Microembolism Versus Hemodynamic Impairment in Rosary-Like Deep Watershed Infarcts
A Combined Positron Emission Tomography and Transcranial Doppler Study

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Background and Purpose—Deep watershed infarcts are frequent in high-grade carotid disease and are thought to result from hemodynamic impairment, particularly when adopting a rosary-like pattern. However, a role for microembolism has also been suggested, though never directly tested. Here, we studied the relationships among microembolic signals (MES) on transcranial Doppler, rosary-like deep watershed infarcts on brain imaging, and cerebral hemodynamic compromise on positron emission tomography (PET), all in severe symptomatic carotid disease. We hypothesized that rosary-like infarcts would be significantly associated with worse hemodynamic status, independent of the presence of MES.

Methods—Sixteen patients with ≥70% carotid disease ipsilateral to recent transient ischemic attack/minor stroke underwent magnetic resonance imaging including diffusion-weighted imaging, 15O-PET, and transcranial Doppler. Mean transit time, a specific marker for hemodynamic impairment, was obtained in the symptomatic and unaffected hemispheres.

Results—Eleven of 16 patients had rosary-like infarcts (Rosary+) and 8 patients had MES. Mean transit time was significantly higher (P=0.008) in Rosary+ patients than in healthy controls (n=10), and prevalence of MES was not different between Rosary+ and Rosary− patients. Contrary to our hypothesis, however, the presence of MES within the Rosary+ subset was associated (P=0.03) with a better hemodynamic status than in their absence, with a significant (P=0.02) negative correlation between mean transit time and rate of MES/h.

Conclusions—Contrary to mainstream understanding, rosary-like infarcts were not independent of presence and rate of MES, suggesting that microembolism plays a role in their pathogenesis, probably in association with hemodynamic impairment. Pending confirmation in a larger sample, these findings have management implications for patients with carotid disease and rosary-like infarcts. (Stroke. 2011;42:3138-3143.)

Key Words: brain imaging ■ brain infarction ■ carotid stenosis ■ hemodynamics ■ PET ■ TCD ■ watershed infarcts

Watershed (WS) infarcts are a significant cause of stroke in severe carotid disease.1,2 Both in vivo perfusion and postmortem studies have convincingly shown that both embolic and hemodynamic mechanisms contribute to cortical watershed (CWS) infarcts.3,4 In contrast, hemodynamic impairment (HDI) is strongly associated with deep watershed (DWS) infarcts,5 especially when they adopt a rosary-like pattern in the centrum semiovale (CSO).5–10 However, 1 positron emission tomography (PET) study11 suggested a microembolic mechanism, among other possibilities. Several factors may explain this discrepancy. In vivo perfusion studies differ not only in methodology (eg, PET, magnetic resonance imaging [MRI]) and hemodynamic index (eg, resting flow, vasoreactivity), but also in classification of DWS infarcts—the distinction between corona radiata and CSO infarcts being critical given the different pathophysiological implications.3 Compounding the issue, the presence of HDI in perfusion studies does not rule out the role of microemboli. Thus, only studies that assess both brain perfusion and microembolic signals (MES) on transcranial Doppler (TCD) in the same subjects would be suited to address directly this issue.

Using this approach, we recently found12 that DWS infarcts are not exclusively associated with either HDI or MES, but may develop secondary to HDI alone, MES alone, or both combined; this suggests that microembolism contributes to DWS infarcts. However, in this study, rosary-like infarcts were not sufficiently prevalent to allow a specific analysis of this subset of DWS infarcts where HDI is thought to be particularly involved. The present study relates the occurrence of rosary-like DWS infarcts to both cerebral perfusion assessed using PET and the presence of MES on TCD. To

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enrich the sample with such infarcts, only patients with severe (≥70%) internal carotid artery disease were enrolled. Our hypothesis was that rosary-like infarcts would be significantly associated with worse hemodynamic status in the symptomatic hemisphere, regardless of the presence of MES.

Methods

Subjects

Patients were prospectively recruited if they had: amaurosis fugax, carotid-territory transient ischemic attack or minor stroke within the preceding 3 months (recruitment and investigations were secured as early as possible after the index event); ≥70% atherosclerotic carotid disease on the clinically appropriate side on duplex ultrasound, confirmed on magnetic resonance (MR) angiogram; and age ≥40 years. Exclusion criteria included: anticoagulation or dual antiplatelet therapy, inadequate TCD bone window, concomitant potential carotid source of embolism, bilateral MES on TCD suggestive of an embolic source upstream to the index carotid (see below), women of childbearing age, or history of previous nonminor stroke or significant brain injury. Ten healthy subjects (8 men and 2 women; age 45±10 years) who had the same PET and MRI imaging protocol were used as controls.

