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Site and Pathogenesis of Infarcts Associated With Carotid Endarterectomy

J.M.J. Krul, MD, J. van Gijn, MD, R.G.A. Ackerstaff, MD, B.C. Eikelboom, MD, T. Theodorides, MD, and F.E.E. Vermeulen, MD

We analyzed perioperative strokes in 658 carotid endarterectomies with the purpose of explaining the pathogenesis from the morphologic aspect of the infarct on cerebral computed tomograms. All endarterectomies were performed with continuous electroencephalographic monitoring. Of the 42 ischemic strokes (6.4% of all endarterectomies), 34 could be studied. Seven infarcts were hemodynamically induced (five watershed infarcts, two patients with bilateral ischemia); all seven occurred during surgery. Twenty-three of the remaining 27 infarcts were within the territory of the middle cerebral artery (20) or anterior cerebral artery (three) and were probably of thromboembolic origin; 13 of these 23 occurred during surgery (57%). If intraoperative stroke was heralded by permanent electroencephalographic changes, these were not related to the moment of cross-clamping. In four patients the computed tomogram was normal. We believe these facts favor the hypothesis that thromboembolism is the most important factor in the pathogenesis of perioperative stroke associated with carotid endarterectomy under conditions of optimal cerebral monitoring. (*Stroke* 1989;20:324–328)

A lthough carotid endarterectomy now is a common operation in Europe and especially in the United States,^{1,2} the procedure has become controversial for two reasons. First, it is actually unknown how many strokes and deaths are prevented by the operation³; only large clinical trials can address this issue, and two are under way, the European Carotid Surgery Trial,¹ since 1982, and the North American Symptomatic Carotid Endarterectomy Trial, since late 1987.⁴ Second, the number of strokes and deaths associated with the operation varies greatly between centers.^{1,2,5-7}

Despite the controversy about the safety of carotid endarterectomy, the pathogenesis of perioperative ischemic stroke has received only limited attention. The purpose of our study was to explain the pathogenesis by analyzing morphologic data on cerebral computed tomograms (CT scans) in patients with ischemic strokes during and after carotid endarterectomy. Provious studies have shown that the anatomic distribution of infarcts serves to distinguish thromboembolic and hemodynamic events.⁸⁻¹¹ Emboli generally give rise to infarcts within the territory of a main arterial trunk or its branches, whereas low-flow states are associated with watershed infarcts between these territories. In addition, we retrospectively studied intraoperative electroencephalograms (EEG recordings), especially with regard to the interval between the onset of EEG abnormalities and carotid cross-clamping.

Subjects and Methods

We reviewed 658 carotid endarterectomies performed in two hospitals; all procedures were carried out with intraoperative EEG monitoring, 406 from January 1982 until May 1987 at the University Hospital, Utrecht, the Netherlands, and 252 from June 1984 until May 1987 at the St. Antonius Hospital, Nieuwegein, the Netherlands. In the latter group an automatic EEG monitoring device as described by Pronk and Simons^{12,13} was used; these patients were shunted only if carotid cross-clamping resulted in moderate to severe asymmetry on the EEG. In the 406 carotid endarterectomies with conventional EEG monitoring, a shunt was routinely placed. In both centers nearly 40% of the endarterectomies were performed in asymptomatic patients.

We analyzed all perioperative ischemic strokes, which refers to those occurring from endarterectomy until discharge (usually 10 days after surgery) or until another operation. Strokes were considered to be major if the patient could no longer lead an independent life, measured as Grade 3 or worse on the modified Rankin scale.¹⁴ We reviewed the available

From the University Departments of Neurology (J.M.J.K., J.v.G.) and Vascular Surgery (T.T.), University Hospital, Utrecht and the Departments of Clinical Neurophysiology (R.G.A.A.) and Vascular Surgery (B.C.E., F.E.E.V.), St. Antonius Hospital, Nieuwegein, the Netherlands.

Address for reprints: J. van Gijn, MD, Department of Neurology, University Hospital, Nic. Beetsstraat 24, 3511 HG Utrecht, The Netherlands.

