2005); and serves on the Speaker's Bureaus for and has received speaker honoraria from Bayer Schering Pharma, Bracco S.p.A., and Siemens Medical Solutions. Dr. Dichgans served as Genetics Section Editor for *Stroke* and receives research

JACC: CARDIOVASCULAR IMAGING, VOL. 5, NO. 4, 2012
APRIL 2012:397–405

Ischemic stroke is one of the leading causes of morbidity and mortality in the western world. Its etiology is highly heterogeneous: Although large vessel disease, cardiac embolism, and small vessel disease account for the majority of cases, most registries failed to establish a definite cause in up to 40% of patients (i.e., cryptogenic stroke) (1). Importantly, currently used stroke classification schemes such as TOAST (Trial of Org 10172 in Acute Stroke Treatment) (2) or A-S-C-O (3) consider atherosclerotic lesions of the carotid bifurcation only as causative, if they are associated with substantial luminal narrowing. However, it has been shown that the degree of luminal stenosis alone is insufficient to determine a plaque's vulnerability (4,5). More specifically, it has been demonstrated that roughly 60% of myocardial infarcts occur in coronary arteries with a stenosis grade of <50% (6,7). Similarly, several case reports have suggested an association between ischemic stroke and nonobstructive atherosclerotic carotid artery plaques (8,9). Thus, arterio-arterial embolism from nonstenotic carotid artery lesions may be an attractive pathophysiological explanation in a substantial number of patients with cryptogenic stroke.

See page 406

ABBREVIATIONS AND ACRONYMS

AHA = American Heart Association

CT = computed tomography

DWI = diffusion-weighted imaging

MR = magnetic resonance

MRI = magnetic resonance imaging

NWI = normalized wall index

PDW = proton density–weighted

TEE = transesophageal echocardiography

TIA = transient ischemic attack

TOF = time-of-flight

Despite these pathophysiological insights, current guidelines for carotid interventions (10), which are based on data from large multicenter trials in the 1990s (11,12), still focus on the degree of luminal stenosis as the only imaging marker. One possible explanation for this paradox is that the ECST (European Carotid Surgery Trial) and the NASCET (North American Symptomatic Carotid Endarterectomy Trial) used conventional angiography as the sole imaging tool; thus, the arterial wall was not visualized. With the recent introduction of imaging modalities, such as contrast-enhanced ultrasound, positron emission tomography/computed tomography (CT), CT, and high-resolution black-blood carotid magnetic resonance imaging (MRI), noninvasive plaque characterization is no longer an elusive goal.

In this study, we applied black-blood carotid MRI, which has been shown to be a valuable tool to accurately characterize and quantify the composition and morphology of human carotid atherosclerotic plaques in vivo with good correlation to histopathology (13–16). Furthermore, black-blood carotid MRI allows classification of plaques according to the criteria of the American Heart Association (AHA) (17). In particular, complicated AHA lesion type VI, which is characterized by intraplaque hemorrhage, thrombus, or rupture of the fibrous cap, can be detected with a sensitivity of 82% and a specificity of 91% compared with histopathology (18).

In a study of patients with symptomatic (i.e., >50%) carotid stenosis, AHA type VI plaques were shown to be significantly more prevalent on the symptomatic side than on the asymptomatic side (19). Furthermore, AHA type VI plaques have been shown to be associated with a particularly high risk for causing stroke by arterio-arterial embolization in patients with >50% carotid stenosis (20,21). Based on these data, we decided to focus on AHA type VI plaques in patients without significant luminal narrowing of the internal carotid artery. Specifically, our goal was to test the hypothesis that AHA type VI plaques are more prevalent in nonstenosing arteries ipsilateral than contralateral to a cryptogenic stroke.

METHODS

Setting and diagnostic workup. This pilot study was conducted at the stroke unit of the Department of Neurology of the Ludwig-Maximilians-University Munich in 2009/2010. All patients were subjected to the following investigations: laboratory analysis (including electrolytes, differential blood count, coagulation studies, and C-reactive protein), 12-lead electrocardiography, Holter monitoring, transthoracic echocardiography and transesophageal echocardiography (TEE), duplex sonography of the extracranial vessels, transcranial Doppler sonography and carotid MRI (including T-1–weighted [T-1W], T-2–weighted [T-2W], and diffusion-weighted imaging [DWI] sequences as well as time-of-flight [TOF] magnetic resonance [MR] angiography). The aortic arch was evaluated for the presence of atherosclerotic plaques by using TEE;

support from BMB, NGFN-Plus, Wellcome Trust, and the Foundation for Vascular Dementia Research; he has been a consultant to Bayer Vital GmbH, Boehringer Ingelheim Pharma GmbH & Co. KG, and Trommsdorff GmbH & Co. KG; and has received honoraria from Bayer Vital GmbH, Boehringer Ingelheim Pharma GmbH & Co. KG, Lundbeck GmbH, Sanofi-Aventis Deutschland GmbH, Shire Deutschland GmbH, DZNE, Georg Thieme Verlag KG, UpToDate, and W. Kohlhammer GmbH. Dr. Saam receives research support from Bayer Schering Pharma and Diamed Medizintechnik. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. A. Schindler and Dr. Schmidt contributed equally to the paper.

