

Natural History of Symptomatic and Asymptomatic Carotid Artery Occlusion Contralateral to Carotid Endarterectomy: A Prospective Study

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The natural history of carotid occlusion (CO) has generally been analyzed in the presence of a contralateral patent but diseased internal carotid artery (ICA). Few previous studies have focused on the fate of CO contralateral to the side of a prior carotid endarterectomy (CEA). The aim of this study was to analyze the mortality rate and the incidence of cerebrovascular events in the hemisphere ipsilateral to CO (HICO) in patients who had undergone contralateral CEA. The 30-day and long-term outcomes of 153 consecutive patients who had CEA for severe symptomatic and asymptomatic ICA lesions contralateral to a symptomatic or asymptomatic CO over a 15-year period were considered. The endpoints of the study were mortality and neurological events in the HICO. Overall, the 30-day mortality and stroke rates were 0.6% (1/153)

and 1.9% (3/153), respectively; the only death was stroke-related and the stroke was ipsilateral to the operated side. The other 2 strokes were ipsilateral to a symptomatic CO. The follow-up was completed for all patients (mean, 7.7 years; range, 1-172 months). Overall, there were 4 late strokes (2.6%), one of them lacunar in a patient with a symptomatic CO, whereas the other 3 were atheroembolic and ipsilateral to the operated ICA. The risk of late stroke in the HICO at 5 and 12 years was 2%. Overall, there were 19 late deaths, none of them stroke-related. CO, with or without symptoms, contralateral to CEA could be considered a locally benign condition in the long term.

Keywords: carotid occlusion; stroke; death; carotid endarterectomy; duplex ultrasound scan

Introduction

The clinical picture developing after the occlusion of an internal carotid artery (ICA) can range from an asymptomatic silent condition to the onset of a dis-

abling, often fatal, stroke.¹ It is mainly the timing of the carotid occlusion (CO) that seems to correlate with the onset of neurological events; when the CO has become established, the subsequent risk of cerebrovascular symptoms appears to be lower.²⁻⁶ The clinical presentation of CO seems to influence the risk of ipsilateral stroke, which is as high as 27% in patients with symptomatic CO^{7,8} and ranges from 0% to 5% per year in patients with no symptoms.^{6,9} A history of stroke in the hemisphere ipsilateral to the CO (HICO) also correlates with a higher incidence of further strokes or death, whereas a presentation with transient ischemic attacks (TIAs) seems to have a more benign course.⁸

The majority of previously published studies have analyzed the natural history of CO in the

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presence of a diseased contralateral ICA.²⁻¹¹ To our knowledge, only 3 studies^{5,12,13} in the recent medical literature (2 large multicenter randomized trials^{5,12} and 1 institutional study, with data extrapolated from 2 previous randomized studies on carotid surgical procedures¹³) have focused on the fate of CO in the case of an apparently healthy contralateral ICA, i.e., after carotid endarterectomy (CEA).

The purpose of this analysis is to evaluate the natural history of patients who had undergone CEA contralateral to a CO, specifically assessing the onset of late neurological events in the HICO.

Methods

A prospective analysis was conducted on all consecutive patients who had undergone primary CEA for severe symptomatic and asymptomatic ICA lesions contralateral to a CO over a 15-year period at our institution, according to the recommendations of the NASCET (North American Symptomatic Carotid Endarterectomy Trial)¹² and the ACAS (Asymptomatic Carotid Atherosclerosis Study).⁵ Patients scheduled for CEA with concomitant coronary artery bypass grafting, patients with associated supra-aortic trunk lesions requiring concurrent surgery, and patients requiring carotid surgery for recurrent disease were excluded.

The patients' demographic data were prospectively collected and recorded, including any history of diabetes mellitus, cigarette smoking, hypertension, and coronary artery disease; other clinical variables, indications for surgery, details of the operation, and hospital stay. Two experienced neurologists dedicated to the study of cerebrovascular diseases clinically evaluated all patients before surgery.

