Medical Complications Associated With Carotid Endarterectomy

Maurizio Paciaroni, MD; Michael Eliasziw, PhD; L. Jaap Kappelle, MD; Jane W. Finan, BScN; Gary G. Ferguson, MD; Henry J.M. Barnett, MD; for the North American Symptomatic Carotid Endarterectomy Trial (NASCET) Collaborators

Background and Purpose—Carotid endarterectomy (CE) has been shown to be beneficial in patients with symptomatic high-grade (70% to 99%) internal carotid artery stenosis. To achieve this benefit, complications must be kept to a minimum. Complications not associated with the procedure itself, but related to medical conditions, have received little attention.

Methods—Medical complications that occurred within 30 days after CE were recorded in 1415 patients with symptomatic stenosis (30% to 99%) of the internal carotid artery. They were compared with 1433 patients who received medical care alone. All patients were in the North American Symptomatic Carotid Endarterectomy Trial (NASCET).

Results—One hundred fifteen patients (8.1%) had 142 medical complications: 14 (1%) myocardial infarctions, 101 (7.1%) other cardiovascular disorders, 11 (0.8%) respiratory complications, 6 (0.4%) transient confusions, and 10 (0.7%) other complications. Of the 142 complications, 69.7% were of short duration, and only 26.8% prolonged hospitalization. Five patients died: 3 from myocardial infarction and 2 suddenly. Medically treated patients experienced similar complications with one third the frequency. Endarterectomy was 1.5 times more likely to trigger medical complications in patients with a history of myocardial infarction, angina, or hypertension ($P<0.05$).

Conclusions—Perioperative medical complications were observed in slightly fewer than 1 of every 10 patients who underwent CE. The majority of these complications completely resolved. Most complications were cardiovascular and occurred in patients with 1 or more cardiovascular risk factors. In this selected population, the occurrence of perioperative myocardial infarction was uncommon. (Stroke. 1999;30:1759-1763.)

Key Words: carotid endarterectomy ■ clinical trials ■ complications

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Endarterectomy Trial showed unequivocal benefit of carotid endarterectomy (CE) in symptomatic patients with high-grade internal carotid artery (ICA) stenosis (70% to 99%).1,2 The parallel study dealing with symptomatic patients with moderate-grade stenosis (30% to 69%) showed benefits of CE only in a carefully selected group of patients.3 Currently, CE is the most common elective peripheral vascular procedure, which in 1997 was performed in $\approx$130 000 patients in the United States.4

Despite benefit in the long term, CE may cause complications either by the operation itself or by concomitant medical conditions. The challenge for the future is to reduce the perioperative risk as much as possible. The incidence and type of complications that are directly related to the surgical procedure have been the subject of many reports,5–10 whereas medical complications that are not directly caused by the procedure have received less attention. The aim of the present study is to describe the incidence and type of medical complications that occurred in patients randomized into NASCET and to determine their association with baseline risk factors.

Subjects and Methods

The methods of the NASCET have been described in detail elsewhere.1,11 Briefly, NASCET was a randomized clinical trial designed to compare the benefit of best medical therapy alone with best medical therapy plus CE in patients with recent transient or nondisabling neurological deficit caused by cerebral or retinal ischemia in the territory of the ICA. Among the exclusions were patients with recent history (6 months) of myocardial infarction, unstable angina pectoris, atrial fibrillation, recent congestive heart failure, and valvular heart disease. For inclusion, the ICA had to have a 30% to 99% stenosis as assessed by selective carotid angiography and to be technically suitable for CE. Baseline evaluations included a detailed medical history and complete physical and neurological examination.

Surgeons were invited to join NASCET if the center had a documented CE stroke and death rate of $\leq$6% in a minimum of 50
consecutive cases over a 2-year period. Surgery was completed at the earliest opportunity after randomization, and patients underwent a second complete physical and neurological examination 30 days after surgery. All medical and surgical complications that caused transient or permanent disability within the 30-day period were recorded.

Medical complications consisted of myocardial infarction (based on ECG and cardiac enzyme changes), arrhythmia (requiring antiarrhythmic medication), congestive heart failure, angina pectoris, hypertension (diastolic blood pressure >100 mm Hg requiring intravenous medication), hypotension (systolic blood pressure <90 mm Hg requiring administration of vasopressor agent), sudden death, respiratory problems (pneumonia, atelectasis, pulmonary edema, or exacerbation of chronic obstructive pulmonary disease), renal failure (doubling of preoperative urea and/or creatinine), depression, and confusion (requiring restraint). Complications were considered mild if they were transient and did not prolong hospital stay, moderate if they were transient but caused delay in hospital discharge, and severe if they were associated with permanent disability or death.

