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ARTICLE *in* STROKE · SEPTEMBER 2014

Impact Factor: 5.72 · DOI: 10.1161/STROKEAHA.114.006800 · Source: PubMed

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Stroke. 2014;45:3423-3426; originally published online September 25, 2014;
doi: 10.1161/STROKEAHA.114.006800
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

Intraplaque Hemorrhage, Fibrous Cap Status, and Microembolic Signals in Symptomatic Patients With Mild to Moderate Carotid Artery Stenosis

The Plaque At RISK Study

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Background and Purpose—In patients with mild to moderate symptomatic carotid artery stenosis, intraplaque hemorrhage (IPH) and a thin/ruptured fibrous cap (FC) as evaluated with MRI, and the presence of microembolic signals (MESs) as detected with transcranial Doppler, are associated with an increased risk of a (recurrent) stroke. The objective of the present study is to determine whether the prevalence of MES differs in patients with and without IPH and thin/ruptured FC, and patients with only a thin/ruptured FC without IPH.

Methods—In this multicenter, diagnostic cohort study, patients with recent transient ischemic attack or minor stroke in the carotid territory and an ipsilateral mild to moderate carotid artery plaque were included. IPH and FC status were dichotomously scored. Analysis of transcranial Doppler data was done blinded for the MRI results. Differences between groups were analyzed with Fisher exact test.

Results—A total of 113 patients were included. Transcranial Doppler measurements were feasible in 105 patients (average recording time, 219 minutes). A total of 26 MESs were detected in 8 of 105 patients. In 44 of 105 plaques IPH was present. In 92 of 105 plaques FC status was assessable, 36 of these had a thin/ruptured FC. No significant difference in the prevalence of MES between patients with and without IPH (P=0.46) or with thick versus thin/ruptured FC (P=0.48) was found.

Conclusions—In patients with a symptomatic mild to moderate carotid artery stenosis, IPH and FC status are not associated with MES. This suggests that MRI and transcranial Doppler provide different information on plaque vulnerability.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01709045.

(*Stroke*. 2014;45:3423-3426.)

Key Words: magnetic resonance imaging ■ plaque, atherosclerotic ■ transcranial Doppler sonography

To date, the degree of luminal narrowing by a carotid artery plaque is used to estimate the risk of recurrence of cerebrovascular events and to stratify therapeutic options.[1] However, other plaque characteristics have gained interest. Detection of atherosclerotic plaques, which are prone to rupture, the so-called vulnerable plaques, might help in determining the best therapeutic approach, especially for patients with a mild to moderate carotid artery stenosis.

Intraplaque hemorrhage (IPH) and fibrous cap (FC) status, as evaluated with MRI, are important features of plaque vulnerability and are associated with an increased risk of future ischemic stroke or transient ischemic attack.[2,3]

Received July 18, 2014; final revision received July 18, 2014; accepted August 6, 2014.

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The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.114.006800/-/DC1.

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Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.114.006800**

Also microembolic signals (MESs) as measured with transcranial Doppler (TCD) ultrasound are predictors of combined transient ischemic attack and ischemic stroke in patients with symptomatic carotid stenosis.[4,5] Consequently, MRI and MES detection are both promising techniques to more precisely identify those patients who are at increased risk of a recurrent cerebrovascular event. As MRI visualizes morphological aspects of the plaque, while TCD is based on physiological aspects, this may imply that these techniques study plaque characteristics in a different way. The aim of the present study was to investigate the association between the occurrence of MES and the presence of IPH and a thin/ruptured FC (TRFC) in patients with a symptomatic mild to moderate carotid artery stenosis.

Methods

Study Population

Patients were included consecutively in the Plaque At RISK (PARISK) study, a multicenter diagnostic cohort study. Details on inclusion and exclusion criteria have been described earlier.[6] For details on the quantification of the luminal stenosis, see online-only Data Supplement. The study was approved by the institutional Medical Ethical Committees. All patients gave written informed consent.

MRI Protocol

All patients were scanned using 3T scanners as previously described.[6] For details on the MRI protocol, see online-only Data Supplement.

Ambulatory TCD

With transcranial duplex ultrasound (IU22, Philips Healthcare, Best, The Netherlands) the main stem of the middle cerebral artery ipsilateral to the symptomatic carotid artery was located and the ultrasound transparency of the transtemporal bone window was investigated. Subsequently, the 1.5-MHz probe of a portable ambulatory TCD instrument (TCD-X, Hemodynamics AG, Bern, Switzerland) was positioned at the location where the window was found. For details on the TCD recording, see online-only Data Supplement.

