The value of urgent carotid surgery for crescendo transient ischemic attacks

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Objective: **This study audited operative risk in patients undergoing urgent carotid surgery for crescendo transient ischemic attacks (TIAs).**

Methods: **Interrogation of the vascular unit database (January 1992 to July 2004) identified 42 patients operated on urgently for crescendo TIAs, which were defined as ≥3 TIAs within the preceding 7 days. Stroke, death, and any major cardiac events were analyzed.**

Results: **Thirty-nine patients underwent conventional endarterectomy, and three underwent interposition vein bypass. Crescendo TIA patients had sustained a median of five TIAs (range, 3 to 20) in the 7 days before surgery. Three patients died or had a stroke after surgery, for a combined stroke/death rate of 7%. This compares with 2.4% in 1000 patients undergoing elective carotid endarterectomy in this unit during the same time period. The combined stroke/death/major cardiac event rate was 14% (n = 6).**

Conclusions: **The combined risk of neurologic and cardiac complications after urgent carotid surgery for crescendo TIA is higher than that expected after elective cases but is still acceptable considering the natural history of patients with unstable neurologic symptoms. (J Vasc Surg 2007;45:1148-54.)**

The role of urgent carotid endarterectomy (CEA) for neurologically unstable patients with deficits of recent onset has not been adequately defined. In the past, reconstruction of the internal carotid artery (ICA) has been offered for several urgent indications such as recurrent or crescendo transient ischemic attacks (TIAs), acute or recurrent stroke, progressing stroke with fluctuating or evolving pattern, and recent total ICA occlusion. Reports on the results of urgent surgical treatment usually group all these urgent indications together or mix outcomes of these procedures with stable symptomatic or even asymptomatic patients.[1-30] Furthermore, they usually report a small number of patients over a long period of time. As a result, reliable evidence about the effectiveness of surgery in the urgent or emergency setting is lacking. An accurate definition of *crescendo TIAs* remains unanswered in the literature because some investigators use the term arbitrarily and others do not provide a definition at all.

Finally, it was our impression that these neurologically unstable patients are also at higher risk for acute cardiac complications as a result of systemic inflammation or atherosclerotic plaque instability, or both, or because of the large burden of coronary artery disease in this population. In this study, we aimed to test the above hypothesis and reviewed our experience with patients presenting with crescendo TIAs during the last 12 years, with a particular emphasis on cardiac events.

METHODS

The vascular database of our unit was interrogated to identify patients undergoing urgent carotid surgery for crescendo TIAs between January 1992 and July 2004. One of the problems in the carotid literature is the lack of an accurate definition of what constitutes TIAs with a crescendo pattern. Traditionally, crescendo TIAs involve repeated TIAs within a relatively short period of time. On each occasion, the neurologic deficit will have fully recovered before the onset of the next event, and these may occur daily or be more frequent and more severe.

Because no agreement has been reached on the actual definition of *crescendo TIAs,* for the purposes of this study, we thus defined crescendo TIAs as ≥3 TIAs in the preceding 7 days. Those operated on urgently for recurrent TIAs but who had experienced <3 TIAs during the previous 7 days were excluded. Patients with crescendo neurologic symptoms undergoing external carotid endarterectomy in the presence of an occluded ICA were also excluded.

Patient details, including age, gender, hypertension, coronary artery disease, smoking, diabetes, peripheral vascular disease, renal impairment, and hypercholesterolemia were collected and were entered in an Excel database (Microsoft Ltd, Reading, UK).

Patients underwent a brain computed tomography (CT) scan to confirm the diagnosis and rule out intracranial hemorrhage, subdural hematoma, or intracranial pathologies other than acute cerebral ischemia. The extracranial carotid arteries and plaque morphology were assessed by duplex scanning performed by an experienced vascular

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technologist. The only indications for proceeding to intra-arterial digital subtraction angiography (DSA) or magnetic resonance arteriography (MRA) were inconclusive findings, such as inability to obtain satisfactory images of the bifurcation, inability to visualize the distal ICA, abnormal common carotid waveform suggestive of proximal disease, and a high-resistance signal in the distal ICA suggestive of a siphon disease.