In the present study, patients were excluded from the analyses if they had serious complications that were directly attributable to the surgical procedure, such as those due to anesthesia, thrombosis at the operative site, wound hematomas requiring surgical intervention, or deficits from a vagus nerve injury interfering with swallowing. These surgical complications are described in detail elsewhere.12 For comparative purposes, a list of complications that occurred in the medically treated arm of NASCET was compiled for the 32-day period after randomization (ie, the 30-day period plus the average 2 days that lapsed from randomization to CE in the surgical arm). In both the surgical and medical arms, patients were censored at the time of a stroke, since the subsequent medical complications are commonly the result of the stroke.

Cox proportional hazards regression modeling was used to identify baseline factors that increased the risk of perioperative medical complications. Adjusted hazard rates and adjusted hazard ratios were used to summarize the results. The estimated hazard ratio (or relative hazard) is a measure of association that can be interpreted as a rate for a factor being adjusted. The modeling strategy consisted of initially fitting a “full” model, which included all factors. A “final” model was determined by eliminating all factors that were not significantly predictive of the medical complications, using a backward selection approach. The “change-in-estimate” strategy was used to determine whether the remaining factors in the final model were independent risk factors. A factor was considered an independent risk factor if the change in hazard ratios between the full and final models was <10%.

Results
A total of 1436 eligible patients were randomized to the surgical arm and 1449 to the medical arm of the NASCET. In the surgical arm, 21 patients were not operated on for various reasons.12 In the medical arm 16 patients crossed over to surgical therapy within 30 days, leaving 1433 patients for analysis. CE was performed in 1415 patients (328 patients with severe stenosis and 1087 with moderate stenosis). Of the 1415, 59 (4.2%) patients had serious surgical complications that excluded them from further analyses, and 115 (8.1%) had medical complications (Table 1). Of the 142 complications, 69.7% were mild, 26.8% were moderate, and 3.5% were severe. Twenty patients had ≥2 complications. No patient had pulmonary embolus, renal failure, or depression requiring medication. Cardiovascular disorders were >4 times as common as all other conditions combined. All 5 severe complications were fatal and were caused by cardiovascular disorders: 3 patients had fatal myocardial infarction, and 2 patients died suddenly. Of the patients with fatal myocardial infarction, 2 patients had massive myocardial infarctions on the day of surgery. In the other patient, CE was prolonged (7 hours) because of intraoperative occlusion of the ICA. Twenty-four hours after CE, the patient had a myocardial infarction followed by cardiac arrest, leaving the patient in a vegetative state. The patient died 2 months later. Two patients died suddenly on days 3 and 6 after CE, and both had a history of previous myocardial infarction. All patients with fatal medical complications were male, and all had multiple cardiovascular risk factors.

After endarterectomy, 11 patients (0.8%) had nonfatal myocardial infarction, 22 (1.6%) had arrhythmia (of whom 11 had atrial fibrillation), 14 (1.0%) had congestive heart failure, and 19 (1.3%) had angina pectoris (68% of which were recurrent). One of the 22 patients with arrhythmia developed atrial fibrillation during the operation. This was followed by a nondisabling stroke on the following day.

For the medically treated patients, the comparable figures were 2 (0.1%) for myocardial infarction, 4 (0.3%) for arrhythmia, 2 (0.1%) for congestive heart failure, and 9 (0.6%) for angina pectoris (89% of which were recurrent). None of the patients had fatal myocardial infarction or sudden death. Of the 9 patients in the medical arm with angina in the 32-day postrandomization period, all but 1 had a prior history of angina or myocardial infarction.

