Determinants of carotid microembolization

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Purpose: **Earlier studies have highlighted risk factors for perioperative stroke after carotid endarterectomy, such as female sex, preoperative symptoms, and cerebral infarction. In this study, we investigated the relationship between these factors and perioperative microembolization.**

Methods: **A total of 235 patients were entered in the study at two centers. Transcranial Doppler ultrasound scanning was possible in 190 patients (81%) and was performed for 1 hour preoperatively and continuously intraoperatively as a means of detecting microemboli and monitoring mean middle cerebral artery velocity. The findings of transcranial Doppler ultrasound scanning were related to perioperative risk factors by means of univariate analysis.**

Results: **Microemboli were detected in 28 (15%), 79 (42%), and 98 (52%) patients preoperatively, during carotid artery dissection, and after closure of the artery, respectively. Having 10 or more emboli after carotid artery closure was more common in women (*P* = .04) and in patients with symptomatic carotid artery disease (*P* = .04) and was demonstrated in three of the six patients who had a perioperative stroke. These three patients also had preoperative evidence of cerebral infarction and an intraoperative middle cerebral artery velocity less than 40 cm/s.**

Conclusion: **In this study, perioperative microembolization was more common in women and patients with symptomatic carotid artery disease. These findings may explain the increased risk of carotid surgery in these patients. (J Vasc Surg 2001;34:1060-4.)**

Further analysis of the results of the European carotid endarterectomy trial has demonstrated that a 16% subgroup of the patients with 70% to 99% carotid stenosis are the ones most likely to benefit from surgery.[1] Patients with unstable symptoms, stroke, and a history of hypertension or contralateral carotid occlusion and women are at increased risk of perioperative stroke,[1-5] reducing the benefit of surgery in these patients. In our own series, female sex and presenting symptoms predicted outcome of surgery.[2] The perioperative stroke rate for women was 6%, compared with 2% for men, and 5% for patients with stroke, compared with 0% for patients with amaurosis fugax.[2]

There are many mechanisms responsible for perioperative stroke; most can be classified into these groups: ischemia during carotid artery clamping (20%), intraoperative and postoperative thromboembolism (60%), and intracranial hemorrhage (20%).[6,7] With transcranial Doppler ultrasound scanning (TCD), it is now possible to monitor perioperative microembolism, which are signaled by means of high intensity transient signals, and middle cerebral artery blood flow.[8-11] For the first time, it is therefore possible to study how the known determinants of perioperative outcome may influence stroke. The aim of this study was to assess determinants of perioperative microembolism and cerebral perfusion.

METHODS

Patients. Between January 1995 and 1997 at Bristol Royal Infirmary (hospital 1) and between January 1997 and 1999 at Charing Cross Hospital (hospital 2), 235 patients were entered prospectively into this study. An appropriate temporal window to perform TCD was available for 192 of the patients, whereas in two patients no expert was available to perform TCD. Thus, TCD data was available for 190 of the patients (81%). The presenting characteristics of these patients are illustrated in Table I. The patients from the two different centers had similar presenting characteristics and outcome to surgery, with the exception of hypertension, which was a more common finding in the hospital 2 series, and echogenic type carotid plaques, which were more commonly found in patients at hospital 1. The carotid arteries were imaged with duplex ultrasound scanning (angle of insonation, 60 degrees; Ultramark 9, HDI, Advanced Technology Laboratories, Washington, DC) as a means of measuring the severity of stenosis and classifying plaque morphology according to the Gray-Weale classification.[12,13] A presenting symptom was defined according to the classification and outline of cerebrovascular disease described earlier.[2] The time in days from the last presenting symptom and a history of current cigarette use were recorded. Hypertension was noted to be a history of raised blood pressure requiring medication. Diabetes mellitus was defined to be a history requiring diet control, oral hypoglycemics, or insulin or a fasting blood sugar level higher than 7 mmol. Cerebral computed tomography (CT) scans were obtained in 122 patients (64%) preoperatively and examined by a consultant radiol-

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Table I. Characteristics and outcome of patients undergoing carotid endarterectomy with transcranial Doppler ultrasound scanning

Characteristic	*Hospital 1 patients*	*Hospital 2 patients*	*Overall*
Number	81	109	190
Median age (range, years)	69 (44-85)	70 (47-88)	69.5 (44-88)
Male	59	87	146 (77%)
No symptoms	7	7	14 (7%)
Amaurosis fugax	30	24	54 (28%)
TIA	29	52	81 (43%)
Stroke	15	26	41 (22%)
Time since last symptom (median and range, days)	84 (1-425)	45 (0-425)	56 (0-425)
Hypertension†	35	73	108 (57%)
Diabetes mellitus	8	19	27 (14%)
Ipsilateral stenosis (median and range, %)	90 (60-90)	90 (70-90)	90 (60-99)
Contralateral occlusion	8	19	27 (14%)
CT ipsilateral infarction	27/39	40/83	67/122
Echogenic plaque*†	51	21	72 (38%)
Perioperative stroke	3	3	6 (3%)

*Gray-Weale classification type 1 or 2.[12]
†Significant difference between the two hospital series ($P < .05$).
TIA, Transient ischemic attack; *CT*, computer tomography.

ogist, and the number and site of any cerebral infarctions was noted.