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cerebral CT scans of patients with a new neurologic deficit after carotid endarterectomy. The morphologic aspect of the infarct was related to the neurologic deficit and categorized according to the classification developed by Ringelstein et al.^{8,9} Based on the studies of Zülch,¹⁰ these authors distinguished infarcts of hemodynamic from those of thromboembolic origin. Watershed infarcts developing in the border zone between major vascular territories and subcortical terminal supply area infarcts in the territory of the medullary and/or lenticulostriate branches of the middle cerebral artery are hemodynamically induced. A more generalized and long-lasting diminution of the cerebral blood flow leads to bilateral parieto-occipital infarcts¹⁵ or to selective damage to the middle cortical layer, resulting in laminar necrosis.¹⁶

Infarcts in the entire or partial territory of a cortical artery are considered to be of thromboembolic origin. Thromboembolism to the stem of the middle cerebral artery may also produce extended lentiform nucleus infarction, in which the entire territory and not only the terminal supply area of the lenticulostriate arteries is involved. These deep cerebral infarcts can be distinguished from smaller, lacunar infarcts that are associated with lipohyalin-osis of single lenticulostriate arteries.^{17,18}

We reviewed EEG recordings from patients with an intraoperative stroke confirmed by CT scanning. The time between the onset of EEG changes and the moment of carotid cross-clamping was analyzed in relation to the CT scan findings. Special attention was paid to EEG asymmetry ipsilateral to the operated side.^{12,13} An obvious time relation between EEG asymmetry and clamping was considered to indicate hemodynamic problems since cerebral blood flow may be seriously impaired during clamping.

We calculated frequencies with exact binomial confidence limits.¹⁹ We assessed the importance of thromboembolic stroke compared with hemodynamic stroke by calculating the relative ratio.

Results

The number of perioperative ischemic strokes in 658 carotid endarterectomies was 42 (6.4%, exact 95% confidence limits 4.64–8.53%); there were 22 minor strokes (3.3%) and 20 major strokes (3%). Mortality was 0.8%. In 34 cases (17 patients with a minor stroke and 17 patients with a major stroke) a cerebral CT scan was made after the onset of the neurologic deficit; in eight patients no CT scan was performed due to the limited scanning facilities.

Table 1 summarizes the infarct types on CT scanning, the number of major strokes, and the number that occurred during surgery. Of the 32 patients with unilateral deficits, 23 had an infarct within the territory of either the middle or anterior cerebral artery, three had border zone infarcts, and two showed infarcts of both types; two patients had bilateral infarcts. Four patients demonstrated a neurologic deficit without CT scan abnormalities. Thirteen of the 23 infarcts within the territory of a main

TABLE 1. Infarct Type on Cerebral Computed Tomograms: Number, Resulting Neurologic Deficit, and Time of Onset

Infarct type	No.	Major stroke	During surgery
Within territory of main arterial trunk			
Middle cerebral artery			
Entire territory	15	12	9
Cortical branches	3	1	1
Lenticulostriate branches	2	0	2
Anterior cerebral artery, lenticulostriate branches	3	0	1
Border zone infarct			
Between middle and posterior cerebral artery	1	0	1
Between cortical and lenticulostriate branches of	2	0	-
middle cerebral artery	2	0	2
Both types	2	1	2
Infarcts in both hemispheres	2	2	2
No infarct	4	1	3
Total	34	17	23

arterial trunk resulted in a major stroke; 13 occurred during surgery. No infarct limited to the border zones produced a major neurologic deficit, and all three developed intraoperatively. The two patients with bilateral infarcts died without regaining consciousness after the operation.

The 23 infarcts in single arterial territories, or 68% of the CT-investigated strokes, were considered to be of thromboembolic origin and the seven watershed or bilateral infarcts (20%) of hemodynamic origin; 12% could not be classified (the four normal CT scans). Of the 23 intraoperative strokes, 13 were thromboembolic (57%, exact 95% confidence limits 34.5-76.8%). A thromboembolic origin was attributed to 10 of the 11 postoperative strokes (91%, exact 95% confidence limits 58.7-99.8%). All seven hemodynamic strokes occurred intraoperatively (100%, exact 95% confidence limits 59-100%). The relative ratio of thromboembolic stroke vs. hemodynamic stroke was 3.29 (95% confidence limits 1.42-7.60). With conventional EEG monitoring, six hemodynamic strokes developed in 406 carotid endarterectomies compared with only one in 252 operations performed with automatic EEG monitoring.