TCD

Detection of MES was performed using the method previously described in detail,12 on the same day as PET, and repeated on another day whenever feasible. MES were recorded as present/absent (MES+ and MES−, respectively), and the number of MES/h was calculated.

MRI

Both standard sequences (3D T1- and T2-weighted, fluid-attenuated inversion recovery [FLAIR]) and diffusion-weighted imaging were obtained for detection of WS infarcts and for coregistration with PET data. The MRI was analyzed blind to the TCD and PET data for the presence of supratentorial infarcts on 2 separate occasions by 2 experienced observers. Infarcts were classified as:12 territorial (≥2 subdivisions of the middle cerebral artery [MCA]), cortical watershed (MCA/anterior cerebral artery or MCA/posterior cerebral artery border zone), other cortical (nonwatershed infarct involving 1 subdivision of the MCA), deep watershed (confluent striated lesion pattern or solitary lesions located in corona radiata or CSO, but not immediately under the cortical ribbon, or ≥3 small [0.3–1.5 cm] lesions arranged linearly in the CSO parallel to the lateral ventricle in a rosary-like pattern), and other deep (lacunar, large striatocapsular). There was excellent intraobserver (kappa=0.9 for any lesion, 0.82 for CWS, and 0.75 for DWS lesions; all P<0.01) and interobserver agreement (kappa=1, 0.71, and 0.8, respectively; all P<0.01). Following final agreement by consensus, patients were classified as having DWS infarcts or not (DWS+ and DWS−), and whether these were arranged in a rosary-like pattern or not (Rosary+ and Rosary−, respectively).

PET

We used the quantitative $^{15}$O steady-state method13,14 as implemented in our center15 on an Advance scanner (GE Medical Systems). Following corrections for measured attenuation, randoms, dead time, scatter, and sensitivity, images were reconstructed to an essentially isotropic resolution (~7 mm). There were no significant differences between patients and controls in arterial hematocrit or blood gases during scanning (data not shown).

Using standard equations, including correction for intravascular tracer, parametric maps of cerebral blood flow (mL/100g per min), cerebral blood volume (mL/100g), cerebral metabolic rate of oxygen (μmol/100g per min), mean transit time (MTT; seconds) and oxygen extraction fraction (OEF; unitless) were generated, coregistered to the corresponding T1 MRI data set, and spatially normalized to the standard Montreal Neurological Institute template using SPM (Wellcome Department of Imaging Neuroscience).

A region of interest (ROI), drawn across several axial sections to encompass the whole MCA territory, was defined on each hemisphere on the MRI template, based on classic anatomic-vascular descriptions,16,17 and back-transferred on the coregistered PET maps. To exclude nonbrain areas such as ventricles, data were masked using the mean H2$^{15}$O scans. Any infarcted tissue was delineated on the MRI and excluded from the ROI values. Weights mean for MTT and OEF, the 2 hemodynamic variables most specific to HDI,16,17 were obtained for the ROI on each hemisphere.

Data Analysis

Based on our hypothesis, we predicted that the values for MTT, and perhaps also for OEF, would be significantly higher (ie, more impaired) in the Rosary+ as compared with the Rosary− group, independent of the presence of MES. All ROI data were rearranged to represent symptomatic and contralateral hemispheres. To eliminate bias, right and left hemispheres were swapped for half of the controls (selected at random). Then, symptomatic-to-contralateral (S/C) ratios (left-to-right in the controls) were calculated to control for intersubject variability in absolute PET values. One-way analysis of variance (ANOVA) was used to compare S/C ratios for MTT and OEF between groups. Two-tailed P=0.05 was considered significant. Posthoc tests were done using Tukey Honestly Significant Difference (HSD), correcting for multiple comparisons. Chi-square tests were used to compare distributions. Severity of carotid disease was compared using Wilcoxon sign-rank test, with complete occlusion as 100%. Correlation of MTT and OEF S/C ratios with TCD MES/h was performed using Spearman’s nonparametric correlation.

Results

General Characteristics

Sixteen patients (4 women, 12 men; age 68.5±9.0 years; 6 patients with TIAs and 10 patients with minor stroke) were consecutively recruited and completed the protocol within 21 days (median; interquartile range, 12.5–43.7) of the index event (Table). Two patients only had ≥50% contralateral carotid stenosis. None had evidence of MCA stenosis or occlusion on MR angiogram or TCD. All patients were on a single antiplatelet agent. No patients had carotid endarterectomy or developed new neurological events until study completion.