The ICA lesion was diagnosed by duplex ultrasound (US) scan and confirmed by traditional digital subtraction angiography (DSA) during the earlier part of this experience (with declining frequency over the years), whereas duplex US scan was the only preoperative ICA imaging study performed in most patients from mid-1998 onward, combined in selected patients with magnetic resonance (MR) angiography, computed tomography (CT) angiography, or DSA. All duplex US scans were performed with an Acuson Sequoia 512 ultrasound system (Mountain View, CA) using a 5.0-MHz linear scan transducer with a 5-mm axial extension of the sample volume and a consistent 60° angle of insonation. To differentiate preocclusive stenosis from occlusion,

our neurosonographers tried to detect extremely low flow values by using the power Doppler scanning mode or by administering echo contrast agents. An angiographic study was performed only if the diagnosis was still unclear, or in case of complex sonographic conditions. Optimal instrument settings and a complete preoperative study of the vertebrobasilar system and intracranial arteries with transcranial Doppler scan in all patients helped to exclude other possible causes of TIA and stroke and gave a more complete picture of cerebral hemodynamics.

Clinical presentation was always classified by the consulting neurologists as TIA (temporary hemispheric symptoms lasting no more than 24 hours, with complete recovery), amaurosis fugax (transient monocular visual loss), or stroke (neurological deficit persisting more than 24 hours, regardless of the mechanism, and related to either cerebral hemisphere). Patients who had nonhemispheric symptoms, such as dizzy spells or vertigo, were included in the asymptomatic group. Preoperative cerebral CT was performed in all symptomatic patients.

All CEA procedures involved traditional CEA with patching or eversion CEA. The technical details of both procedures have been described elsewhere.¹⁴ All CEAs were performed with patients under deep general anesthesia and cerebral protection involving continuous perioperative electroencephalographic monitoring for selective shunting.

Surveillance Protocol

Clinical assessments and duplex US scans were performed systematically in all patients by 2 consulting neurologists and 2 experienced neurosonographers, respectively, at discharge, at 1, 6, and 12 months, and once a year thereafter, to assess neurological status and any recurrent stenosis or occlusion of the operated ICA.¹⁵ *Recurrent ICA stenosis* was diagnosed only if the abnormality became apparent after a normal duplex US scan or more than 12 months after the initial examination. A peak systolic velocity of >140 cm/s with spectral broadening throughout the systole and an increased diastolic velocity were consistent with a ≥50% stenosis (diameter reduction), and a peak systolic velocity of >210 cm/s with an end diastolic velocity between 110 and 140 cm/s were consistent with ≥70% stenosis. If a ≥70% stenosis was identified by duplex US scan, this was confirmed by carotid CT angiography or DSA.¹⁵

The study endpoints were perioperative and late mortality, and stroke in the HICO. *Minor stroke* was defined as any new neurological deficit that lasted for more than 24 hours and that regressed completely within 30 days or raised the National Institutes of Health Stroke Scale (NIHSS) score by less than 3 points. *Major stroke* was defined as any new neurological deficit that persisted more than 30 days and raised the NIHSS score by more than 3 points. Cerebral CT or MR was performed in all patients with a new neurological event after CEA. Other complications and events observed during the follow-up were prospectively recorded according to the guidelines of the Ad Hoc Committee on Reporting Standards for Cerebrovascular Disease, Society for Vascular Surgery/North American Chapter, International Society for Cardiovascular Surgery.¹⁶

Statistical Analysis

Kaplan-Meier life-table analysis was used to calculate freedom from late stroke in the HICO and stroke-free survival rates. Significance was inferred at $P < .05$.

Results

Of more than 1500 CEAs performed at our institution over a 15-year period (1990–2004) by the same surgeon, 153 were contralateral to a CO. Table 1 summarizes patients' demographic and clinical characteristics, with some technical details of the surgical procedure.

Perioperative (30-day) Outcome

The 30-day outcome is summarized in Table 2. Overall, the 30-day mortality and stroke rates were 0.6% (1 of 153) and 1.9% (3 of 153), respectively, with a combined mortality and stroke rate of 2.6%.

