Excimer Laser–Assisted High-Flow Extracranial/Intracranial Bypass in Patients With Symptomatic Carotid Artery Occlusion at High Risk of Recurrent Cerebral Ischemia Safety and Long-Term Outcome

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Background and Purpose—The goal of this study was to determine safety and long-term outcome of the excimer laser–assisted high-flow extracranial/intracranial (EC/IC) bypass in patients with symptomatic carotid artery occlusion (CAO) at high risk of recurrent stroke.

Methods—In a prospectively collected cohort of 103 patients with symptomatic CAO, 15 patients were selected for excimer laser–assisted EC/IC bypass surgery on the basis of predefined selection criteria: (1) transient or moderately disabling symptoms of focal cerebral ischemia, not symptoms of the retina only; (2) continuing symptoms after documentation of the CAO; (3) evidence of a possible hemodynamic origin of symptoms; and (4) informed consent of the patient.

Results—Eleven patients underwent the operation without complications. One patient had a severely disabling stroke (Rankin grade 4) 11 days after the operation; the bypass was found occluded on reoperation. Two other patients had a moderately disabling stroke (Rankin grade 3) immediately after the operation. One patient died of myocardial infarction 1 day after surgery. Median follow-up time was 27 months. Of the 11 patients who underwent the operation without complications, 1 died 17 months after the operation of a brainstem stroke, and another patient had a new stroke ipsilateral to his CAO 10 months after the operation but without a change in Rankin grade.

Conclusions—The excimer laser–assisted high-flow EC/IC bypass operation is a potentially promising procedure in patients with symptomatic CAO and a presumably high risk of recurrent stroke, but the procedure carries a definite risk. This risk is probably related not only to the procedure itself but also to the selection of patients. (Stroke. 2002;33:2451-2458.)

Key Words: bypass surgery ♦ carotid artery occlusion ♦ laser ♦ outcome

Superficial temporal artery to middle cerebral artery (STA-MCA) bypass surgery for the prevention of stroke in patients with symptomatic carotid artery occlusion (CAO) has been largely abandoned throughout the world since the negative results of the international extracranial/intracranial (EC/IC) trial were published in 1985. One of the main points of critique of this trial has been that measurements of cerebral hemodynamics were not performed to select patients who might specifically benefit from the operation. At this time, there is evidence that a compromised flow state in the brain is associated with an increased risk of recurrent cerebral ischemic events in patients with symptomatic CAO. The feasibility of a new EC/IC bypass trial, including only patients who are at high risk of recurrent stroke as identified by the presence of a high oxygen extraction fraction on PET, is currently under investigation.

Another possible reason that the STA-MCA bypass failed to prevent recurrent stroke in patients with symptomatic CAO is the small diameter of the bypass. On the basis of a mathematical model of the circle of Willis, it has been hypothesized that the small caliber of the cortical branch of the MCA may limit the increase in cerebral blood flow that can be obtained by the STA-MCA bypass. This has led one of us (C.A.F.T.) to develop a new EC/IC bypass technique.

For this bypass, the intracranial distal part of the internal carotid artery (ICA) or the proximal part of the MCA is used as the recipient artery. It is not necessary to temporarily clamp the recipient artery because the distal anastomosis is made with an excimer laser–assisted technique. This technique allows construction of a bypass with a recipient artery of a large caliber proximal in the vascular tree.

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2451
We report here the first prospective case series of 15 patients who underwent excimer laser–assisted EC/IC bypass surgery because of recurrent ischemic symptoms of the brain that were transient or at most moderately disabling, associated with CAO, and presumed to have a high risk of recurrent ischemic stroke.

Patients and Methods

Patients

Between September 1995 and July 1998, 15 patients underwent excimer laser–assisted EC/IC bypass surgery. Patients were selected for the operation by predefined criteria described below from 103 prospectively collected, consecutive patients with an angiographically proven occlusion of the ICA. All patients had been referred to the departments of neurology, neurosurgery, or vascular surgery because of recent (<6 months) symptoms of retinal or cerebral ischemia that were transient or at most moderately disabling (Rankin grade 3 or better) and attributable to the CAO. Patients were excluded in case of occlusion of the common carotid artery or if a diagnosis of dissection was made. All patients were interviewed in detail by 1 of 2 investigators (C.J.M.K., L.J.K.) about the type and frequency of symptoms and the presence of vascular risk factors. Special attention was given to clinical characteristics that have classically been associated with a hemodynamic cause of symptoms: limb shaking, or precipitation of symptoms by rising from a sitting or lying position, by exercise, by transfer from a cold to a warm environment, or by a decrease in blood pressure. Retinal claudication was diagnosed when patients experienced transient monocular blindness subsequent to looking into bright light. The presence of infarcts was established on MRI. Occlusive disease of other cerebrovascular vessels, in addition to the CAO, was assessed on the angiogram. The presence of collateral blood flow was ascertained from the angiogram and transcranial Doppler ultrasonography (TCD). Collateral blood flow via the anterior communicating artery (ACoA) was considered present if filling of the MCA or anterior cerebral artery (ACA) on the side of the CAO via the ACoA or when TCD showed reversed flow in the first part of the ACA ipsilateral to the occlusion. Collateral flow via the posterior communicating artery (PCoA) was considered present if filling of MCA branches via the PCoA was visible on the angiogram. Collateral flow via the ophthalmic artery (OphthA) was inferred from reversed flow in the OphthA on TCD. Collateral blood flow via leptomeningeal pathways was diagnosed from filling of superficial cortical branches of the posterior cerebral arteries or the contralateral ACA extending into the vascular territory of the symptomatic ICA on the angiography films.