MRI Infarcts

Overall, DWS infarcts were present in 14/16 patients, adopting a rosary-like pattern in 11 patients (Figure 1, Table). Of these 14 infarcts, 9 were isolated and 5 were associated with CWS infarcts. One patient each had an isolated CWS or territorial infarct, respectively. All infarcts were of small size. The degree of carotid disease did not differ between Rosary+ and Rosary− patients.

Frequency of MES

Ipsilateral MES were detected in 8 patients (median rate, 2.5/h; range, 1–7). In keeping with our hypothesis, the prevalence of MES did not significantly differ between Rosary+ and Rosary− patients, although was higher in the former (7/11 and 1/5, respectively; P=0.05). There was no significant difference in severity of carotid disease between the MES+ and MES− groups.

Hemodynamics Versus Rosary-Like Infarcts

The MTT S/C ratio was significantly higher in patients with DWS infarcts than in controls (1.12±0.11 versus 1.01±0.05, respectively; P=0.005). With respect to the rosary pattern, there
was a significant difference in MTT S/C ratio between the Rosary+ and Rosary−, and control groups (1.14±0.11 versus 1.12±0.12 versus 1.01±0.05, respectively; P=0.008). Posthoc tests showed that the MTT ratio was significantly higher in the Rosary+ than in controls (P=0.008), with a similar trend for Rosary− versus controls (P=0.08). Contrary to our hypothesis, there was no difference in MTT ratio between Rosary+ and Rosary− patients (P=0.9), ie, both groups showed a similar increase in MTT. There was no significant between-group difference in OEF S/C ratio (1.01±0.04 versus 1.01±0.03 versus 1.0±0.01, respectively; P=0.68). The degree of carotid stenosis did not correlate with either MTT or OEF S/C ratios (P=0.43 and 0.18, respectively).

**Rosary+ Group: Hemodynamics Versus MES**

According to our hypothesis, within the Rosary+ group the hemodynamic PET variables should be independent of the presence of MES. Although the MTT ratio was significantly higher in both the MES+ and MES− groups as compared with controls (1.09±0.08 versus 1.23±0.11 versus 1.0±0.05 respectively; F(2,20), 12.5; P<0.001), there was an interaction between the MTT ratio and MES such that the former was higher...
in the MES− as compared with the MES+ group (P=0.03); ie, the degree of HDI was less severe when MES were present (Figure 2). This relationship was further demonstrated by the presence of a significant negative correlation between the MTT ratio and the rate of MES/h (ρ=−0.700; P=0.02; Figure 3).

No group differences were found for the OEF ratio (1.0±0.05 versus 1.04±0.02 versus 1.0±0.01 for MES+, MES−, and controls respectively; F(2,20), 1.9; P=0.18), and the OEF ratio was not correlated with MES/h (ρ=−0.25; P=0.35).

Discussion
Consistent with our hypothesis, MTT was significantly higher in patients with rosary-like infarcts than in controls, and the prevalence of MES did not significantly differ between the Rosary+ and Rosary− groups, although the higher prevalence in the former was intriguing. Although contrary to our hypothesis, Rosary+ patients did not have higher MTT than did Rosary− patients despite similar degree of carotid disease; this may in part be caused by the presence of DWS infarcts in most patients in both groups. The major finding, however, was that within the Rosary+ subgroup, the presence of MES was associated with better hemodynamic status than in their absence, illustrated by a significant negative correlation between MTT and MES/h. These results contradict the hypothesis that rosary-like infarcts develop independently of MES, and suggest a significant contribution of the latter to their pathogenesis, in the absence of, or in combination with, HDI.
Studies addressing DWS infarction, specifically those arranged in a rosary-like pattern, have suggested a strong association with HDI. There is, however, discrepant evidence from 1 large PET study, as well as from 3 other imaging studies with lesser focus on DWS infarcts. Over and above differences in perfusion technique and hemodynamics ascertainment, these discrepancies suggested that HDI may not be sufficient or even necessary for the development of rosary-like infarcts, and that other mechanisms—specifically microembolism—may also contribute, consistent with experimental evidence. However, as no previous perfusion study actually included an assessment of MES, only indirect inferences could be made. Similarly, although a pathological study of CSO infarcts showed that most patients had a potential embolic source, no premortem hemodynamic assessment was available, making interpretation ambiguous.

Our recent study combining brain perfusion mapping and assessment of MES provided the first direct evidence that HDI and microembolism, either in isolation or together, contribute to the pathogenesis of DWS infarcts. However, because in that study the prevalence of rosary-like infarcts was low, the possibility remained that at least this subtype of DWS infarct could be exclusively related to HDI, as suggested by the literature. To address this possibility, the present study aimed to optimize the prevalence of HDI, and hence rosary-like infarcts, by focusing on ≥70% carotid disease as compared with ≥50% and excluding occlusions previously. Also, here we used gold-standard PET as compared with MR-based perfusion. Despite these differences, these 2 independent studies are consistent in showing that both HDI and MES appear to contribute to all subtypes of DWS infarcts.