The only perioperative death was stroke related, and the stroke was ipsilateral to the operated side. The patient underwent a left CEA with patching to treat a severe symptomatic ulcerated ICA lesion. He awoke from anesthesia with no neurological symptoms but subsequently had a progressive right-sided hemiparesis and died of stroke progression on postoperative day 10. Two other strokes (one major and one minor in severity) were both ipsilateral to a symptomatic CO and, judging from the findings on CT images, were most likely hemodynamic.

Table 1. Demographic, Clinical, and Technical Data

Characteristic	Value
Age, y (mean $\pm$ SD)	73.8 $\pm$ 4.1
Gender (M/F)	109/44
Risk factor, n (%)	
Smoking	105 (68.8)
Hypertension	98 (64.0)
Hyperlipidemia	69 (45.1)
Diabetes mellitus	62 (40.5)
Coronary artery disease	79 (51.6)
POAD	70 (45.7)
Occlusion side (left/right)	98/55
Symptom, n (%)	39 (25.5)
Transient ischemic attack	11
Stroke	20
Amaurosis fugax	8
Symptom plus contralateral symptom, n (%)	47 (30.7)
Transient ischemic attack	15
Stroke	24
Amaurosis fugax	8
No symptoms, n (%)	67 (43.8)
Contralateral stenotic side at presentation	
Degree of stenosis	
70%–79%	79 (51.6)
80%–89%	51 (33.3)
90%–99%	23 (15.1)
Symptom, n (%)	57 (37.2)
Transient ischemic attack	25
Stroke	17
Amaurosis fugax	15
Symptom plus contralateral symptom, n (%)	47 (30.7)
Transient ischemic attack	28
Stroke	12
Amaurosis fugax	7
No symptoms, n (%)	49 (32.1)
Surgical procedure in the contralateral stenotic side	
Carotid endarterectomy with patching	52 (34)
Eversion carotid endarterectomy	101 (66)

Note: POAD, peripheral obliterative atherosclerotic disease.

Long-term Results

A complete follow-up (mean, 7.7 years; range, 1–172 months) was obtained in all patients. After ruling out the perioperative death, 152 patients were alive 30 days after CEA. Overall, there were 4 late strokes (2.6%), one of them lacunar and ipsilateral to a symptomatic CO and 3 atheroembolic and ipsilateral to the operated ICA (2 symptomatic and 1 asymptomatic carotid lesions). The patient with a stroke in the HICO had a complete neurological recovery (Table 3). Kaplan-Meier analysis showed that the rates of freedom from late stroke in the

Table 2. Perioperative (30-day) Results

Event	n (%)
Stroke	3 (1.9)
Minor	
Ipsilateral to symptomatic CO	1
Ipsilateral to asymptomatic CO	—
Ipsilateral to symptomatic operated ICA	—
Ipsilateral to asymptomatic operated ICA	—
Major	
Ipsilateral to symptomatic CO	1
Ipsilateral to asymptomatic CO	—
Ipsilateral to symptomatic operated ICA	1
Ipsilateral to asymptomatic operated ICA	—
Death stroke related	1 (0.6)
Ipsilateral to symptomatic CO	—
Ipsilateral to asymptomatic CO	—
Ipsilateral to symptomatic operated ICA	1
Ipsilateral to asymptomatic operated ICA	—
Myocardial infarction	2 (1.3)
Fatal	—
Nonfatal	2
Congestive heart failure	2 (1.3)

Note: CO, carotid occlusion; ICA, internal carotid artery.

HICO at 1, 3, 5, and 12 years were 98.7%, 98%, 98%, and 98%, respectively (Figure 1).

Eight patients experienced a late TIA, 5 of which occurred in the HICO (4 symptomatic and 1 asymptomatic CO); whereas 3 resembled previous retinal TIAs, 2 were new hemispheric transient ischemic events (Table 3).

All these patients were treated with antiplatelet therapy, except for 5 who had anticoagulation therapy because of cardiac valve disease or arrhythmia. The only, albeit asymptomatic, $\geq 50\%$ carotid restenosis detected in our patients was not associated with any neurological events in the HICO. Nineteen late deaths occurred in this series as a whole, the cause of which was primarily cardiac related ($n = 13$) and never stroke related. Kaplan-Meier analysis showed that the stroke-free survival rates at 1, 3, 5, and 12 years were 98.7%, 91.8%, 85.5%, and 65.5%, respectively (Figure 1).

