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Possible Determinants of Early Microembolism After Carotid Endarterectomy

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Background and Purpose—High numbers of microembolic signals (MES) have been associated with increased risk of postoperative stroke after carotid endarterectomy (CEA). We sought to identify factors predictive of postoperative MES.

Methods—Transcranial Doppler monitoring of the ipsilateral middle cerebral artery for MES was performed for 30 minutes during the first postoperative hour in sequential patients undergoing CEA. Stepwise binomial logistic regression analysis was performed to identify preoperative and intraoperative variables that predicted the occurrence of postoperative MES.

Results—We studied 141 patients (mean age, 69 years); 102 (72%) were male, and 69 (49%) had at least 1 MES (range, 1 to 118) detected in the first postoperative hour. The risk of postoperative MES was greater in women ($P=0.027$), patients not receiving antiplatelet therapy ($P=0.033$), and patients undergoing left-sided CEA ($P=0.049$). Other variables such as residual stenosis seen on completion angiography and operative technique were not associated with postoperative MES.

Conclusions—Postoperative MES were most likely in women, patients not receiving preoperative antiplatelet therapy, and patients who had a left CEA. Microembolism might explain why these same factors are associated with higher rates of perioperative stroke. (*Stroke*. 2002;33:2082-2085.)

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

The European Carotid Surgery Trial (ECST) and North American Symptomatic Carotid Endarterectomy Trial (NASCET) investigators reported a clear benefit of carotid endarterectomy (CEA) in the prevention of stroke in patients with high-grade, recently symptomatic carotid stenosis.^{1,2} This benefit is offset by the surgical risk of the procedure. Perioperative stroke and death rate for patients with high-grade stenosis was 7.5% at 30 days in ECST and 5.8% in NASCET. These rates are acceptable given the absolute risk reduction from surgery of 9.6% and 17%, respectively. However, for patients with asymptomatic carotid disease, the risk-to-benefit ratio is narrower, with an absolute risk reduction of only 1.2% per year. Clearly, a better understanding of surgical risk in patients undergoing CEA will aid in the development of strategies to improve the risk-to-benefit ratio of surgery. Identifying risk factors is an important step in this process.

Recently, several risk factors for perioperative stroke associated with CEA have been identified. These include female sex, recent ipsilateral hemispheric stroke, contralateral carotid artery occlusion, left-sided endarterectomy, plaque ulceration, age >75 years, systolic blood pressure >180 mm Hg, peripheral vascular disease, siphon or external carotid artery stenosis, cerebral

(versus ocular) ischemia, and ipsilateral ischemic lesion on CT scan.³⁻⁶ Microembolic signals (MES) detected by transcranial Doppler (TCD) are associated with an increased risk of stroke and new ischemic lesions on MR scans after CEA.⁷⁻¹² In our previous study, >50 MES per hour detected during the first postoperative hour was significantly associated with new ischemic neurological deficits.¹³

At present, factors involved in the generation of MES are poorly understood. Should the use of MES as a surrogate prove useful, their presence might be used to identify patients suitable for preventive measures. We have already reported that intravenous administration of 10% dextran 40 begun intraoperatively reduces postoperative MES.¹⁴ Using the same data set, we now provide an exploratory analysis to identify clinical and operative factors associated with MES.

Subjects and Methods

Sequential patients with carotid artery stenosis undergoing CEA at a major Melbourne University teaching hospital (Austin and Repatriation Medical Centre) and its associated private hospital (Warrigal Private Hospital) were enrolled as part of the ongoing prospective, randomized, double-blind, placebo-controlled trial of Dextran In Carotid Endarterectomy (DICE). The study involves 2 parts: part 1

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tested the hypothesis that dextran reduces MES in the early postoperative period; and part 2 (in progress) is testing the hypothesis that dextran reduces the incidence of perioperative stroke. There were no other primary or secondary outcomes of these studies. The data obtained from part 1 are the basis of this article.

Inclusion and Exclusion Criteria

Patients with symptomatic or asymptomatic carotid artery stenosis in whom CEA was to be performed were considered for inclusion. Exclusion criteria included poor temporal ultrasound window, refusal to consent, and nonatheromatous 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 $<100\,000/\text{mm}^3$, administration of dextran or any other hemodilution agent over the 72 hours before 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. All patients enrolled in the study gave informed consent.