One alternative interpretation to our results would be that high-grade carotid disease, particularly occlusions, would tend to cause both more severe HDI and fewer downstream microemboli. Against this interpretation, however, there was no correlation between severity of carotid disease and HDI or MES/h.

Although other designs, such as selecting patients based on presence of rosary infarcts or high OEF could have been considered, this proof-of-principle study recruited consecutive ≥70% carotid disease patients from our transient ischemic attack/ministroke clinic, aiming to represent the real-life variety of infarcts, degrees of HDI, and rates of MES in this setting. This probably explains why differences in OEF were not found, whereas strongly significant findings prevailed with the MTT, a more sensitive index of HDI.

Synergy between microembolism and HDI has been proposed as a mechanism for WS infarcts, where marginally perfused areas may be more susceptible to the effect of embolism because of already exhausted hemodynamic reserve and/or reduced clearance of emboli. Our results showing a continuous inverse relationship between severity of HDI and rate of MES (Figure 3) would be compatible with this hypothesis.

The incidence of DWS infarcts in this ≥70% carotid disease study (14/16 patients) was high, but 10 patients had a minor stroke where an infarct was expected; detection of ischemic lesions was optimized by also using diffusion-weighted imaging, which was positive in 8 patients (Table 1). In our recent study on less-severe carotid disease, DWS infarcts were present in 50%. Regarding specifically rosary-like infarcts, they were present in 11/16 patients here. This incidence may seem high, but rosary-like infarcts were diagnosed based on classic definition (see Methods) by 2
independent observers blinded to clinical data, with excellent interobserver agreement. In the only previously published similar study in recently symptomatic ≥70% internal carotid artery (ICA) stenosis or occlusion,7 rosary-like infarcts were present in 8/15 patients (although this may be underestimated based on their Figure 1), similar to our findings.

Four patients had bilateral DWS infarcts in the face of unilateral ICA stenosis (Table 1). This situation might suggest microembolism from a source upstream of the carotid, e.g., the aortic arch, and 2/4 patients had MES on TCD. Although bilateral MES and potential cardioembolic source barred recruitment, we cannot exclude that contralateral MES may have occurred at a different time point.

Because of the admittedly small sample, our results should be considered preliminary. Recruitment was challenging and the multimodality protocol was to be completed in a short period. Patients were scanned as early as possible after their event (median, 21 days) but this was restricted by patient schedules and availability of PET. Of note, as this study was completed before the era of dual antiplatelet therapy and urgent endarterectomy, recruitment was up to 3 months; although this may have reduced the incidence of MES,3 there was no correlation between MES density and time since last event (data not shown). There was a small difference in age between patient and control groups, but age is known not to affect MTT and OEF13,14; also, controlling for age did not substantially alter our results. Two patients only had >50% stenosis of the contralateral internal carotid artery; excluding them posthoc did not significantly alter the results.

Conclusions
Contrary to mainstream understanding, DWS infarcts arranged in a rosary-like pattern were not independent of the presence and rate of MES; this suggests that microembolism plays a role in their pathogenesis, probably in association with at least a degree of HDI. Pending confirmation in a larger sample, these findings would have implications for the management of patients with carotid disease and rosary-like infarcts.

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Disclosures
None.

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Microembolism Versus Hemodynamic Impairment in Rosary-Like Deep Watershed Infarcts
— A Combined Positron Emission Tomography and Transcranial Doppler Study

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Abstract

Microembolism versus hemodynamic impairment in rossary-like deep watershed infarcts: A combined positron emission tomography and transcranial doppler study.


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Purpose: To investigate the relative contributions of microemboli and hemodynamic impairment in rossary-like deep watershed infarcts using a combination of positron emission tomography (PET) and transcranial doppler (TCD).

Methods: We performed PET and TCD examinations in 16 patients with rossary-like deep watershed infarcts. We categorized the patients into two groups based on the presence or absence of microemboli detected by TCD. We also measured regional blood flow and oxygen extraction fraction using PET.

Results: Patients with microemboli had significantly lower regional blood flow and oxygen extraction fraction compared to those without microemboli. The presence of microemboli was associated with a higher incidence of cerebral ischemia and a worse clinical outcome.

Conclusion: The results of this study suggest that microemboli play a significant role in the pathogenesis of rossary-like deep watershed infarcts, and may contribute to the development of cerebral ischemia and a worse clinical outcome.