Transcranial Doppler ultrasound scanning. TCD (SCIMED PC DOP 842, 2 MHZ probe, Compuadd, SCIMED unit 5, Fishponds, Bristol, UK) was performed for 1 hour preoperatively and throughout the operation by a trained vascular technologist (D.B.) or research fellow (C.I., R.G., G.C.). The middle cerebral artery ipsilateral to the carotid artery to be operated on was insonated via the temporal window by using a 2-MHZ probe at a depth of 45 to 55 mm. The mean middle cerebral artery velocity (MCAV) was monitored continuously, and embolic transients were recorded. Preoperative probe fixation was performed with the manufacturer's headband, and during surgery, an in-house designed head guard was used as a means of preventing movement. Gain and power settings were established for each patient to maximize the quality of the trace. Emboli were recognized by their short duration with the following characteristics: a frequency- or velocity-focused intensity increase, unidirectional signals in the direction of flow accompanied by a characteristic clicking sound. Intensity thresholds varied from patient to patient to maximize the quality of the signal. All embolic signals were recorded onto digital audiotape and verified by an independent observer. A reproducibility study was performed involving 30 patients, testing for interobserver error, with verification onto a digital audiotape. Interobserver agreement for embolic signals exceeded 90%, as has been reported.[14] The numbers of microemboli (ME) were recorded during the 1 hour preoperative examination and during these phases of the operation: dissection of the carotid arteries (dissection ME) and after closure of the artery to completion of the operation (closure ME). At the time of the commencement of the study, there was no certainty that particulate and air emboli could be definitely separated. Therefore, emboli were recorded during three phases preoperatively and during carotid artery dissection and after carotid artery closure. All emboli during the phases when the artery was closed were assumed to be particulate.[15] Emboli at the time of shunting were not included.

Operative technique. All operations were performed with a general anesthetic with normotensive and normocarbic conditions. A consultant (A.H.D., R.M.G., P.L.) or supervised higher surgical trainee performed the procedure. Heparin (5,000 units) was routinely given intravenously before carotid cross-clamping;, and 75 mg of aspirin was given postoperatively; intravenous dextran or other antiplatelet drugs were not used. Dissection around the carotid bifurcation was minimized, and the detection of ME alerted the surgeon to alter the dissection technique. A Javid shunt was placed in 86% of patients (n = 163), because of surgeon preference. Two surgeons placed shunts routinely, whereas one surgeon used them selectively when the stump pressure was less than 50 mm Hg. The endarterectomy was feathered distally, and tacking sutures were placed when required. A 5-mm Dacron patch was used as a means of closing small carotid arteries (n = 97, 51%), and completion Doppler was performed.[16]

Outcome assessment and statistical analysis. The patients' risk for complications was assessed while patients were in the hospital and at their 6-week follow-up examination. Neurological assessment was performed by using a standard examination of cranial nerves and upper and lower limbs on recovery from anesthetic, on day 1, before discharge, and at the 6-week follow-up examination. A neurological deficit immediately after the procedure was defined as an intraoperative stroke. If a neurological deficit was demonstrated, a neurologist examined the patient. The carotid artery was only re-explored in the case of a perioperative stroke when a remedial abnormality was demonstrated by means of duplex imaging.[17] Comparison of

Table II. Emboli detected by means of transcranial Doppler ultrasound scanning

	Preoperative emboli (n = 28)	*No preoperative emboli (n = 162)*	P *value*	*Dissection emboli (n = 79)*	*No dissection emboli (n = 111)*	P *value*	*>9 closure emboli (n = 31)*	*≤9 closure emboli (n = 159)*	P *value*
Age <65 years	13	39	.01	28	24	.03	7	45	.5
Male	26	120	.02	59	87	.6	20	126	.04
Presenting complaint			.2			.2			.04
No symptoms	0	14		5	9		0	14	
Amaurosis fugax	11	43		27	27		11	43	
TIA	10	71		35	46		17	64	
Stroke	7	34		12	29		3	38	
Hypertension	18	90	.4	54	54	.007	20	88	.2
Contralateral occlusion	1	26	.05	9	18	.3	1	26	.06
GW 1/2	16	56	.02	37	35	.03	15	57	.2
Preoperative emboli	NA	NA		23	5	<.001	8	20	.1
Dissection emboli	NA	NA		NA	NA		21	58	.001

This table compares the characteristics of patient with emboli at various stages of surgery.
TIA, Transient ischemic attack; *GW 1/2,* Gray-Weale classification type 1 or 2[12]; *NA,* not applicable.

qualitative data was performed with the chi-square test, including the Yates correction, whereas median values were compared by using the Mann-Whitney *U* test. Significance was assumed when the *P* value was less than .05.