Manuscript received December 16, 2011; accepted January 20, 2012.

in addition, CT angiography (including the aortic arch) was available in the majority of patients. Additional tests (e.g., cerebrospinal fluid analysis, conventional angiography, screening for prothrombotic conditions) were performed, where clinically indicated. Based on the results, patients were grouped according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification (2).

Patient selection. Consecutive patients with an ischemic stroke in the anterior circulation were screened for eligibility on the basis of inclusion/exclusion criteria (Table 1). The study was approved by the local ethics committee, and all participants provided written informed consent.

MRI protocol. Participants were subjected to black-blood carotid MRI within a mean of 5.8 days (±4.1 days) after the qualifying stroke. All subjects were imaged using a previously published multisequence protocol (22) (TOF MR angiography, axial pre- and post-contrast black-blood T-1W, proton density–weighted (PDW), and T-2W sequences; best in-plane resolution 0.5 × 0.5 mm^2) at 3-T (Magnetom Verio, Siemens Healthcare, Erlangen, Germany). To improve signal-to-noise performance and optimize spatial resolution, a dedicated 4-channel surface coil (Machnet B.V., Eelde, the Netherlands) for bilateral carotid scans was used. Parallel imaging was used for all sequences with a parallel acquisition technique acceleration factor of 2. Imaging time for TOF, T-1W, PDW, and T-2W images were 4:11, 4:38, 2:08, and 2:08 min, respectively, resulting in a total scan time of 17:43 min. Gadolinium-DTPA-BMA (Gadobutrol, Bayer Schering, Leverkusen, Germany) of 0.1 mmol/kg (0.1 ml/kg) was given at a rate of 3 ml/s. Post-contrast T-1W imaging was performed approximately 5 min after intravenous injection of the contrast agent. Fat suppression was used for pre- and post-contrast T-1W, PDW, and T-2W images to reduce signals from subcutaneous and perivascular fat. Scan coverage was 3.0 cm, 4.2 cm, 4.2 cm, and 5.2 cm for T-1W, PDW, T-2W, and TOF images, respectively, resulting in a matched coverage of 30 mm (2-mm slice thickness × 15 matched images across the 5 sequences). This coverage is usually sufficient to image the complete carotid atherosclerotic plaque (23). Images were centered on the carotid bifurcation.

Table 1. Inclusion/Exclusion Criteria

Inclusion criteria
Ischemic stroke in the territory of the anterior or middle cerebral artery <14 days before black-blood carotid MRI (acute DWI lesion and corresponding acute neurological deficit of >24 h duration)
Nonstenosing (i.e., luminal obstruction <50% according to NASCET criteria), eccentric (>2.0 mm*) atherosclerotic plaques in the carotid bifurcation as determined by using duplex sonography
Exclusion criteria
Definite stroke etiology (TOAST 1–5)†
≥1 stroke etiology
Bilateral infarcts on carotid MRI
Known contraindications against MRI
Allergy to contrast material
Impaired renal function (glomerular filtration rate <30 ml/min)
Previous radiation therapy to head or neck
Surgical procedure within 24 h before black-blood carotid MRI

*Plaque diameter was determined using duplex sonography in the horizontal plane. †PFO plus ASA was not regarded as a definite stroke etiology; therefore, patients with PFO plus ASA were not excluded from the study.
ASA = atrial septal aneurysm; DWI = diffusion-weighted imaging; MRI = magnetic resonance imaging; NASCET = North American Symptomatic Carotid Endarterectomy Trial; PFO = patent foramen ovale; TOAST = Trial of Org 10172 in Acute Stroke Treatment.

MR imaging review. An image-quality rating (4-point scale [1 = nondiagnostic, 2 = poor, 3 = good, 4 = excellent]) was assigned to all MR images (22). MR data were independently reviewed by 2 experienced radiologists (T.S. and J.G.) who were blinded regarding the clinical status. In case of discrepancy, a consensus decision was made. To assess inter-reader reproducibility of AHA type VI plaque, the initial independent investigation of the 2 reviewers was used for analysis, and one of the reviewers re-reviewed the images 3 months after the initial assessment. Atherosclerotic plaques in the carotid arteries (on both the ipsilateral and the contralateral side) were recorded and classified according to the modified criteria of the AHA (18). For definition of a complicated AHA type VI plaque, at least 1 of the following 3 criteria was required: fibrous cap rupture, intraplaque hemorrhage, or juxtaluminal hemorrhage/mural thrombus.