TCD Monitoring

Monitoring was performed with 2-MHz pulsed-wave TCD ultrasound (MultiDop T, DWL Elektronische Systeme GmbH, EME-Nicolet TC 2020). 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 and again for 30 minutes during the first postoperative hour. The TCD signal was recorded onto digital audiotape, and blinded observers performed "offline" screening on the EME-Nicolet TC 2020. Possible MES were then further scrutinized jointly by 2 blinded observers. MES were recorded as a continuous variable, but the analysis was performed with MES as a dichotomous variable (present or absent).

Definitions

Patients with ipsilateral hemispheric or retinal symptoms of transient ischemic stroke or stroke occurring ≤ 120 days before CEA were defined as symptomatic in accordance with NASCET criteria.¹ Plaque characteristics were determined from visual inspection by the surgeon when the vessel was opened. These included ulceration (macroscopic evidence of vascular endothelial ulceration) and intraplaque hemorrhage (subendothelial hemorrhage at intraoperative plaque sectioning).

The following risk factors were documented: (1) hypertension, defined as a history of hypertension and/or blood pressure $>140/90$ mm Hg; (2) diabetes, defined as a history of diabetes and/or fasting blood glucose level ≥ 7.5 mmol/L; (3) current smoking, defined as a history of smoking over the preceding 28 days; (4) ischemic heart disease, defined as a history of or treatment for angina pectoris and/or myocardial infarction; (5) atrial fibrillation, defined as atrial fibrillation documented on the preoperative ECG; (6) peripheral vascular disease, defined as a history of intermittent claudication or treatment for peripheral vascular disease; and (7) high cholesterol, defined as a history of high cholesterol and/or fasting blood cholesterol concentration ≥ 5.5 mmol/L.

The degree of internal carotid artery stenosis was assessed preoperatively with either digital subtraction angiography (according to NASCET criteria)¹ or color-flow duplex ultrasonography.¹⁵ The surgeon determined residual stenosis on completion angiogram. MES were defined in accordance with criteria of the Consensus Committee of the Ninth Cerebral Hemodynamic Symposium¹⁶ as high-intensity, transient, unidirectional signals that occurred randomly within the spectral display with a typical high-pitched auditory accompaniment. The signal amplitude above background was ≥ 6 dB.

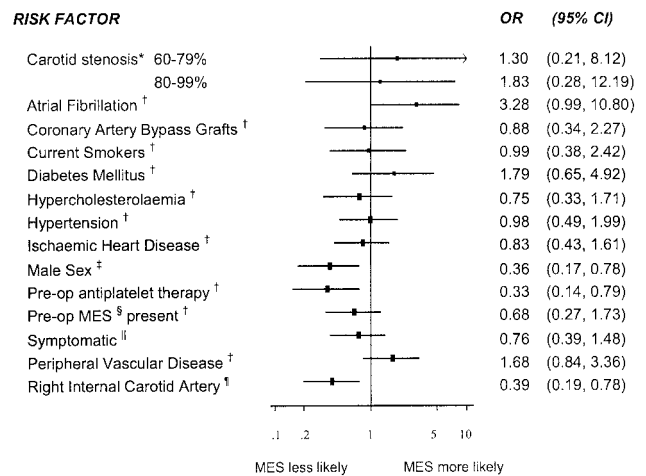


Figure 1. Univariate analysis of the effect of preoperative factors (Pre-op) on the presence of postoperative MES (n=141). *Versus 40% to 59%, NASCET criteria; †versus absence or not used; ‡versus female; §microembolic signal; ||symptoms <120 days versus no symptoms or symptoms >120 days; ¶versus left internal carotid artery.

Statistical Analysis

Exploratory analyses were conducted by use of binomial logistic regression analysis. Preoperative and intraoperative variables were used to identify factors likely to predict the occurrence of postoperative MES (Figures 1 and 2). All variables were dichotomous except for categories of carotid stenosis on the preoperative angiogram and duplex ultrasound studies (whichever modality was available) (40% to 59%, 60% to 79%, 80% to 99%), residual stenosis on completion angiogram (0% to 10%, 11% to 20%, 21% to 30%, 41% to 50%), and age (in years). The analysis was carried out initially in a multivariate fashion by inserting all variables in the model and then using backward stepwise elimination to obtain a global model. The independence of terms in the final global model was confirmed by the absence of interactions. Odds ratios (ORs) and 95% confidence intervals (95% CIs) for all individual variables were estimated by logistic regression analysis. Continuous variables were summarized as mean and SD. The analyses were performed using SYSTAT version 9 (SPSS Inc).

