Source of Microembolic Signals in Patients With High-Grade Carotid Stenosis

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Background and Purpose—In patients with both symptomatic and asymptomatic carotid artery stenoses, the relationship between carotid plaque characteristics and transcranial Doppler (TCD)–detected microembolic signals (MES) is unclear. The purpose of this study was to examine the relationship between macroscopically described plaque characteristics and MES in patients undergoing carotid endarterectomy.

Methods—Sequential patients scheduled for carotid endarterectomy underwent preoperative 30-minute TCD monitoring of the ipsilateral middle cerebral artery to detect MES. TCD signal analysis, by researchers who were blinded to patient information, was performed offline. Clinical variables of patients and macroscopic carotid plaque features seen at surgery were documented prospectively.

Results—Of the 109 patients (74 male, 35 female; mean age, 68.8 ± 8.7 years) enrolled, 71 had ipsilateral carotid territory symptoms. MES were detected in 27 of all patients (25%). Twenty-two of 71 symptomatic patients (31%) compared with 5 of 38 asymptomatic patients (13%) had MES (P = 0.046). Also, symptomatic patients had more emboli (total MES counts) than asymptomatic patients (P = 0.010). The presence or absence of MES was not associated with plaque characteristics.

Conclusions—Our data do not confirm previous reports of an association between MES and macroscopic plaque characteristics. We hypothesize that smaller platelet aggregates and fibrin clots, which are not detected macroscopically, are the most likely sources of TCD-detected MES. (Stroke. 2002;33:2014-2018.)

Key Words: carotid endarterectomy ■ carotid stenosis ■ middle cerebral artery ■ ultrasonography, Doppler, transcranial

Carotid stenosis is an important cause of ischemic stroke, with artery-to-artery embolism being the most common mechanism. In 1991, the European Carotid Surgery Trial (ECST) and North American Symptomatic Carotid Endarterectomy Trial (NASCET) investigators reported a beneficial effect in favor of carotid endarterectomy (CEA) in recently symptomatic patients with high-grade carotid artery stenosis. The reduction in stroke risk is attributed to removal of the cerebral embolic source in most cases.

Asymptomatic cerebral microembolic signals (MES) can be detected in patients with carotid stenosis through the use of transcranial Doppler (TCD). Several observations suggest that MES detected distal to a high-grade carotid stenosis are due to unstable plaque. MES are more common among patients with recent carotid artery stroke and are more commonly detected among patients with more severe carotid artery narrowing. Moreover, CEA tends to result in a rapid decline of MES, suggesting that their temporal source has been removed.

The frequency with which MES can be detected may depend on a number of factors such as duration of monitoring and the interval between symptom onset and TCD study. Reported incidence varies from ≈12% to 100%. MES may also be related to carotid plaque morphology. Valton et al showed that MES were associated with carotid plaque ulceration on angiography, and Sitzer et al demonstrated an association between MES and histologically determined carotid plaque ulceration and surface thrombus. These observations suggest that plaque ulceration and surface thrombus could be significant sources of MES and may be important in the etiology of stroke.

Sitzer and colleagues used histological classification for their study. However, we believe that dissection and excision of the plaque have the potential to disrupt delicate plaque surface thrombus and fragment the plaque. Assessment of plaque characteristics at the time of initial opening of the carotid artery has advantages over postoperative macroscopic inspection and histological processing of an endarterectomy.

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specimen. The purpose of this study was to examine the relationship between macroscopically described plaque characteristics and MES in patients undergoing CEA.

Methods

Sequential patients with carotid artery stenosis undergoing CEA at a major Melbourne university teaching hospital (Austin and Repatriation Medical Center) and its associated private hospital (Warringal Private Hospital) were enrolled as part of an ongoing prospective, randomized, double-blind, placebo-controlled trial of Dextran in Carotid Endarterectomy (DICE). The study involves 2 parts: part 1 tested the hypothesis that dextran reduces MES in the early postoperative period, and part 2 (in progress) tests the hypothesis that dextran reduces the incidence of perioperative stroke. Results from the 30-minute preoperative microembolus detection study performed on patients in part 1 are the basis of this article.