Area measurements of the lumen, wall, outer wall, and tissue components were obtained using a custom-designed semiautomatic image analysis tool CASCADE (University of Washington, Seattle, Washington) (24). The normalized wall index (NWI) was calculated by dividing the wall area by the total vessel area. Tissue components (lipid-rich necrotic core, calcification, and hemorrhage), the status of the fibrous cap (thick vs. thin vs. ruptured), hemorrhage type (type I [early subacute] versus type II [late subacute]), and presence/absence of hemorrhage/thrombus were identified on the basis of previously published criteria (14–16).

Statistical analysis. Categorical variables are presented as absolute and relative frequencies; continuous variables are presented as mean ± SD. Intrareader and

inter-reader reproducibility for identification of AHA type VI plaque were calculated using the Cohen kappa value. Wilcoxon signed rank test was used to test differences for continuous variables, and the McNemar test was used to determine differences between categorical variables.

All analysis was performed using SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina). A p value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics and diagnostic workup. During the recruitment phase, 33 patients were included in the study. Thirty-two of 33 MRI scans (97.0%) had an image quality rating of ≥2 (mean image quality: 3.4). All data presented refer to the 32 remaining patients (22 males [68.8%]; mean age 71.7 ± 11.9 years). One asymptomatic artery with a carotid artery stent was excluded from further analyses, resulting in 32 symptomatic and 31 asymptomatic arteries, which were reviewed.

Most patients had at least 1 of the classical vascular risk factors or comorbidities. In the majority of patients (n = 23 [71.9%]; group A), all diagnostic tests showed completely normal results. In 4 patients (12.5%; group B), diagnostic workup revealed patent foramen ovale plus atrial septal aneurysm but was otherwise not conclusive. Finally, 5 patients (15.6%; group C) had refused to undergo TEE (or were unable to tolerate the procedure), and the diagnostic workup was therefore incomplete; however, in all of them, transthoracic echocardiography was within normal limits. For detailed baseline characteristics of included patients, see Table 2.

Table 2. Baseline Characteristics, Diagnostic Workup, and Patient Subgroups

	n	%
Male	22	68.8
Vascular risk factors/comorbidities		
Nicotine abuse	20	62.5
Arterial hypertension	19	59.4
Hypercholesterolemia	15	46.9
Diabetes mellitus	7	21.9
Positive family history for vascular events	12	37.5
Coronary heart disease	7	21.9
Body mass index >25 kg/m^2	18	56.3
Clinical data		
NIHSS score at admission		
<5	29	90.6
5–10	3	9.4
>10	0	0
Duration of hospital stay, days		
<5	8	25
5–10	17	53.1
>10	7	21.9
Discharge home	22	68.8
Discharge to rehabilitation facility	10	31.2
Baseline medication		
Neither antiplatelet agent nor statin	18	56.2
Antiplatelet agent plus statin	7	21.9
Only antiplatelet agent without statin	5	15.6
Statin only	2	6.3
Diagnostic workup*		
All test results WNL (group A)	23	71.9
PFO plus ASA on TEE (group B)	4	12.5
Diagnostic evaluation incomplete (TEE missing) (group C)	5	15.6

*Numbers refer to patient subgroups A, B, and C.
NIHSS = National Institutes of Health Stroke Scale; TEE = transesophageal echocardiography; WNL = within normal limits; other abbreviations as in Table 1.

Prevalence of AHA type VI plaques ipsilateral and contralateral to cryptogenic ischemic stroke. AHA type VI plaques were detected in 37.5% (n = 12) of the carotid arteries ipsilateral to the ischemic stroke; by contrast, no AHA type VI plaques were found on the contralateral side (p = 0.001) (Fig. 1, Table 3). Representative examples of an AHA type VI plaque from patients in our series are illustrated in Figures 2 and 3.

For all other AHA lesion types, no significant differences were found between the symptomatic and asymptomatic side, although there was a trend for AHA type III as well as AHA type IV/V being slightly more prevalent on the asymptomatic side (Fig. 1, Table 3).

The most common diagnostic feature of AHA LT6 plaques was intraplaque hemorrhage (75%), followed by fibrous plaque rupture (50%) and luminal thrombus (33%) (Table 3). Of the 9 arteries with intraplaque hemorrhage, 5 hemorrhages were classified as type I and 4 hemorrhages as type II. When we focused only on the subgroup of cryptogenic stroke patients with a completely negative workup (group A), the prevalence of AHA type VI plaques on the ipsilateral side increased to 39.1% (9 of 23) (as opposed to 33.3% [3 of 9] in groups B and C together).