The criterion for surgery by carotid noninvasive testing was a ≥70% stenosis of the ipsilateral ICA. No patient in this series had been operated on with a less severe stenosis. If there were either an atypical presentation or concerns about other sources of cerebral embolization, such as cardiac causes, a cardiology opinion and transthoracic or transesophageal echocardiography, or both, were requested. No atypical cases were included in the present series.

After verifying the diagnosis and demonstrating the absence of hemorrhagic infarction, all patients were systemically anticoagulated with at least 1000 U/h of heparin. Patients usually underwent operation on the first available scheduled vascular operating list.

CEA was undertaken with the utmost care during carotid dissection with the aim of achieving early distal ICA control and avoiding distal embolization of loose thrombus and debris. All procedures were performed by a consultant vascular surgeon or supervised trainee with normotensive, normocarbic general anesthesia using loupe magnification, systemic heparinization (5000 U), routine shunting (Pruitt-Inahara, Ideas for Medicine, North Clearwater, Fla), tacking sutures to the distal intimal step to prevent intimal dissection, and routine patch angioplasty. Blood flow velocity in the middle cerebral artery (MCA) was monitored throughout the procedure using 2-MHz pulsed wave transcranial Doppler (TCD) ultrasound imaging with a fixed head probe system (SciMed PC2-64B, Scimed UK Ltd, Bristol, UK) protected by a semi-circular metal head guard.

A 5-mm segment of the anastomosis adjacent to the orifice of the external carotid artery was left open. The shunt was removed, and the lumen was vented and irrigated with heparinized saline. Before final closure and restoration of flow, the lumen was inspected with a flexible hysteroscope (Olympus 1070-48, Hamburg, Germany) to exclude residual luminal thrombus and intimal flaps.

Where simple CEA was not technically feasible, a common-to-internal carotid interposition bypass was performed with the use of reversed great saphenous vein retrieved from the thigh area. After recovery from anesthesia, the patient was transferred to the recovery area of the operating theater or to the high dependency unit for a 3-hour period of TCD monitoring. Previous work in this department has demonstrated postoperative TCD monitoring and selective administration of Dextran-40 emboli to be successful in reducing embolization and progression to stroke.[31] The protocol of our unit was to administer Dextran-40 to any patient who had (1) ≥25 emboli in any 10-minute period or (2) emboli that distorted the MCA waveform, suggesting that they were large.

Table I. Patient demographics

Patient details	*N, (%)*
Age, median (range)	66 (48-87)
Male/female	33/9
Ischemic heart disease	24 (57)
Myocardial infarction	16 (38)
Angina	16 (38)
Hypertension	28 (67)
Diabetes	4 (10)
Renal impairment	4 (10)
Peripheral vascular disease	8 (19)
Hypercholesterolemia	17 (40)
Smokers (current or ex)	32 (76)
Previous contralateral CEA	4 (10)

CEA, Carotid endarterectomy; *CT,* computed tomography

The main outcome measures were stroke, death, and major cardiac events ≤30 days. Any new neurologic deficit lasting >24 hours was classified as a stroke, and these patients were investigated by CT scan/autopsy, duplex assessment of the ICA, and TCD assessment of the intracranial vessels, as appropriate. Major cardiac events were defined as Q and non-Q wave myocardial infarction (MI), congestive heart failure, unstable angina, and ventricular tachyarrhythmias. MI was defined as including two or more of the following criteria: cardiac enzyme levels >5% or troponin concentration >1.3 μg/L, ischemic changes on electrocardiogram (ECG), or chest pain for >30 minutes.

Non-Q wave MI was defined as elevated cardiac enzyme levels with no ECG changes. Minor cardiac events included less severe episodes of angina or arrhythmias not requiring treatment in an intensive care unit/coronary care unit setting. Because some patients may have angina or arrhythmias preoperatively, only new episodes of angina or arrhythmias were recorded. Serial ECGs and cardiac enzyme assays were not obtained routinely and were only requested if there were clinical symptoms, ST segment changes on continuous ECG monitoring, or hemodynamic instability.