Data Analysis

MR images were analyzed according to previously published criteria by a trained observer (M.T.B.T.) using dedicated vessel wall analysis software (VesselMASS, Leiden University Medical Center, Leiden, The Netherlands) blinded to the TCD results.[7] TCD recordings were semiautomatically analyzed with dedicated software (TCDemb, Hemodynamics AG, Bern, Switzerland). For details on the MRI and TCD analysis, see online-only Data Supplement.

Statistical Analysis

To determine whether IPH and FC status were associated with MES, a Fisher exact test was performed. All calculations were made using SPSS (Version 20; IBM SPSS Inc, Chicago, IL).

Results

A total of 113 patients were included. Eight patients were excluded because of too much noise artifacts in the TCD signal. Clinical characteristics of the 105 patients are summarized in the Table. Time interval between clinical event and MRI was 53±20 days (range, 12–100) and 52±20 days (range, 11–100) between clinical event and TCD. Because of absence (n=7) or poor image quality (n=6) of postcontrast images, FC status could be analyzed in 92 patients.

Table. Clinical Characteristics of the 105 Included Patients

	n (%)
Men	84 (80)
Age, y (mean±SD)	67±8.4
Smoking	
Current	26 (24.8)
Former	59 (56.2)
Never	18 (17.1)
Unknown	2 (1.9)
Diabetes mellitus	26 (24.8)
Hypertension	68 (64.8)
History of coronary artery disease	25 (23.8)
Statin therapy	
Before event	48 (45.7)
After event	92 (87.6)

IPH was detected in 44 of 105 (42%) of the patients, and 36 of 92 (39%) plaques had a TRFC. A total of 44 of 92 (48%) had neither IPH nor a TRFC and 28 of 92 (30%) plaques showed both IPH and a TRFC (Figure 1).

In total, 23 034 minutes of TCD signal were recorded (mean, 219; range, 21–379 minutes). Twenty-six MES were detected in 8 of 105 (8%) patients (Figure 2). Every first MES was detected within 175 minutes after commencing the record. Time interval between clinical event and TCD for these 8 patients was 54.1±20.5 days (range, 34–100). Two of the 61 patients (3%) with IPH and 6 of the 44 patients (14%) without IPH had MES (P=0.46). Two of the 49 patients (4%) with a TRFC and 6 of the 43 patients (14%) with a thick FC had MES (P=0.48). Noteworthy, even in the case of abundant MES, as in patient 3, there was no IPH or TRFC present on MRI.

Discussion

In the present study, we did not find an association between the presence of MES and IPH in patients with mild to moderate symptomatic carotid artery stenosis. The same applied for the relationship between MES and a TRFC and for the combination of IPH and a TRFC.

These findings are in contrast with previously published results by Altaf et al[8] in which they studied patients with high-grade carotid stenosis (60%–99%). Their main finding was a highly significant relationship between MES occurrence and the

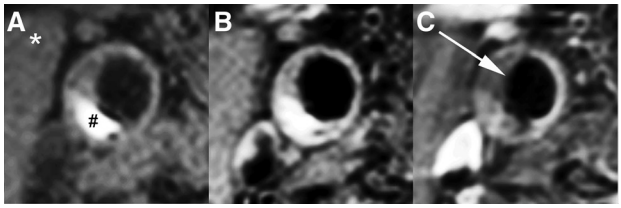

Figure 1. MR images showing T1w inversion recovery turbo field echo (IR-TFE; **A**), T1w quadruple inversion recovery turbo spin echo precontrast (**B**) and postcontrast (**C**). Note hyperintense signal (#) in the IR-TFE image compared with the sternocleidomastoid muscle (*) indicating intraplaque hemorrhage. The absence of signal enhancement between lipid-rich necrotic core and lumen (arrow) indicates a thin/ruptured fibrous cap.

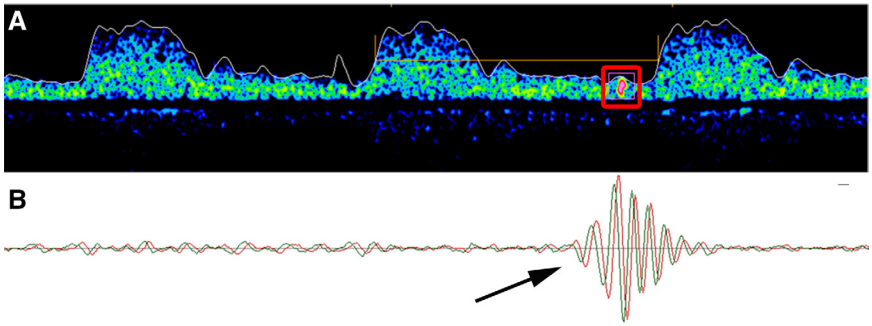

Figure 2. Transcranial Doppler signal showing both the frequency (**A**) and the time (**B**) domain. The red box delineates a microembolic signal, with typical time domain signal (arrow).

presence of a vulnerable plaque on MRI. There are several possible explanations for this difference between the study results.