Data from seven patients with an intraoperative stroke that was heralded by permanent EEG changes are summarized in Table 2. In five cases CT evidence of a thromboembolic stroke could be established; three of these patients developed EEG asymmetry before clamping that did not eventually resolve after shunting. In only one of these five patients was asymmetry noted immediately after cross-clamping but without reaction to shunting. Two of the seven patients showed infarcts of hemodynamic origin on CT scanning; EEG asymmetry was not related to the moment of clamping. One of the two patients

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TABLE 2.	Infarct Type on Cerebral Computed Tomograms in Patients With Intraoperative Stroke and Persisting EEG Changes: Number
Resulting 1	Neurologic Deficit, Use of Shunt, and Type and Time of Onset of EEG Changes

Infarct type	No.	Major stroke	Use of shunt	EEG
Within territory of main arterial trunk				
Middle cerebral artery Entire territory	1	0	+	Asymmetry ipsilateral to operated side 20 minutes after start of operation, before clamping; no reaction to shunting
	1	+	-	Asymmetry ipsilateral to operated side few minutes before clamping
	1	+	+	Asymmetry ipsilateral to operated side after clamping; no reaction to shunting
Cortical branches	1	0	-	Asymmetry ipsilateral to operated side before clamping
Anterior cerebral artery, lenticulostriate branches	1	0	+	Asymmetry ipsilateral to operated side at end of operation
Combination of infarct within territory of main arterial trunk and border zone infarct	1	+	+	Asymmetry ipsilateral to operated side 14 minutes before clamping; no reaction to shunting
Infarcts in both hemispheres	1	+	+	Persisting and severe asymmetry ipsilateral to operated side at end of clamping period

EEG, electroencephalography.

became severely hypotensive at the end of the clamping period.

Discussion

The perioperative stroke rates after carotid endarterectomy vary between 2% and 25% in published series.^{1,2,6} Intracerebral hemorrhage accounts for only a small minority of these strokes (0.5–1% of all operations).²⁰ Cerebral infarction is therefore the most important complication and may be caused by thromboembolism or a low-flow state.^{12,21–27} Cerebral blood flow may be compromised after carotid cross-clamping or as the result of hypotension, whereas perioperative embolization can be regarded as mainly a surgical problem.⁷ Postoperative occlusion of the internal carotid artery may be asymptomatic or may result in either a hemodynamic or a thromboembolic infarct.⁸

Our study showed a preponderance of intraoperative and postoperative thromboembolic strokes (68% of the CT-investigated strokes), which is expressed by the relative ratio of 3.29. Thirteen (57%) of the 23 thromboembolic strokes led to major disability compared with only one of the five nonfatal strokes of hemodynamic origin, although the difference was not significant. Perioperative embolization is a complication inevitably linked to the procedure of carotid endarterectomy itself,⁷ which implies that this type of complication can be reduced only by the experience and skill of the surgeon,²⁸ although this is sometimes contested.²⁹ All postoperative strokes except one were considered to be of thromboembolic origin. It was not possible to establish the exact number of postoperative occlusions associated with these thromboembolic events as postoperative angiography or noninvasive studies were not performed in all patients. Other studies have demonstrated a low incidence of symptomatic postoperative occlusions (Sundt et al, $0.7\%^{21}$; Painter et al, $0.4\%^{30}$);

therefore, most postoperative strokes in our study are probably the result of embolization from the surface of the operated artery.

The number of hemodynamic infarcts was limited (20% of the CT-investigated strokes). All occurred during surgery, which underlines the theoretical importance of optimal cerebral blood flow monitoring. Much attention has been given to the different methods of cerebral protection during carotid endarterectomy, especially with respect to carotid cross-clamping.³¹ Cerebral function can be monitored with intraoperative EEG, 12, 13, 21, 26, 27, 32-34 which indicates the need for a shunt by reflecting an insufficient cerebral blood flow. It is possible that more hemodynamic infarcts would have occurred without EEG monitoring, although this issue has been hotly debated.^{35,36} The protection may be strongest with automatic EEG monitoring; with this technique only one hemodynamic stroke developed in 252 carotid endarterectomies compared with six in 406 operations performed with conventional EEG and routine shunting. The comparison is compounded, however, because the surgical teams were also different.

Although hemodynamically induced bilateral infarcts may produce moderate to severe disability,¹⁵ in our study the two patients with bilateral infarcts died. Unilateral hemodynamic infarcts usually result in mild deficits.⁹ This is explained by the limited (sub)cortical area involved since hemodynamic infarcts develop in the border zones between major vascular territories or between the superficial and deep branches of the middle cerebral artery.^{8,9} In keeping with this notion, four of the five unilateral hemodynamic infarcts in our study resulted in a minor stroke; the single major stroke occurred in a patient with both infarct types on CT scanning. The extent of the thromboembolic infarct in the territory of the middle cerebral artery in this patient could have been mainly responsible for the major deficit.