Quantitative plaque characteristics ipsilateral and contralateral to cryptogenic ischemic stroke. Quantitative data on plaque burden and composition are presented in Table 3. No significant differences were found for minimum and mean lumen areas, maximum and mean total vessel area, maximum wall area, and mean NWI. Mean wall area and

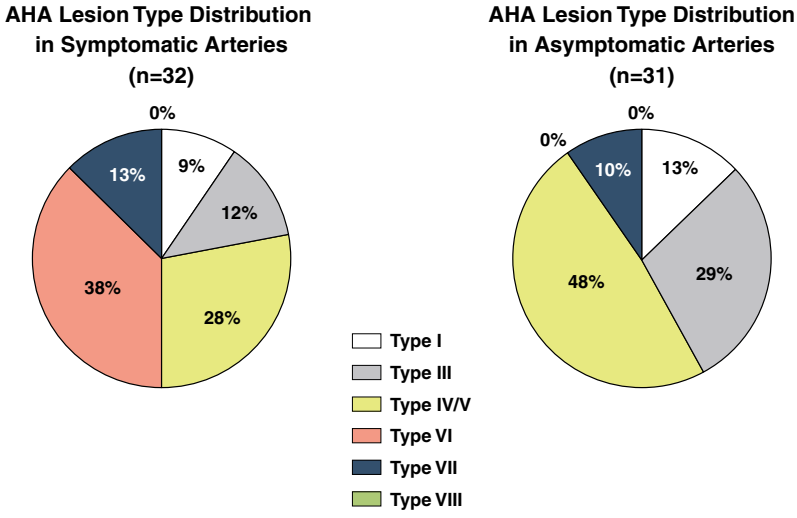

Figure 1. AHA Lesion Type Distribution

The relative frequency of the different American Heart Association (AHA) lesion types is presented for symptomatic and asymptomatic arteries; 1 asymptomatic artery with a carotid artery stent was excluded.

maximum NWI was significantly larger in symptomatic arteries ($p = 0.03$). Furthermore, symptomatic arteries had a significantly larger maximum necrotic core ($p = 0.004$) and maximum hemorrhage areas ($p = 0.02$) than asymptomatic arteries. Maximum calcification areas did not differ between symptomatic and asymptomatic arteries.

Reproducibility. Intrareader and inter-reader reproducibility for identification of AHA type VI plaque was excellent, with a Cohen kappa value of 0.90 ($p < 0.001$) and 0.85 ($p < 0.001$), respectively.

DISCUSSION

In line with our hypothesis of an important contribution of atherothrombotic mechanisms, AHA type VI plaques were found significantly more often on the ipsilateral side than on the contralateral side in the overall group (37.5% vs. 0.0%; $p = 0.001$). These data suggest that in a subgroup of our patients previously classified as cryptogenic, the stroke was caused by arterio-arterial embolization from these nonobstructive but complicated atherosclerotic lesions.

In addition to the AHA classification, plaques were also analyzed with respect to several quantitative parameters. Although parameters indicating plaque composition were significantly different between symptomatic and asymptomatic arteries, no significant differences were noted for measurements reflecting the degree of luminal stenosis as well as for the majority of parameters reflecting pure plaque burden; thus, this observation adds further evidence to the concept of plaque composition being a major determinant of plaque vulnerability of atherosclerotic lesions.

From an overall perspective, our data confirm the recent findings of Parmar et al. (25), who, in a large sample of patients referred with clinically suspected acute transient ischemic attack (TIA) or stroke found type VI lesions to be significantly associated with ipsilateral acute TIA or stroke. Their study highlights the general pathophysiological relevance of type VI plaques but did not directly address their role specifically for cryptogenic stroke. In detail, there are a number of differences between both studies. First, the patient selection criteria used by Parmar et al. (25) were substantially different: the authors focused not only on manifest strokes but also included cases with TIA or transient monocular blindness. Beyond this, Parmar et al. (25) included patients irrespective of the degree of carotid stenosis. In addition, their study was not performed in the standardized setting of a stroke unit (i.e., without neurologists as an integral part of the study team). As a consequence of this overall setting and due to the specific recruitment strategy from both inpatients and the emergency department, their study cohort is more heterogeneous than our sample. Moreover, phenotypes of patients were determined only retrospectively on the basis of chart review.

Strengths of our study include: 1) an interdisciplinary study team comprising both vascular neurologists and (neuro)radiologists; 2) prospective pa-

JACC: CARDIOVASCULAR IMAGING, VOL. 5, NO. 4, 2012
APRIL 2012:397–405

Table 3. Plaque Characteristics Ipsilateral and Contralateral to Cryptogenic Ischemic Stroke