Risk Factors

The following variables were entered into the model: age, sex, side of surgery, degree of carotid artery stenosis, atrial fibrillation,

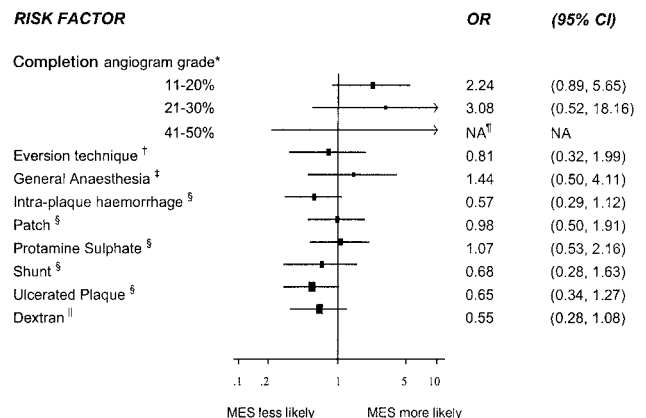


Figure 2. Univariate analysis of the effect of intraoperative factors on the presence of postoperative MES (n=141). *Versus 0% to 10%, NASCET criteria; †versus standard technique; ‡versus local anesthetic; §versus absent or not used; ||versus placebo; ¶only 1 patient had 41% to 50% residual stenosis.

diabetes mellitus, hypercholesterolemia, hypertension, ischemic heart disease, peripheral vascular disease, preoperative stroke or transient ischemic attack, past coronary artery bypass grafts, smoking within 28 days of surgery, preoperative antiplatelet therapy, preoperative MES, plaque ulceration or intraplaque hemorrhage, anesthetic (general or local), treatment with dextran, surgical technique (eversion or longitudinal), shunt, patch versus primary closure, reversal of heparin with protamine sulfate, and residual stenosis seen on completion angiogram.

Results

Of the 150 patients randomized in part 1 of DICE, 2 patients did not have CEA, 1 withdrew from the study, 3 did not have TCD recordings, 2 did not have a technically satisfactory recording, and 1 tape recording was lost. Thus, satisfactory postoperative TCD recordings were obtained from 141 patients, with a mean age 69.3 years (range, 41 to 84 years; SD, 8.35 years). Of the 141 patients, 102 (72%) were male, 80 (57%) were symptomatic, 96 (68%) had hypertension, 18 (13%) had diabetes, 61 (43%) had ischemic heart disease, 51 (36%) had peripheral vascular disease, and 21 (15%) were current smokers.

One hundred seven patients (76%) received aspirin the week before surgery, and 15 patients (11%) were taking other antiplatelet drugs. Nineteen patients (13%) were not taking antiplatelet drugs. Seventy-two patients (51%) received dextran begun on skin incision and continued for 16 hours; the remainder received placebo. Degree of stenosis by digital subtraction angiography (96 patients) or duplex (45 patients) was 40% to 59% in 5 patients (4%), 60% to 79% in 39 patients (28%), and 80 to 99% in 97 patients (69%).

One hundred twenty-five operations (89%) were performed in patients under general anesthetic. All patients received an intraoperative bolus dose of heparin (5000 or 7000 U). Protamine sulfate was administered to 94 patients (67%) at the discretion of the attending surgeon after arteriotomy closure. Eighty-three procedures (59%) were primary closure (versus patch angioplasty), and 23 (16%) were performed with an eversion technique. In 111 patients (79%), a common carotid-to-internal-carotid-artery shunt was inserted. Completion angiogram showed <10% residual stenosis in 61 patients (43%), 11% to 20% in 27 patients (19%), 21% to 30% in 6 patients (4%), and 41% to 50% in 1 patient (<1%). In the remaining 46 patients (33%), the angiogram result was either missing or not performed.

Embolic Signal Detection

Sixty-nine patients (49%) had at least 1 MES (range, 1 to 118) detected within the first postoperative hour. This served as the dependent variable.

Adequate preoperative TCD signals were obtained in 110 patients. Twenty-seven patients (25%) had at least 1 MES (range, 1 to 9 per hour; SD, 1.51) detected preoperatively.