Four CT scans failed to show signs of infarction. This can be explained in two cases by the timing of the CT scan (within 3 days after the onset of the neurologic deficit) or by infarcts in the vertebrobasilar territory (in the other two cases).³⁷

Analysis of the interval between the onset of EEG asymmetry and carotid cross-clamping supports our conclusions concerning the pathogenesis of intraoperative stroke based on CT findings. Of seven patients with permanent EEG changes, five had CT evidence of a thromboembolic stroke; in only one of the five was a distinct relation between EEG asymmetry and carotid clamping demonstrated. In this patient, however, the asymmetry did not resolve after shunting, which makes a hemodynamic origin less probable. The other four patients developed a persisting EEG asymmetry unrelated to the clamping period, which implicates intraoperative embolization. Of the seven patients, two had a hemodynamic stroke on CT scanning. EEG asymmetry was also unrelated to the clamping period, although the hemodynamic origin could at least be confirmed in one patient who developed severe EEG asymmetry at the end of the operation after a prolonged period of hypotension.

Morphologic analysis of a cerebral infarct on a CT scan is the most direct method of establishing the pathogenesis of perioperative stroke in carotid endarterectomy, but most studies deal with the problem in a more indirect way. Rosenthal et al²⁴ found no significant difference in the intraoperative stroke rate between patients operated on with a shunt, without a shunt, and with only EEG monitoring; their conclusion was that ischemic infarction was caused not by insufficient collateral circulation but by technical imperfections leading to intraoperative embolization. Sundt et al²¹ did not attribute intraoperative infarction to inadequate cerebral protection during carotid occlusion because shunts were used whenever doubt existed regarding the adequacy of cerebral perfusion. However, these authors explained the majority of postoperative problems as due to cerebral hyperperfusion resulting from enhanced cerebral blood flow after clearing the carotid obstruction combined with defective autoregulation. Finally, Steed et al,25 who performed endarterectomy under local anesthesia, concluded that intraoperative stroke had to be caused by thromboembolism as a hemodynamically induced neurologic deficit should have been noticed immediately, especially during carotid cross-clamping.

In conclusion, our study shows that hemodynamic factors play only a limited role in the pathogenesis of perioperative stroke in carotid endarterectomy performed with optimal cerebral protection. Thromboembolism is the most important pathogenetic factor in stroke associated with carotid endarterectomy.

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References

- Warlow C: Carotid endarterectomy, does it work? Stroke 1984;15:1068-1076
- Dyken M, Pokras R: The performance of endarterectomy for disease of the extracranial arteries of the head. Stroke 1984; 15:948-950
- Fields WS, Maslenikov V, Meyer JS, Hass WK, Remington RD, Macdonald M: Joint study of extracranial arterial occlusion. JAMA 1970;211:1993-2003
- North American Symptomatic Carotid Endarterectomy Study Group: Carotid endarterectomy: Three critical evaluations. Stroke 1987;18:987-989
- Barnett HJM: A critique of surgical treatment in cerebral ischemia, in McDowell F, Caplan LR (eds): Cerebrovascular Survey Report. 1985, pp 189-209
- Toronto Cerebrovascular Study Group: Risks of carotid endarterectomy. Stroke 1986;17:848-852
- Lusby RJ, Wylie EJ: Complications of carotid endarterectomy. Surg Clin North Am 1983;63:1293-1302
- Ringelstein EB, Zeumer H, Angelou D: The pathogenesis of strokes from internal carotid artery occlusion. Diagnostic and therapeutical implications. *Stroke* 1983;14:867-875
- Ringelstein EB, Zeumer H, Schneider R: Der Beitrag der zerebralen Computertomographie zur Differentialtypologie und Differentialtherapie des ischämischen Grosshirninfarktes. Fortschr Neurol Psychiatr 1985;53:315-336
- Zülch KJ: Ueber die Entstehung und Lokalisation der Hirninfarkte. Zentralbl Neurochir 1961;21:158-178
- Torvik A: The pathogenesis of watershed infarcts in the brain. Stroke 1984;15:221-223
- Pronk RAF, Simons AJR: Automatic EEG monitoring during anesthesia, in Prakash O (ed): Computing in Anesthesia and Intensive Care. Boston, Martinus Nijhoff Publishers, 1983, pp 227-257
- Pronk RAF, Simons AJR: Automatic recognition of abnormal EEG activity during open heart and carotid surgery, in Buser PA, Cobb WA, Okuma T (eds): Kyoto Symposia (EEG Supplement 36). Amsterdam, Elsevier Biomedical Press, 1982, pp 590-602
- Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJA, van Gijn J: Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;19:604-607
- Ross Russel RW, Bharucha N: The recognition and prevention of borderzone cerebral ischaemia during cardiac surgery. Q J Med 1978;NS47:303-323
- Adams JH, Brierley JB, Connor RCR, Treip CS: The effect of systemic hypotension upon the human brain. Clinical and neuropathological observations in 11 cases. *Brain* 1966; 89:235-268
- Pullicino P, Nelson RF, Kendall BE, Marshall J: Small deep infarcts diagnosed on computed tomography. *Neurology* 1980;30:1090-1096
- Santamaria J, Graus F, Rubio F, Arbizu T, Peres J: Cerebral infarction of the basal ganglia due to embolism from the heart. Stroke 1983;14:911-914
- Armitage P, Berry G: Statistical Methods in Medical Research, ed 2. Oxford, Blackwell Scientific Publications, 1987, pp 118–119
- Schroeder T, Sillesen H, Boesen J, Laursen H, Soelberg Sorensen P: Intracerebral hemorrhage after carotid endarterectomy. *Eur J Vasc Surg* 1987;1:51-60
- Sundt TM, Sharhrough FW, Piepgras DG, Kearns TP, Messick JM, O'Fallon WM: Correlation of cerebral blood flow and electroencephalographic changes during carotid endarterectomy. *Mayo Clin Proc* 1981;56:533-543
- Collins GJ Jr, Rhich NM, Andersen CA, McDonald PT: Stroke associated with carotid endarterectomy. Am J Surg 1978;135:221-225
- Jernigan WR, Hamman JL: The causes and prevention of stroke associated with carotid artery surgery. Am Surg 1982; 48:79-84