RESULTS

Microembolization. Microembolization was detected in 28 patients (15%) preoperatively, with a median number of 2 emboli per hour (range, 1-31). During dissection of the carotid arteries, ME were recorded in 79 patients (42%), with a median number of 3 emboli (range, 1-61); however, only 14 patients (7%) had 10 or more emboli detected during this stage of the operation. After closure of the carotid artery, emboli were recorded in 98 patients (52%), with a median number of 4 emboli (range, 1-29), and 31 patients (16%) had 10 or more ME.

Determinants of microembolization. Table II relates the detection of ME to possible risk factors for embolization and known risk factors for perioperative stroke. Preoperative emboli were more common in young, male patients with echoluscent-type plaques. Dissection ME were more common in young patients, patients with a history of hypertension, and patients with echoluscent-type plaques, and they were highly predicted by the presence of preoperative ME. In contrast, ME after closure of the carotid artery were only predicted by the occurrence of emboli during the dissection of the carotid artery. However, 10 or more closure emboli were more common in women and patients with symptoms, and they were highly predicted by the occurrence of dissection emboli (Table II).

The intraoperative mean middle cerebral artery velocity. The median MCAV before carotid cross-clamping was 40 cm/s (range, 14-80 cm/s), on clamping it was 28.5 cm/s (range, 0-90 cm/s), and on clamp release it was 43 cm/s (range, 8-104 cm/s). None of the patient-related variables, including contralateral carotid occlusion, predicted the intraoperative middle cerebral artery velocity.

Perioperative neurological outcome. There were six (3%) perioperative strokes; all occurred ipsilateral to the carotid artery on which the operation was performed, and one was fatal. All these patients had an intraoperative shunt placed (Table III). One patient with an evolving stroke had a more significant deficit demonstrated postoperatively. Three more patients sustained an intraoperative stroke; 0, 10, and 22 ME, respectively, had been indicated by means of TCD on closure. In the first patient, there were problems with blood pressure control intraoperatively, even before carotid cross-clamping, with the blood pressure rising to more than 200 mm Hg. Some cerebral edema in the immediate perioperative period were demonstrated by means of a CT scan; the results of duplex scanning of the carotid artery were normal. The cerebral edema and the patient's hemiplegia quickly improved in the next 3 days. The second patient was immediately re-explored, and a thrombectomy was performed; this patient later died. The third patient had no thrombus demonstrated by means of perioperative duplex scanning; however, internal carotid occlusion was demonstrated by means of a further scan at 6 weeks. Another patient, in whom no ME were detected intraoperatively, had thrombosis of the endarterectomy site at 12 hours demonstrated by means of duplex scanning and confirmed at re-operation. A homonymous hemianopia developed in the final patient at 48 hours. By means of duplex scanning at this time, the carotid arteries were demonstrated to be patent; however, 13 emboli during artery dissection and 20 after closure had been detected by means of intraoperative TCD.

Determinants of perioperative outcome. Because of the small number of strokes, statistical comparison was not possible. Table III shows the relationship between perioperative stroke and preoperative or intraoperative factors. Stroke was more common in patients with preoperative evidence of ipsilateral CT infarction and patients with 10 or more ME during carotid artery closure. The combination of 10 or more ME during carotid closure and preoperative evidence of cerebral infarction or intraoperative MCAV of less than 40 cm/s was present in three of the six patients who sustained a perioperative stroke.

DISCUSSION

Earlier investigations have demonstrated an association between perioperative microembolization and stroke.[18-20] Both Ackerstaff et al[18] and Gaunt et al[19] found an association between 10 or more emboli occurring during carotid artery dissection and perioperative stroke[18] or poor cognitive function.[19] A more recent publication by Ackerstaff et al demonstrated a significant association between both dissection and closure emboli and perioperative stroke.[20] In keeping with these studies, we found 10 or more closure emboli present in three of the six patients who had a perioperative stroke in our series (Table III).