RESULTS

During the study period, 42 patients (33 men, 9 women) with a median age of 66 years (range, 48 to 87 years) underwent urgent carotid surgery. The patient demographics and medication history are summarized in Tables I and II, respectively. All were taking aspirin (n = 39) or clopidogrel (n = 3) preoperatively. Patients had experienced a median of five TIAs during the 7 days before admission (range, 3 to >20). Presenting symptoms were typical lateralizing TIAs in 41 patients, amaurosis fugax and TIA in 11, and recurrent episodes of amaurosis fugax in one. No patient presented with atypical symptoms.

All but two were systemically heparinized for a median of 3 days (range, 1 to 7 days). These two patients were planned admissions from the urgent waiting list for an elective CEA. During pre-clerking, however, they admitted to having experienced multiple TIAs within the previous

Table II. Medication history at time of admission*

Medication	*N*
Aspirin	39
Warfarin	2
Dipyridamole	12
Clopidogrel	3
Statin	21
β-blockers	9
Diuretics	19
Calcium-channel blockers	11
ACEI	9

ACEI, Angiotensin converting enzyme inhibitors.
*All patients were receiving aspirin or clopidogrel preoperatively.

Table III. Operative details*

Operative data	*N*
General anesthesia	42
Procedures	
Carotid endarterectomy	39
Interposition vein bypass	3
TCD monitoring	39
Middle cerebral artery	36
Posterior cerebral artery	3
Plaque morphology	
Smooth stenosis	3
Ulceration (no overlying debris)	4
Ulceration + overlying debris/thrombus	31
Intra-plaque hemorrhage	4
Shunting	40
Shunt time (min)	45 (31-96)
Clamp time 1 (min)	2 (1-6)
Clamp time 2 (min)	4 (3-12)
Angioscopy	39
Positive angioscopy	4

TCD, Transcranial Doppler; *Clamp time 1*, time from clamping to shunt release; *Clamp time 2,* time from shunt clamping to flow restoration.
*Values are expressed as medians (range).

few days, but neither had sought medical advice. They were administered an immediate oral dose of clopidogrel (75 mg) the same evening and underwent surgery the next morning. In addition to duplex scanning, only two patients underwent further imaging of the carotid arteries. One patient underwent carotid angiography, and one patient proceeded to MRA.

The operative details are summarized in Table III. A total of 39 patients underwent a conventional endarterectomy, all with patch closure (34 Dacron and 5 vein). Three patients underwent interposition vein bypass, one because of extreme tortuosity and two because of a very thin posterior wall after CEA. At operation, macroscopic examination of the excised plaques revealed ulcerated plaques with overlying debris or thrombus in 74% of patients. TCD monitoring of the ipsilateral MCA was used in 39 patients. In three patients, there was no temporal window. None of the three developed any cerebrovascular complications.

Completion angioscopy was performed successfully in 39 patients. Angioscopy was not performed in three patients because of equipment failure, the operation was performed out of hours, logistical problems, and two simultaneous CEAs. Angioscopy was positive in four patients (10%), where residual thrombus was detected and removed before flow restoration; presumably, it had formed due to bleeding from vasa vasorum or inadequately flushed arteriotomy. No technical defects had been detected in this series. No patient received Dextran-40 postoperatively because none fulfilled the unit criteria for TCD-directed Dextran therapy.

Table IV. Operative results

Outcome	*Crescendo TIAs (n = 42) (%)*
All complications	16
Stroke	2 (4.8)
Cardiac	8
Myocardial infarction	1
Left ventricular failure	2
Angina	1
Angina (unstable)	2
Arrhythmias	2
Respiratory	2
Cranial nerve dysfunction	2
Neck hematoma	1
Retroperitoneal hematoma	1
30-day mortality	2 (4.8)
Stroke/death rate	3 (7)
Stroke/death/major cardiac event rate	6 (14)

The operative results are summarized in Table IV. A total of 16 complications occurred in 13 patients (31%). Two patients (4.8%) had a postoperative stroke. The first occurred in the vertebrobasilar territory on the first postoperative day due to basilar artery thrombosis and he died 2 days later. The presence of thrombosis and pre-existing vertebrobasilar occlusive disease was confirmed at autopsy. The second patient developed acute congestive heart failure and severe cardiorespiratory distress requiring reintubation and ventilation for 48 hours in the intensive care unit. He was noted to have right arm weakness when he was extubated, and a brain CT scan confirmed an infarct in the ipsilateral MCA territory.