	Symptomatic Side (n = 32)	Asymptomatic Side (n = 31)*	p Value†
AHA lesion type distribution			
Type VI	37.5 (12)	0.0 (0)	0.001
Intraplaque hemorrhage	9/12 (75%)	0.0 (0)	
Fibrous cap rupture	6/12 (50%)	0.0 (0)	
Thrombus	4/12 (33%)	0.0 (0)	
Type I	9.4 (3)	12.9 (4)	0.66
Type III	12.5 (4)	29.0 (9)	0.13
Type IV/V	28.2 (9)	48.4 (15)	0.13
Thin fibrous cap	4/9 (44%)	2/13 (15%)	
Thick fibrous cap	5/9 (56%)	11/15 (73%)	
Type VII	12.5 (4)	9.7 (3)	0.71
Type VIII	0.0 (0)	0.0 (0)	
Plaque burden			
Minimum lumen area (mm^2)	12.9 ± 5.8	13.9 ± 5.9	0.45
Mean lumen area (mm^2)	28.9 ± 10.4	28.8 ± 9.6	0.93
Maximum wall area (mm^2)	60.0 ± 22.7	55.0 ± 18.0	0.10
Mean wall area (mm^2)	36.8 ± 12.0	32.3 ± 9.2	0.01
Maximum total vessel area (mm^2)	107.9 ± 37.4	107.6 ± 34.0	0.95
Mean total vessel area (mm^2)	65.7 ± 19.7	61.1 ± 16.3	0.08
Maximum NWI	0.71 ± 0.11	0.66 ± 0.10	0.03
Mean NWI	0.57 ± 0.07	0.54 ± 0.08	0.09
Plaque composition (mm^2)			
Maximum necrotic core area	9.1 ± 9.1	3.8 ± 4.7	0.004
Maximum calcification area	1.3 ± 1.9	1.8 ± 2.9	0.31
Maximum hemorrhage area	3.7 ± 8.2	0.0 ± 0.0	0.02

Values are % (n), n/N (%), or mean ± SD unless otherwise indicated. *One asymptomatic artery with a carotid artery stent was excluded. †Wilcoxon signed rank test or paired *t* test.
AHA = American Heart Association; N/A = not applicable; NWI = normalized wall index.

tient recruitment, using a pre-defined set of inclusion/exclusion criteria in the setting of a single large stroke unit in a tertiary referral center; and 3) reliable phenotyping of all patients based on comprehensive and standardized neurological and etiological workup. The criteria we used for the definition of cryptogenic stroke were rather strict; for example, patients with ≥2 potential stroke etiologies (which according to the TOAST classification qualify as cryptogenic) as well as patients without evidence of an obvious source of cardiac embolism but with bilateral infarcts (i.e., with a high degree of suspicion of cardioembolic stroke) were not included in our study. Furthermore, as part of the routine workup, in most patients we also performed an evaluation of the aortic arch (using TEE or CT angiography) to exclude more proximal potential sources of arterio-arterial embolism.

In our trial, plaque imaging data were obtained not as part of the acute stroke imaging MR protocol but in a separate dedicated imaging session. Therefore, the latency between the qualifying stroke and black-blood carotid MRI was roughly 1 week in the majority of patients, which is obviously longer than in the study by Parmar et al. (25). However, because plaque morphology has been shown to be relatively stable over a long period of time (26), our findings at the time of data acquisition most likely adequately reflect the status of the atherosclerotic plaques at the time of the qualifying stroke. Furthermore, because black-blood carotid MRI was not performed in the peracute setting, patients were more likely to be in a clinically stable condition, allowing adequate compliance with the study protocol; accordingly, image quality was consistently high in 32 of our 33 patients (97.0%), as opposed to the recent 1.5-T study of Parmar et al. (25), who had to exclude 20% of studies because of poor image quality (e.g., due to motion artifacts). The number of subjects excluded in our study due to insufficient image quality is also substantially lower than in a recent 1.5-T multicenter trial by Boussel et al. (27), in which 32.5% of all subjects had to be excluded. A further reason for the lower number of excluded examinations in our study compared with previous 1.5-T MR studies might be the signal gains associated with the higher field strength at 3-T in combination with the shorter scan time due to the parallel imaging techniques used in our study (22). This short scan time is easier to tolerate for the patients and might therefore result in less motion artifacts as well as artifacts due to patient swallowing.

To further expand on the findings presented here, future trials (including control patients with other defined stroke etiologies) will have to determine the therapeutic implication the finding of a complicated AHA type VI plaque ipsilateral to a cryptogenic stroke has (i.e., whether these patients may benefit from an escalated medical [dual platelet inhibition] or interventional/surgical treatment approach). To this purpose, it will be essential to generate both clinical and imaging follow-up data, including event rates for secondary strokes; these and other aspects will be addressed in a recently initiated prospective study (Carotid Plaque Imaging in Acute Stroke [NCT01284933]).