First, Altaf et al studied patients with a high-grade carotid stenosis, whereas we investigated symptomatic patients with a mild to moderate stenosis. MESs are more common in patients with a severe carotid artery stenosis than in those with a mild to moderate stenosis.[9] This might explain the difference between studies in prevalence of MES-positive patients (44% versus 8%). Another difference in the selected patient population concerns potential cardiac sources of MES alike atrial fibrillation and in patients with heart valve prostheses.[10] In our study, we excluded patients with possible causes of MES other than the carotid arteries. Furthermore, the majority of our patients (88%) used lipid-lowering therapy, which is known to decrease the presence of MES.[11]

Finally, the time window between event and TCD recording differs between studies. MES are highly dependent on the latency between clinical event and TCD recording.[12] In the present study, the latency is relatively long (52±20 days) as compared with the one reported by Altaf et al (19 days; interquartile range, 12–27 days). Yet, in our study, no MESs were found in the 14 patients who had their TCD recording within 30 days of the neurological event (21.7±5.4 days), whereas we would expect 6 of 14 patients to be MES positive based on the prevalence mentioned by Altaf et al. The number of MES might even have been higher than 6 of 14 because we recorded ≈3.5 hours, which was 3.5× longer than in the previous study. This longer recording time, made possible by the use of the mobile TCD device, is known to increase the number of MES-positive patients.[13]

On the contrary, IPH and the FC status on MRI have shown to be much more stable in time.[14] So, the difference between the incidence of MES on the one hand and the presence of IPH or a TRFC on the other hand fits with that concept and underlines that both techniques have a different approach toward studying plaque features.

Another plaque feature of interest other than the degree of stenosis might be inflammation. Moustafa et al[15] studied the correlation between MES and signs of plaque inflammation by means of ^{18}F-fluorodeoxyglucose positron emission tomography and they were able to show an association between the 2 parameters in recently symptomatic patients. So, ^{18}F-fluorodeoxyglucose positron emission tomography might be another modality for identifying high-risk carotid artery plaques.

To conclude, our study suggests that, in symptomatic patients with mild to moderate stenosis, IPH presence and TRFC on MRI do not relate to the presence of MES. Hence, MRI and TCD are likely to provide different information on plaque vulnerability. The present study concerns a baseline analysis of the PARISK study.[6] The clinical follow-up data on clinical events will become available in the summer of 2016. We expect to determine which imaging approach allows for the best individual risk stratification and has the highest predictive value for a (recurrent) stroke in patients with mild to moderate carotid artery stenosis.

Appendix

Participating centers: Academic Medical Center, Amsterdam (Dr Nederkoorn); Atrium Medisch Centrum, Heerlen (A.H.C.M.L. Schreuder); Erasmus Medical Center, Rotterdam (Dr Lugt, P.J. Koudstaal); Flevoziekenhuis, Almere (M. Limburg); Kennemer Gasthuis, Haarlem (M. Weisfelt); Laurentius Ziekenhuis, Roermond (A.G. Korten); Maasstad Ziekenhuis, Rotterdam (R. Saxena); Maastricht University Medical Center (Drs Kooi, Oostenbrugge, and Mess); Orbis Medisch Centrum, Sittard (N.P. van Orshoven); Sint Antonius Ziekenhuis, Nieuwegein (S.C. Tromp); Sint Franciscus Gasthuis, Rotterdam (S.L.M. Bakker); Slotervaartziekenhuis, Amsterdam (N.D. Kruyt); Tergooi Ziekenhuizen, Hilversum/Blaricum (J.R. de Kruijk); University Medical Center Utrecht (Dr Hendrikse, G.J. de Borst); Viecuri Medisch Centrum, Venlo (B.J. Meems); Vlietland Ziekenhuis, Schiedam (J.C.B. Verhey); IJsselland Ziekenhuis, Capelle a/d IJsel (A.D. Wijnhoud).

Sources of Funding

This research was performed within the framework of the Center for Translational Molecular Medicine (www.ctmm.nl), project PARISK (Plaque At RISK; grant 01C-202) and supported by the Dutch Heart Foundation.

Disclosures

Dr Kooi is supported by an Aspasia grant from the Nederlandse Organisatie voor Wetenschappelijk Onderzoek (015.008.047). Dr Lugt has a research grant and speaking engagements from GE Healthcare. Dr Aaslid is director of R&D and majority shareholder of Hemodynamics AG, Bern, Switzerland. The other authors report no conflicts.