No statistical association was detected between the presence of previous infarct on CT and stroke or death (1/11 vs 2/31, $P = .4$). There were eight cardiac complications (5 major, 3 minor). Overall, the 30-day event rates were 4.8% for mortality, 7% for stroke/death, and 14% for combined stroke/death/cardiac.

DISCUSSION

Although the natural history of crescendo TIAs has not been evaluated prospectively in large series, such symptoms are considered a precursor to stroke.[13] Medical treatment alone is associated with a poor prognosis, an opinion largely based on anecdotal data from the 1970s and 1980s.[13,14,24,32] Crescendo TIAs represent disabling, recurrent transient cerebral or retinal ischemia characterized by an increased frequency, duration, or severity of events.[13]

Table V. Studies reporting on patients being operated upon urgently for crescendo transient ischemic attacks*

Author & year	*Patients (M/F)*	*Mean age (range)*	*Stroke (%)*	*Stroke and mortality (%)*	*Stroke, mortality and major cardiac events*
Diaz,[2] 1985	8† (4/4)	58 (40-72)	1 (12)	1 (12)	1 (12)
Ricotta,[3] 1985	3 (NA)	NA	0	0	0
Wilson,[13] 1993	12 (NA)	61(42-69)	0	0	0
Nehler,[14] 1993	29 (26/3)	63 (51-83)	1 (3)	2 (6)	4 (13)
Greenhalgh,[15] 1993	7 (5/2)	62 (55-72)	1 (14)	1 (14)	1 (14)
Golledge,[20] 1996	26 (6/20)	65 (38-82)	4 (15)	7 (27)	7 (27)
Schneider,[22] 1999	31(NA)	NA	0	0	0
Paterson,[25] 2000	2 (2/0)	66 (63-69)	0	0	0
Brandl,[26] 2001	7(6/1)	69 (60-84)	1 (14)	1 (14)	1 (14)
Kasper,[27] 2001	7 (NA)	NA	0	0	0
Present series, 2006	42 (33/9)	66 (48-87)	2 (5)	3 (7)	6 (14)
Total	174 (82/39)	64 (40-87)	10 (6)	15 (9)	20 (11.5)

NA, Information not available; *M,* male; *F,* female.
*Only studies detailing information on stroke, stroke/death, and combined stroke/death/major cardiac events have been included.
†Includes four extracranial-intracranial bypasses.

The underlying etiology is thought to be an acutely unstable plaque with overlying thrombus, and the patient is at high risk of stroke. However, no consensus has been reached on the number of TIAs or the time period needed to define an unstable neurologic state as crescendo TIA symptomatology.

The Charing Cross group rejects the term *crescendo TIA*, because "this implies that the deficit is temporary, whereas at the time of surgery, it is unknown whether the patient is going to progress or to improve again from this deficit."[4] In their series of patients with actively changing neurologic deficits, surgical intervention occurred during an attack, and therefore, the outcome without surgery was unknown.

In our experience, along with that from other centers, most patients with crescendo TIA symptoms have usually been operated on during a symptom-free interval in an attempt to arrest progression of the frequent TIAs to a complete stroke.[13,14,24] Several small series report a recovery rate of 70% to 100% after urgent carotid surgery.[24] In a collective review of the literature (unpublished data), we found a 6% rate for stroke and 9% for combined stroke/death in 132 patients undergoing surgery for crescendo TIAs during the last two decades (Table V).[2,3,13-17,25-27] Comparable figures were 4.8% and 7% in our series. The combined stroke/death rate of 1000 patients undergoing elective CEA in this unit during the same time period was 2.4%. Nevertheless, this apparent difference was not statistically significant (24 [2.4%] in 1000 vs 3 [7%] in 42; $P = .058$). A recent meta-analysis from Oxford confirmed that CEA for crescendo TIA had a much higher risk than elective CEA for single episodes of TIA (odds ratio, 7.5; 95% confidence interval, 3.7 to >10; $P < .001$).[33] This was based on the results of only two series, however.[9,20]