Interestingly, results from several studies suggest that certain plaque characteristics, including in particular intraplaque hemorrhage, as determined by black-blood carotid MRI, may indeed predict a less favorable clinical outcome. A prospective in vivo MRI study (20) investigated plaque character-

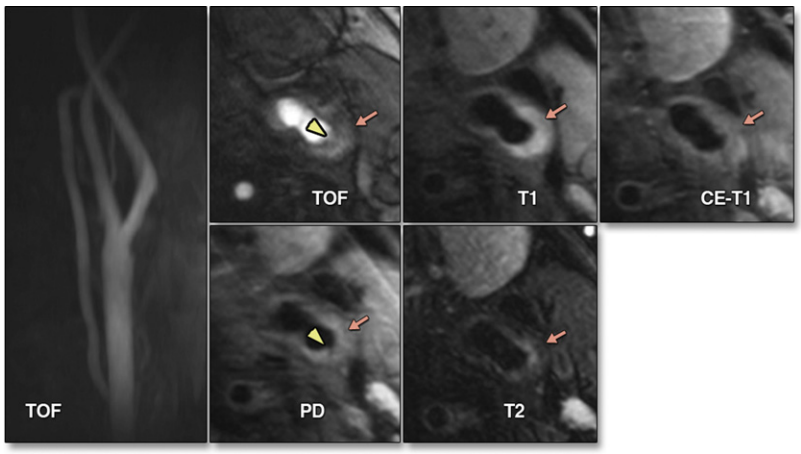

Figure 2. Nonobstructive AHA Type VI Plaque

This nonstenosing plaque was detected in a 66-year-old male patient with a cryptogenic stroke ipsilateral to the lesion. The **arrowheads** on the time-of-flight (TOF) and proton density–weighted (PDW) images point to the site of the plaque rupture. The **arrows** point to a large lipid/necrotic core with type I hemorrhage, which does not cause substantial luminal narrowing (see TOF images on the **left**). Abbreviation as in Figure 1.

istics in 154 subjects with an initially asymptomatic 50% to 79% carotid stenosis. Plaques with intraplaque hemorrhage and larger mean intraplaque hemorrhage area were found to be significantly associated with subsequent cerebrovascular events over a mean follow-up period of 38.2 months. Similar observations were made in a study of 66 patients with high-grade symptomatic stenosis (28), in which intraplaque hemorrhage significantly increased the risk of a secondary stroke. Based on these and other similar data (29,30), future studies will have to address the predictive value of plaque characteristics specifically for patients with cryptogenic stroke.

Study limitations. Scan coverage ranged from 3.0 cm for T-1W and 5.2 cm for TOF images. Therefore, carotid lesions further up-stream or down-stream could have been missed due to insufficient coverage. However, based on our experience, carotid endarterectomy specimens are usually short and rarely exceed 2 cm in length (14). Thus, we believe that we have covered the majority of lesions that were centered around or at the carotid bifurcation.

No histology data were available in our patients, and our results therefore rely by design on the in vivo MRI data. However, black-blood MRI has been extensively validated against histopathology (14,15,18,31,32); in particular, AHA type VI plaque can be reliably identified using MRI with excellent sensitivity and specificity. However, spatial resolution of MRI is limited, and we may therefore have missed small hemorrhages, thrombi, or fibrous cap ruptures. The true prevalence of AHA type VI plaque might be higher than reported in our paper.

The majority of patients included in our study had one or more of the classical vascular risk factors, which obviously increased the a priori probability of finding evidence for atherosclerosis-mediated stroke mechanisms. Thus, the yield of complicated plaques might have been substantially lower in a cohort of cryptogenic stroke patients with a less pronounced vascular risk factor profile. However, we feel that this patient selection by no means limits the impact of our results; given the high prevalence of patients with multiple risk factors in most stroke units, we are convinced that our cohort adequately reflects the phenotype of a "typical" stroke patient. Similarly, only patients with eccentric plaques at the carotid bifurcation of $\geq$2 mm were included, which may also have caused some overestimation of the prevalence of AHA type VI plaque. However, to avoid unnecessary and expensive carotid MRI examinations, it is both economically and medically reasonable to use ultrasound as a screening tool.

One might argue that our overall cryptogenic group was contaminated by some patients with incomplete diagnostic workup (group C) or with findings of unclear causality (group B). However, we can exclude that these factors substantially biased our results because the prevalence of AHA type VI plaques even increased when we focused exclusively on the group of patients with the strictest definition of cryptogenic stroke.

