Frequency and Prognostic Significance of Silent Coronary Artery Disease in Patients with Cerebral Ischemia Undergoing Carotid Endarterectomy

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To evaluate the prevalence and prognostic role of silent coronary artery disease (CAD) in patients with symptomatic high-grade carotid stenosis (70 to 99%) undergoing carotid endarterectomy, and with neither history nor symptoms of CAD, 106 patients (76 men, 30 women, mean age 58.7 years [range 42 to 71]) with recent cerebral ischemia were prospectively studied. Patients were stratified as to the presence (n = 27, 25%) or absence (n = 79, 75%) of silent CAD defined by concordant abnormal exercise electrocardiographic testing and thallium-201 myocardial scintigraphy. The male sex, the severity of the symptomatic carotid lesion (>90%), and the coexistence of contralateral carotid disease identified patients with higher probability of coexisting CAD. The 106 patients underwent 121 operations (bilateral in 15). In the perioperative period, no deaths or cardiac events occurred, 1 patient suffered a recurrent stroke and 3 had a transient ischemic attack. During a mean follow-up period of 5.4 years, 9 patients died (1.7%/year): fatal myocardial infarction occurred in 5 (all in the silent CAD group), cancer in 3 and vertebrobasilar stroke in 1. Nonfatal events occurred in 9 patients: myocardial infarction in 1 (without silent CAD), unstable angina in 3 (with silent CAD), and cerebral ischemic attacks in 5. After 7 years, the Kaplan-Meier estimated survival free from coronary events was 51% in patients with silent CAD, and 98% in patients without CAD (p <0.01).

In conclusion, among patients with symptomatic high-grade carotid stenosis undergoing carotid endarterectomy, even in absence of history or symptoms of CAD, a silent CAD is detectable in one fourth of the patients. Silent CAD did not affect the perioperative outcome, but strongly influenced the long-term prognosis. These results suggest the need for routine screening of silent CAD in patients with severe carotid stenosis to identify those at high long-term risk of cardiac events, for whom a more aggressive management should be warranted.

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Patients with transient ischemic attacks or stroke are at high risk for coronary artery events.[1–4] The cardiac mortality of 5%/year, observed in the follow-up of patients with cerebral ischemia, exceeds even the cardiac mortality rate of patients with angina pectoris, so that a cerebral ischemic attack should be considered a warning signal of future cardiac events.[5] In patients with symptomatic high-grade carotid stenosis undergoing carotid endarterectomy, myocardial infarction accounts for one-half of perioperative deaths[6,7]; during the long-term follow-up, the risk of fatal myocardial infarction is 2 to 5 times greater than the risk of fatal stroke.[6–10] Whereas the risk of cardiac events is well known in patients with a history of myocardial infarction or angina who are undergoing carotid endarterectomy, no data are available concerning the cardiac risk in patients with clinically silent coronary artery disease (CAD). The aim of the present study is to assess the prevalence and prognostic role of silent CAD in patients with no history, symptoms or electrocardiographic (ECG) signs of cardiac disease who are undergoing carotid endarterectomy for symptomatic high-grade carotid stenosis.

METHODS

Patients: One hundred six consecutive patients admitted to the Department of Neurosurgery of our hospital for carotid endarterectomy fulfilled the following inclusion criteria: (1) transient ischemic attack or minor stroke of the carotid territory; (2) high-grade carotid stenosis (70 to 99%), ipsilateral to cerebral symptoms; (3) no history, symptoms or ECG signs of CAD; and (4) ability to perform adequate exercise ECG testing.

Basal investigation: Patients underwent a standardized neurologic investigation consisting of history, neurologic examination, computed tomography scan of the brain and 4-vessel cerebral angiography. The cardiologic investigation consisted of history, physical examination, 12-lead electrocardiogram, chest x-ray, 2-dimensional echocardiography, exercise ECG testing and, in patients with abnormal exercise ECG testing, thallium-201 myocardial scintigraphy. Silent CAD was defined by concordant, abnormal exercise ECG testing and thallium-201 myocardial scintigraphy.

Exercise electrocardiographic testing: Exercise ECG testing was performed by treadmill, using a Marquette Case II recorder, according to a modified Bruce protocol (exercise stages of 2 minutes starting from level 0). Patients with bundle branch block and left ventricu-

lar hypertrophy were excluded from the study. A 12-lead electrocardiogram and blood pressure were recorded before, at the end of each stage, at peak exercise and at 2-minute intervals in the recovery phase. During exercise the 12 ECG leads were continuously monitored. Exercise ECG testing was maximal or limited by exhaustion, symptoms, systolic blood pressure ≥240 mm Hg, or ST-segment depression ≥3 mm. Exercise ECG testing was considered abnormal if ST depression ≥1 mm or ST elevation ≥1.5 mm were present.