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ONLINE SUPPLEMENT

Evaluation of moderate symptomatic carotid artery stenosis with MR and TCD; the Plaque At RISK (PARISK) study

M.T.B. Truijman, A.A.J. de Rotte, R. Aaslid, A.C. van Dijk, J. Steinbuch, M.I. Liem, F.H.B.M. Schreuder, A.F.W. van der Steen, M.J.A.P. Daemen, R.J. van Oostenbrugge, J.E. Wildberger, P.J. Nederkoorn, J. Hendrikse, A. van der Lugt, M.E. Kooi, W.H. Mess

Supplemental Methods

Patient selection: Eligible for the study were patients with a transient ischemic attack, amaurosis fugax or minor stroke (modified Rankin scale ≤3) of the carotid artery territory and an atherosclerotic plaque with a < 70% stenosis of the ipsilateral internal carotid artery who were not scheduled for a revascularization procedure. Patients needed to be eligible for imaging within three-months after initial ischemic event. Exclusion criteria were a probable cardiac source of embolism, a clotting disorder, severe comorbidity, standard contraindications for MRI, a documented allergy for MRI or CT contrast agent or a renal clearance of <30 ml/min. Degree of stenosis was be determined with clinically obtained Doppler US or CT angiography. The upper cutoff value of 70% was based on the North American Symptomatic Carotid Endarterectomy Trial criteria.[1] The lower cutoff value was an atherosclerotic plaque with a thickness of at least 2–3 mm, which corresponds to an European Carotid Surgery Trial stenosis of 30%.[2]

MRI protocol: All patients were scanned using 3T scanners (Achieva and Ingenia, Philips Healthcare, Best, The Netherlands; Discovery MR750 system, GE Healthcare, Milwaukee, WI) and dedicated phased-array carotid surface coils (Shanghai Chenguang Medical Technologies Co, Shanghai, China or Machnet B.V., Roden, the Netherlands). T1-weighted (T1w) inversion recovery turbo field echo (IR-TFE) or spoiled gradient echo (SPGR) as well as T1w pre- and postcontrast quadruple inversion recovery turbo spin echo (QIR TSE) or T1w double inversion recovery fast spin echo (DIR FSE) images were obtained. The postcontrast images were acquired 6 minutes after the injection of 0.1 mmol/kg of a gadolinium-based contrast agent with an injection rate of 0.5 mL/s.

MRI analysis: IPH was scored as being present if a hyperintense signal (compared with the adjacent sternocleidomastoid muscle) was visible in the bulk of the plaque on IR-TFE or SPGR images. With the precontrast T1w QIR TSE or T1w DIR FSE image as baseline for comparison, lipid-rich necrotic core (LRNC) was identified on the postcontrast images as an area in the bulk of the plaque with no or slight contrast enhancement compared with the surrounding, more strongly enhanced fibrous tissues. Subsequently, FC status was scored by comparing pre- and postcontrast images for the presence of a continuous signal enhancement on the postcontrast images between LRNC and the lumen (thick FC) or an interrupted or no continuous signal enhancement (thin/ruptured FC).

TCD recording: An axial sample volume setting of 5.1 mm was used, and probe aiming (2-axis servo-control), pulse repetition frequency, depth, and power were optimized using dedicated software on a laptop which was connected to the ambulatory unit. The automatic servo system for optimizing probe aiming was activated, and the laptop was disconnected. Raw quadrature Doppler data were stored on an SD-memory card. Patients were asked to turn the device off after four hours of ambulatory monitoring.

TCD analysis: Fast Fourier transforms (128 points) were performed with an overlap of 90-95%. The normal blood signal amplitude was monitored continuously and defined as the upper quartile of the spectral speckle peaks. At a preset speckle peak amplitude (15 dB in the present study) above this level, the signal was analyzed further by the software. In order to qualify the signal as a MES candidate, the mirror amplitude (negative velocity) had to be much lower (15 dB) than the positive velocity peak amplitude. Furthermore, the duration of the spectral peak had to be compatible with the expected duration given the sample volume size and the flow velocity. These criteria eliminated practically all artifacts due to probe and patient movements as well as spectral bands due to speech and vocalizations. The remaining possible MES events were saved in a separate file. These signals were inspected both audibly and visually (spectral analysis) by two independent observers (M.T.B.T. and W.H.M.). Only those events agreed upon by both were classified as MES (figure 2). To validate and optimize the algorithms, the first 40 hours or recordings were analyzed and listened to by two independent observers (M.T.B.T. and A.A.J.d.R.). All possible MES were listed and checked by a third observer (W.H.M.). The software settings were adjusted in such a manner that no MES detected by the human observers were missed.

Supplemental Table

Table 1: Crosstabs indicating the prevalence of MES in patients with and without IPH (A) and the prevalence of MES in patients with a thick or thin/ruptured FC (B).

A.	IPH+	IPH-	
MES+	2	6	8
MES-	42	55	97
	61	44	105

B.	FC thin/ruptured	FC thick	
MES+	2	6	8
MES-	47	37	84
	49	43	92

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