JACC: CARDIOVASCULAR IMAGING, VOL. 5, NO. 4, 2012
APRIL 2012:397–405

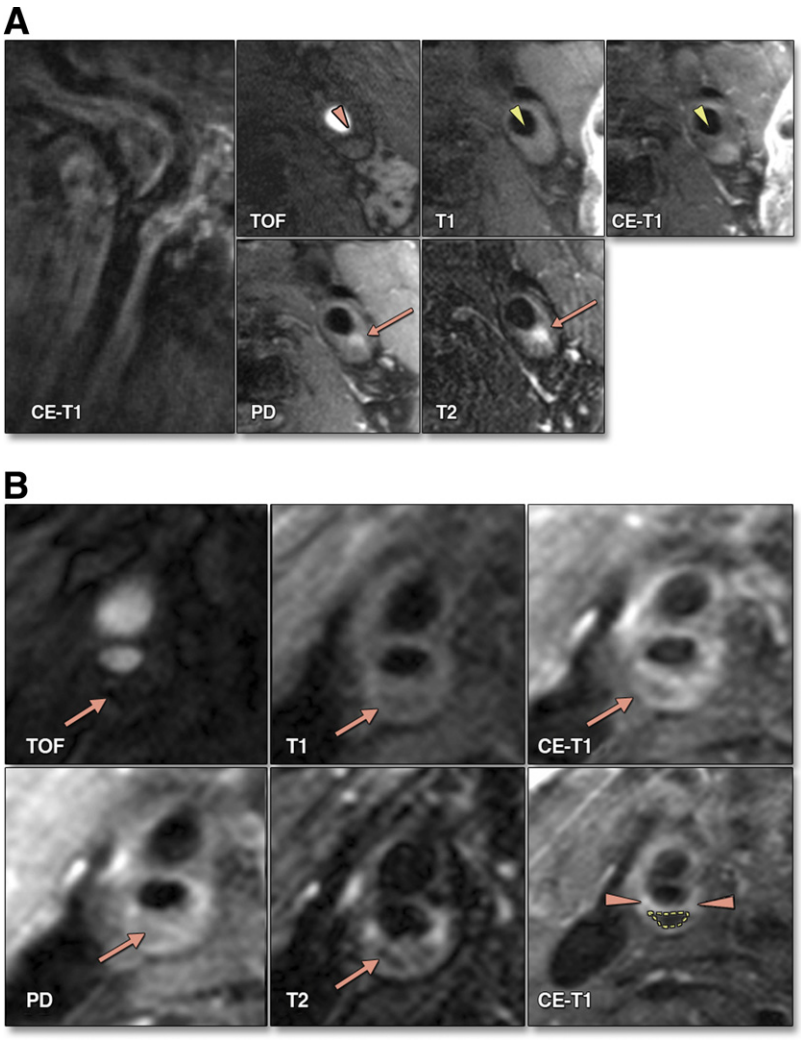

Figure 3. Nonobstructive AHA Type VI and Type IV/V Plaques

(A) This nonobstructive AHA type VI plaque was detected in a 78-year-old male with a cryptogenic stroke ipsilateral to the lesion 5 days before the magnetic resonance imaging scan. The **arrow** points to a hyperintense area on PDW and T-2–weighted (T-2W) images, which is indicative of juxtaluminal hemorrhage/thrombus. The **arrowheads** on the TOF, T-1W, and CE–T-1W images point to the site of possible plaque rupture. The lesion consists of a large necrotic core, which does not cause substantial luminal narrowing (see coronal CE–T-1W images on the **left**). **(B)** Images of the same patient showing an obstructive atherosclerotic lesion contralateral to the cryptogenic stroke, causing luminal narrowing of 60%. The **arrow** points to a region, which is isointense on T-1W and TOF images and isointense to hypointense on PDW and T-2W images and does not show any contrast enhancement on post-contrast T-1W images, consistent with a lipid/necrotic core. The CE–T-1W images show an enhancing area that is covering the lipid/necrotic core, consistent with a thick fibrous cap. The images on the **right (lower panel)** show the lipid/necrotic core area surrounded by a **yellow dotted line**; the thick fibrous cap is marked by **arrowheads**. This lesion is consistent with an AHA lesion type IV/V. CE = contrast-enhanced; other abbreviations as in Figures 1 and 2.

CONCLUSION

Using black-blood carotid MRI, we provide compelling evidence that a substantial proportion of strokes previously classified as cryptogenic is related to nonstenosing, complicated AHA type VI plaques (i.e., atherothrombotic mechanisms).

Reprint requests and correspondence: Dr. Tobias M. Freilinger, Neurologische Klinik und Poliklinik und Institut für Schlaganfall- und Demenzforschung, Klinikum Großhadern der Ludwig-Maximilians-Universität München, Marchioninistrasse 15, 81377 München, Germany. *E-mail: tobias.freilinger@med.uni-muenchen.de.*