After initial intravenous heparinization, some surgeons performed emergency CEA, usually within an interval of 12 to 24 hour,[13] whereas others waited slightly longer in an attempt to achieve neurologic stabilization and avoid emergency surgery.[14] The Portland group, for example, maintained heparin anticoagulation for a mean of 5 days before they proceeded to surgery. One symptomatic common carotid occlusion and one asymptomatic ICA occlusion occurred during preoperative heparin therapy.[14] The median delay to surgery in our series was 3 days. The delay for the individual patient had been influenced by both clinical and logistic reasons, the main factors being whether the patient became asymptomatic on heparin and the availability of an emergency operating room, TCD monitoring, and an experienced vascular technologist. Providing the TIAs were controlled on heparin, we preferred, as others,[14] to avoid high-risk CEAs out of hours in suboptimal conditions and wait until the next available elective list.

Although many of these patients become asymptomatic on heparin, some may continue to experience sporadic TIAs, as seen in 13 of 29 patients in the Portland group and in four patients in the present series. Perhaps these patients represent a subgroup at higher risk that would warrant earlier intervention. Five of these 13 patients experienced TIAs when heparin therapy was briefly discontinued for carotid angiography.[14] Possible reasons for the discrepancy between the two studies may be the shorter delay to surgery in our series and that only one patient underwent carotid angiography.

Two of our crescendo TIA patients (who had been on routine aspirin) were given 75 mg of clopidogrel the night before their operation instead of receiving preoperative heparin anticoagulation. This decision was left to the discretion of the responsible consultant but was based on recent work from this unit that showed that combining aspirin and clopidogrel reduces cerebral embolization in patients undergoing CEA.[34]

One might thus question whether clopidogrel should replace heparin as appropriate initial therapy in these patients. Most patients in our practice are being referred from stroke physicians and neurologists, and they are already receiving a heparin infusion by the time they are seen by the

vascular surgeons. Current evidence is not sufficient to support the use of clopidogrel instead of intravenous heparin as the initial therapy in crescendo TIA patients. Although our personal preference may change toward that direction in the future, this policy is not evidence-based and relies on personal experience of only two crescendo TIA patients and extrapolating data from clopidogrel treatment on elective CEA patients.

Of course, one might argue against this strategy given the results of the Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attacks or Ischemic Stroke (MATCH) trial that demonstrated the added risk without benefit of using both aspirin and clopidogrel in recently symptomatic patients.[35] One might also argue about the optimal dose of clopidogrel, because loading with 300 to 600 mg is necessary to achieve effect within a day. Naturally, the latter dose would have a better antiplatelet and anticoagulant effect; however, this should be balanced against the increased risk of bleeding complications seen after CEA. In any case, such data are not available.

Others have attempted to control emboli preoperatively in patients with recurrent or crescendo TIAs using TCD-directed Dextran therapy before surgery.[36] These workers studied 19 patients who had experienced two or more TIAs within the preceding month and had TCD-detected microemboli. Patients were given Dextran 40 infusion for a median of 5 days (range, 1 to 10 days), a policy that was successful to control both TIAs and TCD microembolization in all cases. One patient died from a myocardial infarction before carotid surgery, and a nondisabling stroke occurred in one of the 18 patients who underwent CEA. The main limitation was that this study excluded patients with TIAs, but without emboli, and patients with emboli and no symptoms.