Thallium-201 myocardial scintigraphy: Patients with abnormal results on exercise ECG testing underwent bicycle exercise thallium-201 myocardial imaging within 2 weeks. At the appearance of at least 1.0 mm ST-segment depression, 74 MBq of thallium-201 were injected intravenously, and the patient was requested to continue the exercise for another 60 to 90 seconds. Each patient underwent imaging in the supine position with a PHO gamma V scintillation camera immediately and after isotope administration (exercise), and 4 hours later (delayed test) for the redistribution scan. Each image was subdivided into 3 or 4 segments corresponding to the territories of distribution of left anterior descending, circumflex and right coronary arteries for a total of 8 segments. Images were stored in a computer for processing, semiquantitative analysis, and elaboration of circumferential profiles.

Treatment and follow-up: Preoperatively, during and after surgery, patients with silent CAD were treated with β blockers and nitrates. Nifedipine was administered if β blockers were contraindicated. Aspirin or ticlopidine were given to all patients after surgery. During the follow-up, a neurologic and cardiologic evaluation was done every 6 months. Patients with silent CAD performed exercise ECG testing every year. Medical therapy, initiated before surgery in patients with CAD (aspirin, β blockers, and so forth), was continued during the follow-up.

Statistical analysis: Continuous data are given as mean ± standard deviation. Student's *t* test was used for differences between the mean of different observations, and the chi-square test to determine the difference between proportions. The occurrence of new cardiac events was compared between groups of patients by the construction of Kaplan-Meyer survival curves. A p value <0.05 was required for statistical significance.

RESULTS

Study population: Patients were aged 58.7 ± 8.4 years (range 42 to 73) and 76 (72%) were men. According to the inclusion criteria no patient had a history or symptoms of CAD. Echocardiograms never showed evidence of wall motion abnormalities and the ejection fraction was ≥45% in all patients.

Exercise ECG testing was abnormal in 39 patients (37%) without angina. All these patients underwent thallium-201 myocardial scintigraphy, which confirmed a silent CAD in 27 (25% of the study population) (perfusional defects of 2.2 ± 0.9 segments, reversible in all patients). Among the 27 patients with silent CAD and the remaining 79, there were no significant differences for age, atherosclerotic risk factors, transient ischemic attack or stroke prevalence, and coexistence of intermittent claudication. In patients with CAD, the male prevalence was significantly higher (p <0.05) (Table I). A carotid stenosis of 70 to 90% was observed in 13 patients (48%) with CAD and in 59 (75%) without CAD. Conversely, a more severe carotid stenosis of 90 to 99% was observed in 14 patients (52%) with CAD and in 20 (25%) without CAD (p <0.01). A contralateral carotid occlusion or stenosis ≥70% was observed in 17 patients (63%) with CAD and in 30 (38%) without CAD (p <0.05). Finally, the presence of ischemic areas at computed tomography scan of the brain was similar in the 2 groups (Table II).

TABLE I Distribution of Conventional Risk Factors and Type of Cerebral Ischemia by Presence of Silent Coronary Artery Disease

	CAD		
	Absent (n = 79) n (%)	Present (n = 27) n (%)	p Value
Mean age (yr)	65 ± 8	64 ± 7	NS
Men/women	51 (65)/28 (35)	24 (89)/3 (11)	<0.05
Current smoking	54 (68)	20 (74)	NS
Systemic hypertension	45 (57)	16 (59)	NS
Diabetes mellitus	17 (21)	5 (18)	NS
Hypercholesterolemia (≥200 mg/dl)	34 (43)	11 (41)	NS
Claudication	22 (28)	6 (22)	NS
Transient ischemic attack	61 (77)	20 (74)	NS
Stroke	18 (23)	7 (26)	NS

CAD = coronary artery disease; NS = not significant.

TABLE II Severity of Symptomatic Carotid Lesions, and Prevalence of Contralateral Carotid Disease and Ischemia at Computed Tomography Scan of the Brain by Presence of Silent Coronary Artery Disease

	CAD		
	Absent (n = 79) n (%)	Present (n = 27) n (%)	p Value
Ipsilateral carotid lesion			
70–90%	59 (75)	13 (48)	<0.01
90–99%	20 (25)	14 (52)	
Contralateral carotid lesions (≥70%)			
Presence	30 (38)	17 (63)	<0.005
Absence	49 (62)	10 (37)	
Computed tomography brain scan			
Ischemia	34 (43)	11 (41)	NS
Normal	45 (57)	26 (59)	

CAD = coronary artery disease; NS = not significant.