REFERENCES

1. Amarenco P. Underlying pathology of stroke of unknown cause (cryptogenic stroke). Cerebrovasc Dis 2009;27 Suppl 1:97–103.
2. Adams HP Jr., Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. Toast. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993; 24:35–41.
3. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici MG. New approach to stroke subtyping: the A-S-C-O (phenotypic) classification of stroke. Cerebrovascular Dis 2009;27:502–8.
4. 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;108:1772–8.
5. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: part I. Circulation 2003;108:1664–72.
6. Ambrose JA, Tannenbaum MA, Alexopoulos D, et al. Angiographic progression of coronary artery disease and the development of myocardial infarction. J Am Coll Cardiol 1988; 12:56–62.
7. Falk E, Fuster V. Angina pectoris and disease progression. Circulation 1995; 92:2033–5.
8. Freilinger T, Dimitriadis K, Nikolaou K, Reiser MF, Dichgans M, Saam T. Stroke while squeezing a pimple: traumatic rupture of a vulnerable carotid artery plaque. Neurology 2011;76: 305–6.
9. Trivedi RA, U-King-Im JM, Graves MJ, Gillard J, Kirkpatrick PJ. Non-stenotic ruptured atherosclerotic plaque causing thrombo-embolic stroke. Cerebrovascular Dis 2005;20:53–55.
10. Adams RJ, Albers G, Alberts MJ, et al. Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack. Stroke 2008;39:1647–52.
11. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1991;325:445–53.
12. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet 1998;351:1379–87.
13. Saam T, Hatsukami TS, Takaya N, et al. The vulnerable, or high-risk, atherosclerotic plaque: Noninvasive MR imaging for characterization and assessment. Radiology 2007;244:64–77.
14. Saam T, Ferguson MS, Yarnykh VL, et al. Quantitative evaluation of carotid plaque composition by in vivo mri. Arterioscler Thromb Vasc Biol 2005;25:234–9.
15. Kampschulte A, Ferguson MS, Kerwin WS, et al. Differentiation of intraplaque versus juxtaluminal hemorrhage/thrombus in advanced human carotid atherosclerotic lesions by in vivo magnetic resonance imaging. Circulation 2004;110:3239–44.
16. Hatsukami TS, Ross R, Polissar NL, Yuan C. Visualization of fibrous cap thickness and rupture in human atherosclerotic carotid plaque in vivo with high-resolution magnetic resonance imaging. Circulation 2000;102:959–64.
17. Stary HC. Natural history and histological classification of atherosclerotic lesions: an update. Arterioscler Thromb Vasc Biol 2000;20:1177–8.
18. Cai JM, Hatsukami TS, Ferguson MS, Small R, Polissar NL, Yuan C. Classification of human carotid atherosclerotic lesions with in vivo multicontrast magnetic resonance imaging. Circulation 2002;106:1368–73.
19. Saam T, Cai J, Ma L, et al. Comparison of symptomatic and asymptomatic atherosclerotic carotid plaque features with in vivo MR imaging. Radiology 2006;240:464–72.
20. Takaya N, Yuan C, Chu B, et al. Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: a prospective assessment with MRI—initial results. Stroke 2006;37:818–23.
21. Singh N, Moody AR, Gladstone DJ, et al. Moderate carotid artery stenosis: MR imaging-depicted intraplaque hemorrhage predicts risk of cerebrovascular ischemic events in asymptomatic men. Radiology 2009;252:502–8.
22. Saam T, Raya JG, Cyran CC, et al. High resolution carotid black-blood 3T MR with parallel imaging and dedicated 4-channel surface coils. J Cardiovasc Magn Reson 2009;11:41.
23. Chu B, Zhao XQ, Saam T, et al. Feasibility of in vivo, multicontrast-weighted mr imaging of carotid atherosclerosis for multicenter studies. J Magn Reson Imaging 2005;21:809–17.
24. Kerwin W, Xu D, Liu F, et al. Magnetic resonance imaging of carotid atherosclerosis: plaque analysis. Top Magn Reson Imaging 2007;18: 371–8.
25. 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; 122:2031–8.
26. Kwee RM, van Oostenbrugge RJ, Mess WH, et al. Carotid plaques in transient ischemic attack and stroke patients: one-year follow-up study by magnetic resonance imaging. Invest Radiol 2010;45:803–9.
27. Boussel L, Arora S, Rapp J, et al. Atherosclerotic plaque progression in carotid arteries: monitoring with high-spatial-resolution MR imaging—multicenter trial. Radiology 2009;252: 789–96.
28. Altaf N, MacSweeney ST, Gladman J, Auer DP. Carotid intraplaque hemorrhage predicts recurrent symptoms in patients with high-grade carotid stenosis. Stroke 2007;38:1633–5.
29. Altaf N, Daniels L, Morgan PS, et al. Detection of intraplaque hemorrhage by magnetic resonance imaging in symptomatic patients with mild to moderate carotid stenosis predicts recurrent neurological events. J Vasc Surg 2008;47:337–42.
30. Yamada N, Higashi M, Otsubo R, et al. Association between signal hyperintensity on T1-weighted MR imaging of carotid plaques and ipsilateral ischemic events. AJNR Am J Neuroradiol 2007;28:287–92.
31. 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;112:3437–44.
32. 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;104:2051–6.

Key Words: AHA type VI plaque ■ atherosclerosis ■ cryptogenic ■ ischemic stroke ■ plaque.