Prediction of Postoperative MES

The best predictive model of postoperative MES included sex, antiplatelet therapy, and side of procedure. Women ($P=0.027$), patients not receiving preoperative antiplatelet therapy ($P=0.033$), and patients having a left-sided endarterectomy ($P=0.049$) were more likely to have MES (the Table). No other preoperative variables and none of the

Multivariate Analysis of Independent Predictors of Postoperative MES

Risk Factor	OR	95% CI	P
Male sex*	0.40	0.18 to 0.90	0.027
Preoperative antiplatelet therapy†	0.37	0.15 to 0.92	0.033
Right internal carotid artery‡	0.47	0.23 to 0.99	0.049

*Versus female sex.

†Versus no antiplatelet therapy.

‡Versus left internal carotid artery.

intraoperative variables were associated with postoperative MES (Figures 1 and 2), including age ($P=0.88$).

Discussion

This is the first study in which clinical and intraoperative factors associated with postoperative MES have been reported. We identified 3 factors associated with postoperative MES: female sex, left-sided CEA, and the absence of treatment with preoperative antiplatelet therapy. Treatment with dextran was not independently associated with the presence (versus absence) of MES, but we previously reported that dextran lowered the number of emboli (Wilcoxon-Mann-Whitney U test, $P=0.052$ at 0 to 1 postoperative hour, $P=0.043$ at 2 to 4 postoperative hours).¹⁴

Interestingly, only preoperative variables were significantly associated with postoperative MES. Two of these were nonmodifiable risk factors (sex and side of surgery), leaving only preoperative antiplatelet therapy as a modifiable factor influencing outcome.

The observation that antiplatelet therapy reduced early postoperative MES is important because some surgeons do not begin aspirin prophylaxis until several days after surgery. Aspirin treatment in patients undergoing CEA can reduce the risk of postoperative stroke.^{17,18}

Dextran has antiplatelet, rheologic, and intravascular volume expansion effects. Lennard and colleagues, in an open-label, uncontrolled series, observed that postoperative administration of 10% dextran 40 reduced the rate of TCD-detected MES after CEA.¹⁹ Our previous study was the first blinded, randomized trial to show that perioperative administration of 10% dextran 40 reduces early postoperative MES.¹⁴ Although a reduction in embolic signals from treatment with dextran may reduce the risk of postendarterectomy stroke, this remains to be proven. Other antiplatelet agents that reduce postoperative MES are S-nitrosoglutathione²⁰ and L-arginine.²¹

Preoperative stroke is reportedly more common in patients undergoing left-sided CEA.^{3,5} The explanation might be that dominant-hemisphere infarcts are likely to result in clinically detectable neurological dysfunction. However, we found that MES were more likely in patients after a left-sided CEA, and the stringent assessment of stroke, rather than differences in reporting, supports an embolic process.^{3,5,6} Indeed, some right-handed surgeons find operating on the left carotid artery from the left side of the patient technically difficult. Of interest, the surgeons participating in the present study are all right handed.

Compared with men, women experience a higher rate of stroke after CEA⁴ and after coronary artery bypass graft surgery.^{22,23} The smaller vessel lumen diameter in women is thought to increase the technical difficulty of surgery. It is conceivable that technical difficulty increases the likelihood of postoperative MES.

In both NASCET and ECST, cerebral rather than ocular events were associated with increased risk of stroke and death after CEA.^{3,4} Although the type of vascular event was not differentiated in the present study, time from the qualifying event to CEA (≤ 120 days of surgery) was considered but was found to be nonsignificant. Similarly, time since a qualifying event in NASCET and ECST was not associated with perioperative stroke, although it should be noted that surgeons participating in ECST were advised not to operate until at least 1 month after the qualifying event.⁴

None of the intraoperative variables examined in NASCET and ECST were associated with increased perioperative stroke.^{3,4} Similarly, we did not identify any intraoperative variables associated with postoperative MES. Plaque ulceration and intraplaque hemorrhage should not influence postoperative MES because the source of MES during dissection is removed before postoperative TCD assessment.

This study has several potential limitations. First, it is possible that >30 minutes is needed to identify the embolizing artery. Second, we cannot clearly determine whether lesions of the intracranial vessels or heart were also responsible for the MES. It is important to note that the analysis reported here was retrospective and exploratory, so no a priori estimates of minimal sample size were made. The study may have been underpowered given the number of patients in this analysis and therefore could have resulted in a type 2 error. Alternatively, the number of variables studied could have increased the likelihood of a type 1 error.

In conclusion, postoperative MES were most likely in women, patients not receiving perioperative antiplatelet therapy, and patients who had a left-sided CEA. Microembolism might explain why these same factors are associated with higher rates of perioperative stroke.

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