Twenty-four patients in the surgical arm had perioperative hypertension, with the systolic blood pressure ranging from 180 to 260 mm Hg and diastolic blood pressure from 70 to 120 mm Hg. Effective management was achieved with intravenous medication (nitropresside, nitroglycerin, clonidine, hydralazine, nifedipine, or labetolol) for a period of 9 to 48 hours. None suffered from hyperperfusion syndrome, and 1 patient had transient hypertensive encephalopathy. In patients with hypotension, the systolic values ranged from 60 to 90 mm Hg and the diastolic values from 30 to 60 mm Hg. In 8 of the 24 patients, effective management was achieved with one bolus of medication (dopamine, ephedrine, dobutamine, or phenylephrine). In 16 patients, perioperative hypotension required continuous intravenous medication for a period of 8 to 24 hours. Six patients had temporary confusion (the duration ranging from 24 to 72 hours) due to acute alcohol withdrawal or severe electrolyte imbalance or of unknown cause.

The baseline factors considered in the regression model are shown in Table 2, with corresponding adjusted hazard rates and ratios. Only a history of myocardial infarction or angina and a history of hypertension remained statistically significant in the final model (Table 3). Since the hazard ratios in the final model for both these factors are within 10% of the corresponding hazard ratios in the full model, they may be considered independent risk factors for medical complications. In each case, the risk of a medical complication is increased >1.5-fold. It is interesting to note that these 2 factors correspond to the 2 most prevalent medical complications listed in Table 1, namely, cardiovascular disorders and hypertension. Two other factors, elderly age and history of diabetes, increased the risk of a complication in the full model.
but failed to reach statistical significance in the resulting backward selection process. None of the other factors listed in Table 2 appeared to increase the risk by any clinically important amount.

### Discussion

The present study described the risks and types of perioperative medical complications associated with CE in a large number of patients. Perioperative medical complications occurred in <10% of the patients that underwent CE, but few (0.4%) had severe complications. The risk of a medical complication was increased in patients with a history of cardiac disease and a history of hypertension.

In patients who are candidates for vascular surgery, the prevalence of coexisting coronary lesions is high, but perioperative nonfatal and fatal myocardial infarction occurred in only 14 (1.0%) of the 1415 patients and resulted in a mortality rate of ~0.2%. This may have been related to the exclusion from the trial of patients with a recent history of myocardial infarction, unstable angina pectoris, or recent congestive heart failure. It may also be related to the administration of enteric-coated aspirin to all subjects. The 2 sudden deaths were probably caused by myocardial ischemia. The risk of myocardial infarction after CE in symptomatic patients has been reported but varies in different settings. Fatal perioperative myocardial in-
fraction varies in incidence from 1% to 1.7%.10,13,16 By having strict cardiac exclusion criteria, the NASCET minimized the risk of myocardial infarction.

The patients who died of medical complications in the perioperative period all died from cardiac causes, and all had multiple cardiovascular risk factors. A routine of preoperative noninvasive cardiac investigation is generally adequate to identify patients at high risk of future coronary events.17 The preoperative investigation must include careful history taking with particular emphasis on previous myocardial infarction, past or persisting angina, decreased exercise tolerance, other evidences of past or persisting congestive failure, and history of or persistence of rhythm disorder. ECG and chest radiography to ascertain heart size should be routine.18,19 A trans-thoracic and, when indicated, a transesophageal echocardiogram, a stress test, and rhythm monitoring should be obtained when there is doubt. A cardiology consultation is a prudent measure when the cardiac features are not straightforward. If cost were of no consequence, the use of all or most of the tests mentioned would make an interesting study. This luxury did not exist in the NASCET protocol, nor was it designed to evaluate the contributions of the more expensive tests. Others have reviewed them with cost-effectiveness as the focus.20

The risk in the postoperative period of developing angina pectoris for the first time was more than triple in patients who had CE in comparison to medically treated patients within the same period. These comparisons suggest that most of the cardiovascular complications were triggered by the procedure. Previous studies have also identified an increased incidence of cardiac complications. Wong et al21 reported at least 1 cardiac complication of angina, myocardial infarction, congestive heart failure, or dysrhythmia in 8.9% of 291 patients.