Perioperative outcome: The 106 patients underwent 121 operations (9 had bilateral carotid endarterectomies and 6 a contralateral extraintracranial arterial bypass). No deaths occurred during the perioperative period (within 30 days after surgery). One patient had carotid stroke, ipsilateral to the surgical lesion, and 3 patients had a transient ischemic attack (Table III).

Long-term prognosis: During a mean follow-up period of 5.4 years, 9 patients died (1.7%/year): a fatal myocardial infarction occurred in 5 (all with silent

TABLE III Morbidity and Mortality in 106 Patients Undergoing Carotid Endarterectomy

	CAD	
	Absent (n = 79) n (%)	Present (n = 27) n (%)
Early (< 30 days)		
Total deaths (n = 0)		
Nonfatal events (n = 4)		
Myocardial infarction	0	0
Transient ischemic attack	2	1
Stroke	0	1
Late (> 30 days)		
Total deaths (n = 9)		
Myocardial infarction	0	5
Cancer	3	0
Stroke	1	0
Nonfatal events (n = 9)		
Myocardial infarction	1	0
Unstable angina	0	3
Transient ischemic attack	3	0
Stroke	2	0

CAD = coronary artery disease.

TABLE IV Exercise ECG Testing and Thallium-201 Myocardial Scintigraphy Findings in Patients with Silent CAD as to the Presence of Coronary Events During a Mean Follow-Up of 5.4 Years

	Silent CAD (n = 27)		
	Coronary Events (n = 8)	No Coronary Events (n = 19)	p Value
Exercise ECG testing			
Total duration (min)	6.2 ± 1.1	6.4 ± 1.7	NS
Onset of 1 mm ST depression (min)	3.2 ± 2.1	4.9 ± 2.4	NS
Rate-pressure product at onset 1 mm ST depression ($\times 10^3$)	15.4 ± 4.6	21.3 ± 4.9	< 0.05
Max. ST depression (mm)	2.5 ± 0.5	2.1 ± 0.7	NS
Rate-pressure product at peak exercise ($\times 10^3$)	21.0 ± 4.9	27.1 ± 4.8	< 0.05
Persistence of ST depression in the recovery phase (min)	7.8 ± 1.5	5.2 ± 4.2	NS
Thallium-201 myocardial scintigraphy			
Extent of perfusion defects (segments)	2.6 ± 1.1	2.0 ± 0.7	NS

ECG = electrocardiographic; other abbreviations as in Table I.

CAD at preoperative evaluation), cancer in 3, and vertebrobasilar stroke in 1. Nonfatal myocardial infarction occurred in 1 patient with normal preoperative cardiac evaluation, and 3 patients with silent CAD became symptomatic for unstable angina. During the follow-up, recurrences of cerebral ischemia occurred in 5 patients (Table III). Among patients with silent CAD the rate-pressure product at 1 mm ST-segment depression and at peak exercise were the only parameters of exercise ECG testing predictive of coronary events during the follow-up, whereas the extent of myocardial ischemia at thallium-201 myocardial scintigraphy was not significantly different between the 2 groups (Table IV). Coronary angiography was performed in a patient with very low threshold of silent ischemia and, during the follow-up, in the 2 patients who developed unstable angina. These three patients later underwent coronary revascularization.

After 7-year follow-up, Kaplan-Meyer estimated survival free from fatal and nonfatal coronary events was 51% in patients with silent CAD and 98% in patients without CAD at preoperative evaluation ($p < 0.01$) (Figure 1).

DISCUSSION

Cardiac events in patients undergoing carotid endarterectomy: Patients with symptomatic, severe carotid stenosis, undergoing carotid endarterectomy have a high risk of coronary events both during the perioperative pe-

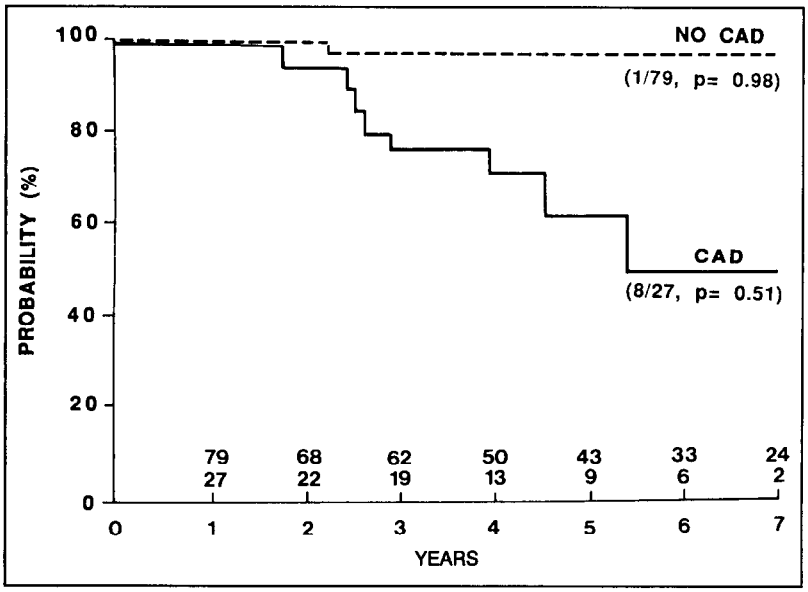

FIGURE 1. Probability of survival free from fatal and nonfatal coronary events in patients undergoing carotid endarterectomy. After 7-year follow-up, the probability was 51% in patients with silent coronary artery disease (CAD) and 98% in those without CAD.