Inclusion and Exclusion Criteria

We studied both symptomatic and asymptomatic patients in whom a decision had already been made to perform CEA. Exclusion criteria included poor temporal ultrasound window, refusal of consent, and nonatheromatous (eg, fibromuscular dysplasia, postradiotherapy) carotid stenosis. Because all patients participated in DICE part 1, there were additional exclusion criteria related to dextran: congestive cardiac failure, unstable angina or acute myocardial infarction within 3 months of surgery, serum creatinine >0.20 mmol/L, platelet count <100 000 per 1 mm$^3$, administration of dextran or any other hemodilution agent over the 72 hours preceding surgery, history of sensitivity to dextran, or continuous intravenous heparin therapy over the first 24 postoperative hours.

Ethics

Ethics Committee approval for this project was obtained for both centers, and all patients enrolled in the study gave informed consent.

Definitions

Patients were defined as symptomatic if they had symptoms referable to the ipsilateral carotid artery within ≤120 days of TCD study. The degree of internal carotid artery (ICA) stenosis was assessed preoperatively with either color-flow duplex ultrasonography$^{14}$ (30 patients) or digital subtraction angiography$^2$ (DSA; 79 patients). The sensitivity and specificity of duplex in our laboratory compared with DSA for diagnosis of >70% stenosis (NASCET criteria) in 81 cases selected for DSA were 88% and 96%, respectively (unpublished). At our institution, CEA is usually performed on the basis of carotid duplex results alone except when there is doubt about the accuracy of duplex, and then DSA is performed for clarification. MES were defined as high-intensity, transient, unidirectional signals that occurred randomly within the spectral display, in accordance with thresholds of 6 dB.

The following risk factors were documented: (1) history of hypertension and/or blood pressure ≥140/90 mm Hg, (2) history of diabetes and/or fasting blood glucose level ≥7.5 mmol/L, (3) history of smoking over the preceding 28 days, (4) history of high cholesterol and/or fasting blood cholesterol concentration ≥5.5 mmol/L, and (5) atrial fibrillation documented on the preoperative ECG.

Plaque characteristics were categorized according to presence or absence of the following: (1) ulceration (macroscopic evidence of vascular endothelial ulceration), (2) thrombus (thrombus adherent to the surface of the plaque and/or propagating into the arterial lumen), and (3) intraplaque complications (intraplaque hemorrhage [subendothelial hemorrhage at intraoperative plaque sectioning] and/or degenerate atheroma [loose, friable, or semiliquid plaque]).

Plaque Morphology

Plaque surface characteristics were judged macroscopically at the time of CEA on initial inspection of the plaque by the surgeon. Particular care was taken not to disturb the plaque surface by irrigation or suctioning. Plaque contents were assessed during endarterectomy when the plaque was incised either longitudinally (conventional endarterectomy) or transversely (eversion endarterectomy).

TCD Monitoring

Monitoring was performed within 48 hours before CEA with a 2-MHz, pulsed-wave TCD ultrasound (MultiDop T, DWL Elektro-nische Systeme GmbH; or EME-Nicolet TC 2020, Überlingen, Germany [128-point FFT]). Depth of insonation was between 45 and 55 mm. TCD monitoring for MES was performed for 30 minutes from the ipsilateral middle cerebral artery ≤48 hours before surgery. TCD signals were recorded onto digital audio tape, and blinded observers performed “offline” screening on the EME-Nicolet TC 2020. Possible MES were then further scrutinized jointly by 2 observers.

Statistical Analysis

The effect of plaque characteristics on the presence of MES was analyzed with stepwise binomial logistic regression (SYSTAT, version 9, SPSS Inc). The number of MES detected in asymptomatic patients was compared with that in asymptomatic patients with 1-way analysis of variance (ANOVA; StatXact 3.1, Cytel Software Corporation). Binomial logistic regression was used to determine whether symptomatic plaques were more likely to have particular plaque characteristics compared with asymptomatic plaques. The effect of severity of stenosis (80% to 99% versus <80%) on the presence or absence of symptoms or MES was analyzed by a test on equality of odds (odds ratio [OR] = 1).