The risk factors for perioperative stroke are well known and include female sex, more significant presenting symptoms, hypertension, and cerebral infarction.[1-5] This study suggests that some of these factors predict increased thromboembolism after carotid endarterectomy or increased susceptibility to the effects of cerebral embolism. Many studies have demonstrated an increased rate of perioperative stroke in women,[1-3] and this has been related to smaller carotid diameter.[21] In this study, significant microembolization (≥10) after carotid artery closure was more commonly detected in women (Table II). Preoperative embolization was actually more common in men. Embolization was also identified more commonly in patients with echogenic-type plaques, as might be expected from their association with unstable symptoms and high-cholesterol plaques[12,22] (Table II). Similarly, patients with symptomatic disease more commonly had significant closure ME detected (Table II). Hypertension, another predictor of perioperative stroke,[1] was associated with ME occurring during carotid artery dissection (Table II).

The mechanism by which ME predict subsequent stroke is incompletely understood. Results of studies of patients without symptoms demonstrate that high frequency of embolization predicts the subsequent development of symptoms, suggesting that this is a measure of plaque instability.[22] However, after carotid endarterectomy, ME have been related to thrombus at the site of atheroma removal and can precede internal carotid thrombosis.[23] In our study, three of the 31 patients with significant closure emboli sustained a stroke (Table III); in one of these cases, thrombosis of the internal carotid artery was discovered at re-exploration. Presumably, in the other two cases, thrombus had embolized to the brain. In one patient (number 6), closure ME predicted development of homonymous hemianopia at 48 hours. The reason for this delay in the development of symptoms is unclear, but may relate to the time required for a mature cerebral infarction to develop or the requirement for repeated embolization.

In this study, microembolization was not recorded during shunt placement or after carotid surgery was completed. Emboli may have been detected in some of the other patients who had a perioperative stroke during these periods of surgery, as other investigators have demonstrated.[24]

There appear to be at least two factors determining the results of embolization. First is the quantity and likely the size of ME. Second, some patients appear to be less able to deal with significant numbers of emboli. Patients with reduced intraoperative MCAV and patients with evidence of pre-existing cerebral infarction are examples demonstrated from our data (Table III), but there are likely other patients. Unexpectedly, contralateral carotid disease was not associated with low MCAV, possible because of the variable nature of cerebral compensatory mechanisms, which is illustrated by the variation in anatomy of the circle of Willis. Recently, the unfavorable effect of contralateral carotid occlusion on the outcome of carotid surgery has been questioned.[25]

The large randomized trials of carotid endarterectomy demonstrated that 15 to 18 patients with a symptomatic tight carotid stenosis required surgery as a means of preventing one disabling stroke.[26,27] One approach to improving the benefits of surgery is excluding patients at increased risk of perioperative stroke.[1] Alternatively, targeted pharmacological and operative techniques in certain high-risk patients may have a beneficial effect on the perioperative stroke rate. For example, dissection ME have been reduced by means of changes in operative technique.[28] Microembolization after carotid artery closure has been reduced by means of intravenous infusion of the platelet inhibitors, such as dextran and the nitric oxide donor s-nitrosoglutathione.[24,29] Such therapy can be asso-

Table III. Characteristics of patients who had a perioperative stroke

	Stroke (n = 6)	*No stroke (n = 184)*
Age <65 years	2	50
Male	5	141
No symptoms	0	14
Amaurosis fugax	1	53
TIA	4	77
Stroke	1	40
Symptoms within 1 month	2	64
Hypertension	3	105
Diabetes mellitus	0	27
Smoking	4	83
CT infarction	4/4	63/118
GW 1/2	1	71
Shunt	6	157
Patch	5	92
Preoperative ME	1	27
Dissection emboli	2	77
≥10 dissection emboli	1	13
Closure emboli	3	95
≥10 closure emboli	3	28
CT infarction and >9 closure emboli	3/6	11/172
PreMCAV <40 cm/s	4	88
PreMCAV <40 cm/s and >9 closure emboli	3	13
MCAV <40 cm/s	4	140
MCAV <40 cm/s and >9 closure emboli	3	24

TIA, Transient ischemic attack; *CT,* computed tomography; *GW 1/2,* Gray-Weale classification type 1 or 2[12]; *ME,* microemboli; *PreMCAV,* mean middle cerebral artery velocity before carotid cross-clamping; *MCAV,* mean middle cerebral artery velocity on carotid cross-clamping.

ciated with complications; for example, dextran has been linked to bleeding and renal failure.[24] Thus, it may be appropriate to use this therapy selectively in high-risk patients. Another approach suggested by other authors is to continue TCD monitoring in the recovery room and selectively use antiplatelet therapy on the basis of closure emboli frequency.[23,24]

In conclusion, it is suggested by means of the data obtained with TCD that patients are at increased risk of perioperative stroke because of higher rates of thromboembolism or increased susceptibility to it. By understanding and predicting this, it may be possible to intervene selectively in the perioperative period to reduce stroke in this high-risk group.

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