riod or in the follow-up. Hertzer et al,[11] in a series of 390 patients undergoing carotid endarterectomy, observed a perioperative myocardial infarction in 4% of those with a history of CAD, and in 0.5% of the control subjects. During a follow-up period of 1 to 11 years, a fatal myocardial infarction occurred in 25% of patients with known CAD and in 13% of the others. Ennix et al[12] reported perioperative mortality rates (due mainly to myocardial infarction) of 18% in cerebrovascular patients with angina pectoris and 1.5% in the control patients. Yeager et al[13] observed perioperative myocardial infarction in 6% of patients with active CAD, in 3% of those with a history of CAD, and in 1.5% of control patients. During a 21-month follow-up, the death rate was 15.2, 12.5 and 10.2%, respectively. Early and late survival, however, were similar in the 3 groups ($p < 0.05$). Recently, among patients who underwent carotid endarterectomy, Mackey et al[14] found that patients with overt CAD had reduced 30-day ($p = 0.03$) and late survival ($p < 0.0001$). In the latter study, among patients without overt CAD, the presence of coronary risk factors identified those with worse prognosis.

Need for a routine investigation of coronary artery disease: The diagnosis of CAD in patients undergoing carotid endarterectomy is usually based on history of myocardial infarction, angina pectoris or "ischemic" ST segment on the electrocardiogram at rest. Since a standardized cardiac investigation is not routinely performed, even in patients without history or clinical signs of cardiac disease, the prevalence of CAD in this population may be underestimated. Whisnant et al[15] suggested that the poor relationship between the clinical evidence of CAD and the survival rate after a stroke could be explained by the unknown prevalence of silent CAD in patients without overt cardiac disease. The high prevalence of silent CAD in patients with cerebral ischemia was first assessed, a few years ago, in a large angiographic study of 200 patients without history or symptoms of CAD, undergoing carotid endarterectomy. Coronary lesions were identified in 86% of patients, severe ($\geq 70\%$) in 40%.[16]

Nevertheless, a screening based on coronary angiography in patients undergoing carotid endarterectomy has an unfavorable cost-effectiveness ratio. A noninvasive evaluation consisting of exercise ECG testing and thallium-201 myocardial scintigraphy should be considered a reliable alternative, their sensitivity and specificity being high in a population with a high prevalence of CAD.[17-20] In previous noninvasive studies the prevalence rate of CAD in cerebrovascular patients was 10 times greater than in a control group of healthy subjects,[21,22] although the real prevalence of silent CAD is probably underestimated because of the study protocol used. Moreover, in patients unable to exercise, a silent CAD was identified by dipyridamole myocardial imaging in >50% of the patients.[23]

Clinical implications: The present study first assessed the prevalence of silent CAD in patients with neither history nor symptoms of CAD undergoing carotid endarterectomy. One fourth of these patients showed abnormal concordant exercise ECG testing and myocardial scintigraphy. Furthermore, in patients with silent CAD, the severity of the carotid lesions and the coexistence of contralateral carotid disease were significantly greater. Silent CAD did not affect the perioperative outcome in patients given adequate anti-ischemic therapy, but strongly influenced the long-term prognosis. During a 5.4-year follow-up, coronary events occurred in 29% of patients with silent CAD, but in only 1.2% of those without CAD; the probability of survival free from coronary events is significantly worse in patients with silent CAD. Most deaths were of cardiac origin and all the patients who died from myocardial infarction had CAD on preoperative evaluation.

Conclusions: Whereas 2 large randomized clinical trials have recently demonstrated that carotid endarterectomy can significantly improve the neurologic prognosis of patients with symptomatic high-grade carotid stenosis,[10,24] the unfavorable cardiologic long-term prognosis suggests the need for careful cardiac evaluation of these patients. According to our experience, and recent studies dealing with patients undergoing vascular surgery,[25] a noninvasive screening for CAD should be performed in all patients undergoing carotid endarterectomy, even in those without history or symptoms of CAD, in order to identify patients who need more aggressive monitoring and management during the follow-up.

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