Uncontrolled hypertension and hypotension were also frequent medical complications in the NASCET patients. They were easily managed in all cases, and prolonged hospitalization was necessary only twice. It is important to monitor the blood pressure carefully and to treat it appropriately. Ischemic stroke, in association with this finding, has been reported,21 but not in the present study. Postoperative hypertension may be caused by the surgical interference with the baroreceptors. Humoral factors, including renin and vasopressin released into the carotid circulation from the endarterectomy site, have been implicated.22–24 Sustained hypertension after CE has been reported,5,21 but in NASCET the long-term effect on blood pressure was similar between the medial and surgical patients.25 Postoperative hypertension has been associated with hemorrhagic stroke and cerebral edema within the context of a cerebral hyperperfusion syndrome, caused by a sudden increase in perfusion pressure.26–32 In the present study, none of 20 patients with postoperative hypertension had a perioperative hemorrhagic stroke,12 although 1 patient was diagnosed with transient hypertensive encephalopathy. Hypotension, presumably caused by baroceptor dysfunction, may have serious consequences after CE, but in NASCET none of the patients with this phenomenon had a subsequent stroke. In addition, none of the NASCET patients had a pulmonary embolism. Early mobilization, usual after CE, appears to avoid this serious complication.

### TABLE 2. Adjusted Hazard Rates and Ratios From Full Cox Regression Model

<table>
<thead>
<tr>
<th>Baseline Factor</th>
<th>Adjusted Hazard Rates</th>
<th>Adjusted Hazard Ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 vs &lt;65 y</td>
<td>9.9 6.2</td>
<td>1.6</td>
<td>0.03</td>
</tr>
<tr>
<td>Male vs female sex</td>
<td>8.1 8.0</td>
<td>1.0</td>
<td>0.97</td>
</tr>
<tr>
<td>Stroke vs TIA as presenting event</td>
<td>8.5 7.7</td>
<td>1.1</td>
<td>0.63</td>
</tr>
<tr>
<td>Hemispheric vs retinal event</td>
<td>7.8 9.1</td>
<td>0.9</td>
<td>0.51</td>
</tr>
<tr>
<td>Hx stroke or TIA &lt;6 mo vs none</td>
<td>8.5 7.7</td>
<td>1.1</td>
<td>0.61</td>
</tr>
<tr>
<td>Hx hypertension vs none</td>
<td>9.3 6.5</td>
<td>1.4</td>
<td>0.08</td>
</tr>
<tr>
<td>Hx diabetes vs none</td>
<td>10.7 7.5</td>
<td>1.4</td>
<td>0.09</td>
</tr>
<tr>
<td>Hx myocardial infarction or angina vs none</td>
<td>10.8 6.9</td>
<td>1.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Hx hyperlipidemia vs none</td>
<td>8.7 7.8</td>
<td>1.1</td>
<td>0.58</td>
</tr>
<tr>
<td>Hx intermittent claudication vs none</td>
<td>8.8 7.9</td>
<td>1.1</td>
<td>0.66</td>
</tr>
<tr>
<td>Hx smoking within past year vs none</td>
<td>9.2 7.4</td>
<td>1.2</td>
<td>0.29</td>
</tr>
<tr>
<td>Stenosis 50–99% vs &lt;50%</td>
<td>7.3 9.0</td>
<td>0.8</td>
<td>0.27</td>
</tr>
<tr>
<td>Appropriate CT lesion vs none</td>
<td>7.6 8.5</td>
<td>0.9</td>
<td>0.57</td>
</tr>
<tr>
<td>Length of operation &gt;4 vs ≤4 h</td>
<td>10.1 7.8</td>
<td>1.3</td>
<td>0.34</td>
</tr>
</tbody>
</table>

TIA indicates transient ischemic attack; Hx, history.

### TABLE 3. Adjusted Hazard Rates and Ratios From Final Cox Regression Model

<table>
<thead>
<tr>
<th>Baseline Factor</th>
<th>Adjusted Hazard Rates</th>
<th>Adjusted Hazard Ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hx myocardial infarction or angina vs none</td>
<td>11.7 7.1</td>
<td>1.6*</td>
<td>0.007</td>
</tr>
<tr>
<td>Hx hypertension vs none</td>
<td>10.0 6.5</td>
<td>1.5†</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*95% CI, 1.2–2.4.
†95% CI, 1.1–2.3.
In summary, the NASCET had a low rate of serious perioperative medical complications, and the occurrence of perioperative myocardial infarction was uncommon. Nevertheless, since CE is a relatively common vascular procedure, neurologists and surgeons must strive to reduce the incidence of postoperative complications to an absolute minimum. Special attention to risk factors, detailed preoperative cardiac investigations, and strict blood pressure control can reduce complications in high-risk patients.

Acknowledgment

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References

2. European Carotid Surgery Trialists' Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. Lancet. 1991;337:1235–1243.
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