Results

One hundred thirty sequential patients scheduled for CEA underwent 30-minute TCD monitoring of the ipsilateral middle cerebral artery to detect MES. Fifteen patients were excluded from our study because of inadequate TCD signal and 6 because of insufficient assessment of plaque morphology, leaving 109 patients available for analysis.

The mean age was 68.8 years (range, 41 to 84 years); 74 patients (68%) were male. Two patients had 40% to 59% ICA stenosis; 31 had 60% to 79% stenosis; and 78 had 80% to 99% stenosis. Seventy-one patients (65%) had symptomatic carotid artery stenosis; 38 were asymptomatic. Forty-nine symptomatic patients (69%) and 27 asymptomatic patients (71%) had >80% to 99% carotid stenosis (OR = 1.089, P = 0.836). Fifty-eight symptomatic patients (82%) and 28 asymptomatic patients (74%) received antiplatelet therapy at the time of surgery. Of the 109 patients, 74 (68%) had hypertension, 14 (13%) had diabetes, 16 (15%) were smokers; 65 of 90 (72%) had high cholesterol, and 12 of 107 (11%) had atrial fibrillation.

All patients underwent a coagulation profile, including prothrombin time, activated partial thromboplastin time, and platelet count, as part of their preoperative workup, and there were no patients with significant coagulation disorders. No patients had mechanical heart valves.

MES were detected in 27 patients (25%), 22 of 71 (31%) with prior ipsilateral symptoms and 5 of 38 (13%) asymptomatic patients (binomial logistic regression, P = 0.046). MES were detected in 20 of 76 patients (26%) with 80% to 99% stenosis compared with 7 of 33 (21%) with lesser stenosis (OR = 1.327, P = 0.57).

Ninety-one patients (83%) underwent conventional endarterectomy, and 18 (17%) underwent eversion endarterectomy.
Of 108 plaque specimens, ulceration was detected in 68 (63%), surface and/or intraluminal thrombus was found in 23 (21%), and intraplaque complications were seen in 82 (76%). Fifty symptomatic patients (71%) and 18 asymptomatic patients (47%) had ulceration (binomial logistic regression, \( P=0.002 \)); 17 symptomatic patients (24%) and 6 asymptomatic patients (16%) had thrombus (binomial logistic regression, \( P=0.145 \)); and 53 symptomatic patients (76%) and 29 asymptomatic patients (76%) had intraplaque complications (binomial logistic regression, \( P=0.900 \)). Stepwise binomial logistic regression revealed no significant associations between the presence of MES and plaque variables (the Table). There was an association between ulceration and thrombus, but it had no impact on the presence of MES (\( P=0.110 \)).

In MES-positive patients, the mean number of MES per 30 minutes was 2.5 (median, 2; range, 1 to 9). Symptomatic patients had more emboli (total MES counts) than asymptomatic patients (ANOVA, \( P=0.010 \)).

**Discussion**

This study indicates that MES are more likely to be detected among symptomatic patients compared with asymptomatic patients and that higher numbers of MES are more common among symptomatic patients. Symptomatic patients were more likely to have plaque ulceration and overlying thrombus, although neither of these plaque types was independently associated with MES. The presence of MES was not predicted by any of the plaque variables.

Plaque ulceration can be detected in carotid plaques with angiography, gross morphological assessment at operation, and histological assessment of operative specimens.\(^{13,16–18}\) Variation in incidence of carotid plaque ulceration may relate to differing definitions and testing modalities\(^{19}\); hence, the significance of plaque ulceration as a source of artery-to-artery embolism remains unclear. MES have been associated with both angiographically\(^{20–22}\) and histologically\(^{13}\) assessed ulceration, and the lack of association between MES and ulceration in this study may be due to the use of the macroscopic inspection technique to describe ulceration. The proportion of patients with ulceration in other studies ranges from 19% to 44%,\(^{13,20–22}\) whereas ulceration was diagnosed in 62% of our patients.