Discussion

The perioperative mortality and stroke rates of 0.6% and 1.9%, respectively, in the patients in this series closely parallel those of other published studies¹⁷⁻²⁰ and confirm our previous experiences,^{21,22} demonstrating that CEA can be performed safely in this patient population too. The 0.6% rate of recurrent

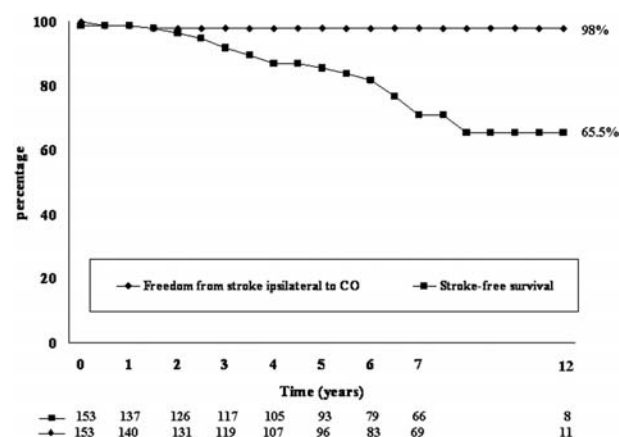


Figure 1. Kaplan-Meier curves show the freedom from stroke in the hemisphere ipsilateral to the carotid occlusion (CO) and the stroke-free survival rates. Percentages on the right represent rates of freedom from stroke and stroke-free survival at 12 years. The standard error was less than 10% at each time point in each curve. Raw numbers of the patients at risk analyzed in each subset at each time point are provided below the figure.

stenoses $\geq 50\%$ is further proof of the durability of the surgical procedure.¹⁵

Internal carotid artery occlusion represents the terminal event of a progressive process that begins with a plaque and is complicated by ulceration and/or intraplaque hemorrhage. This condition is generally thought to correlate with the onset of an ischemic stroke when the CO occurs,³⁻⁵ but when the CO has become established, the subsequent risk of neurological events seems to be lower.^{2,6} In a prospective study following ICA stenosis up to CO with serial duplex US scans, Nicholls et al⁴ noted that 25% of their patients had a stroke at the time of CO. This finding correlates well with the report from Bornstein and Norris⁶ on a contemporary serial duplex US scan study regarding 2 groups of asymptomatic patients, 21 patients with severe ICA stenosis progressing towards CO and 19 already with CO at the time of referral; 3 patients in the first group had a stroke in the HICO during the study period (3.8% per year) as opposed to none in the second. Some COs may be clinically silent, however, depending on the chronicity and degree of the previous stenosis and the extent of collateral vessels development.⁸ More than a quarter of our patients had symptoms in the HICO at presentation, with an incidence of stroke higher than 50%, whereas the silent CO rate was 43.8%.

The risk of stroke in the HICO seems to depend on the initial clinical presentation, the incidence being as high as 27% per year in patients with symptomatic CO^{7,8} but ranging from 0% to 5% per year in

Table 3. Long-term Outcomes^a

Event	n (%)
Late strokes	4 (2.6)
Lacunar	
Ipsilateral to symptomatic CO	1
Ipsilateral to asymptomatic CO	—
Ipsilateral to symptomatic operated ICA	—
Ipsilateral to asymptomatic operated ICA	—
Atheroembolic	
Ipsilateral to symptomatic CO	—
Ipsilateral to asymptomatic CO	—
Ipsilateral to symptomatic operated ICA	2
Ipsilateral to asymptomatic operated ICA	1
Transient ischemic attack	8 (5.2)
Ipsilateral to symptomatic CO	4
Ipsilateral to asymptomatic CO	1
Ipsilateral to symptomatic operated ICA	2
Ipsilateral to asymptomatic operated ICA	1
All late deaths	19 (12.5)
Cardiac	13
Malignancy (extracranial)	3
Others	3
Restenosis ≥50%	1 (0.6)
Symptomatic	—
Asymptomatic	1
Contralateral to symptomatic CO	—
Contralateral to asymptomatic CO	1

^aMean, 7.7 years; range, 1-172 months.