One reason why we reviewed our experience was an impression that (in addition to a higher of death/stroke) these urgent patients also seemed to be at higher risk for acute cardiac events. The prevalence of coronary artery disease in patients with peripheral arterial disease is well documented. In a classic study from The Cleveland Clinic, hemodynamically significant coronary artery disease was demonstrated (angiographically) in 32% of patients with carotid artery disease.[37] The average rate of perioperative myocardial infarction after elective CEA is about 1.0%,[38] whereas the overall cardiac event rate ranges between 2.4% and 3.3%.[39,40] This observation contrasts with the 17% cardiac event rate encountered in the current series. This rate may also have been underreported because the present study was retrospective and serial ECGs and cardiac enzyme assays were not obtained routinely. Moreover, the cumulative stroke/death/major cardiac event rate was 14%.

The relatively high incidence of perioperative cardiac complications after urgent carotid surgery may seem surprising, but a similar trend has been observed after other urgent arterial procedures.[37] The reasons for this are unclear. Among possible explanations is an incomplete preoperative assessment with a failure to correct all preoperative medical risk factors. Nevertheless, the higher likelihood of cardiac complications in the neurologically unstable patient undergoing urgent carotid surgery may also point toward a common systemic cause for atherosclerotic plaque disruption in both the carotid and coronary vascular beds. Acute coronary and cerebrovascular syndromes, as well as severe peripheral artery disease, are commonly associated with systemic evidence of inflammation, and several studies have suggested that plaque vulnerability may be a systemic phenomenon.[41-43]

Rothwell et al[44] have shown an association between angiographic plaque irregularities in the carotid arteries and plaque instability and rupture in the coronary arteries, providing indirect evidence that some individuals have a systemic predisposition to irregularity and rupture of atherosclerotic plaques. Conversely, complex coronary plaques in a small group of patients were associated with complex carotid plaques and the high prevalence of both plaque types in patients with acute coronary syndrome was indicative of a systemic process contributing to complex plaque formation and instability.[45]

In a larger study, the prevalence of complex carotid plaques was significantly higher in unstable vs stable angina patients.[46] On multivariate analysis, unstable angina and raised C-reactive protein level were independently associated with complex carotid plaques. Similar associations have been observed between peripheral arterial disease and coronary events.[47,48] Carotid plaque morphology has been infrequently addressed in previous studies reporting on patients with crescendo TIAs.[13,22] At operation, approximately 80% of our patients were found to have friable and unstable ulcerated plaques with overlying debris or thrombus.

Of course, one might argue against the hypothesis of systemic plaque instability as a reason for increased cardiac morbidity. The latter may simply reflect selection bias and that these patients have significant pre-existing coronary artery disease. To our knowledge, no studies have compared the extent of coronary artery disease in cerebrovascular patients presenting with crescendo TIAs and those presenting with single TIAs or stable neurologic symptoms. An alternative explanation could be the low use of perioperative β-blockade and statins. Naturally, this series spans a 12-year period, and many of these patients had been treated before the cardioprotective effect of perioperative β-blockers and the anti-inflammatory properties of statins were well documented. In modern vascular practice, one could argue that, considering the data of Poldermans et al,[49] it is equally important to spend the 0 to 3 days preoperatively getting the patients appropriately β-blocked as it does getting them adequately anticoagulated.

Finally, it may well be that the conclusions of the present study could simply represent a statistical error because of the small numbers. The latter was the reason why a formal statistical analysis for any potential significant variables with impact on outcome, such as patch type, the

use of angioscopy, and plaque morphology was not performed.

CONCLUSION

The combined risk of neurologic and cardiac complications after urgent CEA for unstable, crescendo-type neurologic symptoms is higher than that expected after elective cases— but still acceptable—considering the natural history of patients with unstable neurologic symptoms. The increased likelihood of cardiac events would suggest that a systemic trigger may mediate acute atherosclerotic plaque disruption or may reflect the large burden of coronary artery disease in this population.

AUTHOR CONTRIBUTIONS

Conception and design: CK, GM, AN, MD, MM
Analysis and interpretation: CK, GM, MD, MM, NL, AN
Data collection: CK, GM, MD, MM, RS, NL, AN
Writing the article: CK, GM, MD, MM, AN
Critical revision of the article: CK, GM, MD, MM, RS, NL, AN
Final approval of the article: CK, GM, MD, MM, RS, NL, AN
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Overall responsibility: CK

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