There is some evidence that plaque surface thrombus may be an important cause of embolic stroke.\(^{23–26}\) Harrison and Marshall\(^{26}\) found thrombus in 66% of the 24 carotid plaques taken within 4 weeks of the most recent ischemic event but in only 21% of 28 plaques taken \( > 1 \) month after. However, surface thrombus is also a common finding in asymptomatic patients, present in \( \approx 30\% \) to 56% of patients.\(^{13,17,18,27,28}\) Fisher and Ojemann\(^{28}\) detected surface thrombus in plaques obtained from CEA specimens among both symptomatic and asymptomatic patients. They argued that surface thrombus was probably not a significant source of embolism on the basis of the presence of large thrombus in a few asymptomatic vessels and the absence of thrombus in some asymptomatic plaques. They may have overlooked the fact that thrombus could have dislodged to a distal branch of the cerebral vasculature at the time of symptoms.\(^{26}\)

TCD studies of MES and surface thrombus are also conflicting. Sitzer et al\(^{13}\) reported that MES were very common in plaques with ulceration and surface thrombus, whereas Manca and colleagues\(^{29}\) detected MES in only 2 of 6 patients with histological evidence of surface thrombus. Although their sample was small, it is feasible that another mechanism may be responsible for MES independent of the presence of surface thrombus.

The significance of intraplaque hemorrhage in the etiology of stroke is unclear. Lusby and colleagues\(^{30}\) noted recent intraplaque hemorrhage in 49 of 53 plaques from symptomatic patients taken at endarterectomy compared with 7 of 26 plaques from asymptomatic patients, supporting a role for intraplaque hemorrhage in symptom development. However, intraplaque hemorrhage is also a common finding in asymptomatic arteries with \( > 60\% \) ICA stenosis similarly determined by histology of endarterectomy specimens.\(^{18}\) Indeed, Bassiouny et al\(^{27}\) and Hatuskami et al\(^{31}\) reported that intraplaque hemorrhage was equally common in symptomatic and asymptomatic carotid plaques examined histologically after CEA.

Although in some studies intraplaque hemorrhage determined histologically or macroscopically has been associated
with the development of symptoms, it seems logical that it is not associated with MES in the absence of ulceration or surface thrombus. Moreover, in the present study, there was no difference in prevalence of intraplaque complications between symptomatic and asymptomatic plaques, but this could simply reflect the high number of patients (79%) taking antiplatelet drugs.

This study has several potential limitations. First, interrater reliability studies were not conducted for surgeon categorization of plaque features. The surgeons may have been biased in their interpretation of the plaque characteristics because they were not blinded to the clinical details or degree of ICA stenosis, although they were blinded to data on MES. Second, it is possible that >30 minutes of monitoring is needed to identify the embolizing artery. However, only 2 of 5 other studies in which a longer period of monitoring was performed had substantially higher rates of MES-positive arteries. Third, the number of patients in this analysis would have been adequate to show a doubling of the rate of MES-positive cases with intraplaque complications, ulceration, thrombus, and previous symptoms. However, for a 50% increase in the rate of MES-positive cases, the study was underpowered and therefore could have resulted in a type 2 error.

Furthermore, patients did not undergo transesophageal echocardiography testing to exclude a possible source of embolism from the heart or aortic arch. It is possible that lesions in the heart and great vessels were responsible for symptoms; alternatively, it is possible that microscopic thrombus and ulceration were missed by our method of macroscopic evaluation of plaques. Gower et al examined 10 carotid plaques from CEA patients for potential sources of emboli using a scanning electron microscope. Platelet aggregates were observed in only 1 specimen, whereas fibrin networks were observed in 70% of the specimens and several specimens contained peels of material probably comprising subendothelial matrix. The latter were more highly variable in size (30 to 1500 μm) compared with the platelet aggregates (10 to 35 μm). Asymptomatic MES probably comprise platelet aggregates and smaller emboli (fibrin clots and subendothelial matrix), which cannot be visualized macroscopically, as opposed to larger mural thrombi, which may be visualized and would appear more likely to cause symptoms. Indeed, Markus et al were able to detect particulate MES as small as 20 to 100 μm using TCD. The fact that MES were asymptomatic may be due in part to their small size or relatively low numbers in this study. The precise relationship between MES and the risk of cerebral ischemic events still requires elucidation.

Our data using macroscopic plaque description do not confirm previous reports of an association between plaque ulceration and surface thrombus and MES. We believe that smaller platelet aggregates and fibrin clots, which are not detected macroscopically, are more likely sources of TCD-detected MES.

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