- Rosenthal D, Zeichner WD, Lamis PA, Stanton PE Jr: Neurologic deficit after carotid endarterectomy: Pathogenesis and management. Surgery 1983;94:776-780
- Steed DL, Peitzman AB, Grundy BL, Webster MW: Causes of stroke in carotid endarterectomy. Surgery 1982;92:634-641
- Cho I, Smullens SN, Streletz LJ, Fariello RG: The value of intraoperative EEG monitoring during carotid endarterectomy. Ann Neurol 1986;20:508-512
- Evans WE, Hayes JP, Waltke EA, Vermilion BD: Optimal cerebral monitoring during carotid endarterectomy: Neurologic response under local anesthesia. J Vasc Surg 1985; 2:775-777
- Luft HS, Bunker JP, Enthoven AC: Should operations be regionalized? The empirical relation between surgical volume and mortality. N Engl J Med 1979;301:1364-1369
- Kempczinski RF, Brott TG, Labutta RJ: The influence of surgical specialty and caseload on the results of carotid endarterectomy. J Vasc Surg 1986;3:911-916
- Painter TA, Hertzer NR, O'Hara PJ, Krajewski LP, Beven EG: Symptomatic internal carotid thrombosis after carotid endarterectomy. J Vasc Surg 1987;5:445-451

- Sundt TM, Houser OW, Sharbrough FW, Messick JM Jr: Carotid endarterectomy: Results, complications, and monitoring techniques. Adv Neurol 1977;16:97-119
- Whittemore AD, Kaufman JL, Kohler TR, Mannick JA: Routine electroencephalographic (EEG) monitoring during carotid endarterectomy. *Ann Surg* 1983;197:707-713
 Chiappa KH, Burke SR, Young CB, Young RR: Results of
- Chiappa KH, Burke SR, Young CB, Young RR: Results of electroencephalographic monitoring during 367 carotid endarterectomies. *Stroke* 1979;10:381-388
- Baker JD, Gluecklich B, Watson CW, Marcus E, Kamat V, Callow AD: An evaluation of electroencephalographic monitoring for carotid study. Surgery 1975;78:787-794
- Ferguson GG: Intraoperative monitoring and internal shunts: Are they necessary in carotid endarterectomy? *Stroke* 1982; 13:287-289
- Sundt TM: The ischemic tolerance of neural tissue and the need for monitoring and selective shunting during carotid endarterectomy. *Stroke* 1983;14:93-98
- Caplan LR, Stein RW: Stroke. A Clinical Approach. Boston, Butterworths, 1986, pp 51-58

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