Note: CO, carotid occlusion; ICA, internal carotid artery.

patients with asymptomatic CO.^{6,9} A history of stroke at the time of the diagnosis also correlates with a high incidence of further strokes or death, whereas a presentation with TIA seems to have a more benign course. In our series, the only patient with a late stroke in the HICO had a TIA at presentation and a complete neurological recovery within 4 months.

Most previously published studies were of patients with CO contralateral to a diseased but patent ICA.²⁻¹¹ In the recent medical literature, few reports have focused on the natural history of CO contralateral to CEA.^{5,12,13}

The only late stroke in the HICO (0.6%) that occurred in our series (giving rise to a 98% stroke-free rate at 12 years) correlates well with the 2 late strokes in the HICO (3.2%) observed by AbuRahma et al¹³ in a group of 63 patients who had undergone contralateral CEA, resulting in a 96% stroke-free rate at 5 years. On the other hand, the incidence of late strokes in the HICO in a series of 212 patients with CO contralateral to a diseased ICA followed up by Nicholls et al⁷ for a mean 24.9 months was 9.4%, resulting in an 85% stroke-free rate at 5 years (an annual adjusted stroke rate of 3%). This figure is

similar to the one observed by Faught et al⁸ in their retrospective analysis of 167 patients with CO evaluated by duplex US scan for a mean 39 months (ie, a 12% stroke rate in the HICO), resulting in a stroke-free rate of 85% at 5 years. Although more than 60% of all strokes occurring in both these series were in the HICO, the authors noted that contralateral disease did not seem to affect the stroke rate in the HICO.^{7,8} AbuRahma et al¹³ came to a different conclusion, however, reporting that patients with recurrent ≥ 50% stenosis after CEA carried a significantly higher risk of neurological events (TIA and stroke) in the HICO than did patients with no recurrent stenosis (40% vs 10%, $P < .001$). The lack of any restenoses associated with neurological events in our series prevented us from drawing any useful comparisons.

The lower incidence of stroke in the HICO after CEA, as reported by us and other authors,^{7,13,17} would suggest that contralateral CEA tends to protect the HICO against further neurological events. In a recently published prospective cerebral hemodynamics study of 39 patients who had undergone CEA for severe symptomatic and asymptomatic lesions contralateral to symptomatic and asymptomatic CO and who were followed up with duplex US scan studies for a mean of 10 years,²³ we found that blood flow increased significantly in the HICO after CEA and that the effect of CEA on the lasting improvement in blood flow was unrelated to the clinical presentation vis-à-vis CO. This persistent recovery apparently had no beneficial influence on late mortality and morbidity rates in this patient population, however. In the present series, cardiac-related events accounted for more than 65% of late deaths, whereas there were no stroke-related late deaths, resulting in a 65.5% stroke-free survival at 10 years, a figure comparable with previous reports.^{8,13,24} Excellent freedom from stroke was not translated into a longer survival, however, because none of the late deaths were related to neurological events.

Limitations of the Study

Although this analysis is prospective and the follow-up relatively long and complete in all patients, the low incidence of neurological events during the study and the absence of late occlusions and recurrences after CEA led to the study's lacking power and prevented any useful comparison and definitive statistical analysis. The involvement in the study of experienced neurologists and neurosonographers nonetheless ensures a careful and thorough collection

of clinical and ultrasonographic findings before surgery and during the follow-up.

At the time of the study design, cognitive decline was not considered an endpoint; this is the reason why we did not perform serial brain MR imaging scans or neuropsychological evaluations on our patients. This could have determined an underestimation of the number of late neurological events (silent lacunar infarcts), whose burden might have caused a vascular dementia. At the end of the follow-up, however, no patients were diagnosed demented by the consulting neurologists.

Conclusion

Carotid occlusion contralateral to CEA, whether symptomatic or asymptomatic, could be considered a locally benign condition in the long term. An excellent freedom from stroke rate was not translated into a longer survival rate in our patients, however, because late mortality never correlated with neurological events.

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