Selection criteria for excimer laser–assisted high-flow EC/IC bypass operation were as follows: (1) cerebral symptoms, not symptoms of the retina only; (2) continuing symptoms after documentation of the CAO despite antithrombotic medication; (3) evidence of a possible hemodynamic origin of symptoms; which could consist of symptoms classically associated with a hemodynamic cause (see above), a border-zone infarct, low CO2 reactivity, or a combination of these criteria; and (4) informed consent of the patient. Each candidate for surgery was discussed in a consensus meeting of neurologists and neurosurgeons before the final decision was made. CO2 reactivity was calculated as the relative change in blood flow velocity in the MCA from the mean baseline blood flow velocity and was expressed as a percentage. Details of the clinical presentation and outcome of the entire cohort operated patients, including those who were not operated on, and the TCD and CO2 reactivity measurements have been described previously. In addition to excimer laser–assisted EC/IC bypass surgery, all patients were treated with antithrombotic medication (low-dose aspirin in 12, oral anticoagulants in 3), and risk factors were rigorously managed. In case of a ≥70% stenosis of the contralateral ICA (measured according to the criteria of the North American Symptomatic Carotid Endarterectomy Trial), endarterectomy was carried out before EC/IC bypass surgery. Endarterectomy of the external carotid artery ipsilateral to the CAO was not a treatment option in any of the 15 operated patients because none of them had a severe stenosis of this vessel.

All patients were followed up for recurrence of retinal or cerebral ischemic events, myocardial infarction, or death until November 1, 1999. Any event that occurred within 30 days of surgery was considered a complication of the procedure. In all patients, patency of the EC/IC bypass was assessed 6 months after the operation by TCD. At the same time, we repeated CO2 reactivity measurements, performed MRI studies to look for clinically silent infarcts, and determined the Rankin grade.

The Institutional Review Board of the University Medical Center Utrecht approved the study protocol.

Excimer Laser–Assisted EC/IC Anastomosis

After frontotemporal craniotomy according to standard procedures, a platinum ring with a diameter of 2.8 mm was stitched to the exterior of the recipient vessel, either the distal part of the ICA or the proximal part of the MCA (Figure 1a). Then, the donor vessel, either the greater saphenous vein or the radial artery, was connected to the target vessel at the site of the platinum ring (Figure 1a). The other part of the donor vessel was connected to the STA by means of a conventional end-to-side technique and temporarily clipped (Figure 1b). Subsequently, the excimer laser was introduced into the donor vessel via an artificially made side branch or by interruption of the donor vessel until its tip rested on the wall of the recipient artery inside the platinum ring. High vacuum suction was applied to ensure firm fixation of the wall of the recipient artery to the tip of the laser catheter. By means of laser pulses, the portion of the wall of the recipient artery within the platinum ring was punched out and removed by retraction of the laser catheter. Then, the artificial side branch was clipped, or the 2 parts of the donor vessel were reconnected (Figure 1c). The anastomosis became functional by removal of the temporary clips from the donor vessel. Subsequently, patients received 2500 U heparin IV. Starting the day after the operation, patients were given 500 mL Rheomacrodex IV (dextran in sodium chloride solution) over 3 days. Venous thrombosis prophylaxis (Nadroparine) was started the second day after the operation, and low-dose aspirin or oral anticoagulants were begun the fourth day. More technical details can be found in previous reports.

Results

The Table summarizes the characteristics of the 15 patients (12 men, 3 women; age range, 46 to 69 years; median, 58 years) who underwent excimer laser–assisted EC/IC bypass surgery. Six patients had presented with recurrent transient symptoms only, and in addition to the transient symptoms, 8 patients had permanent deficits that were not more than slightly or moderately disabling. One patient (patient 5) had had 2 moderately disabling strokes and no transient ischemic attacks (TIAs). Seven patients had symptoms suggestive of a hemodynamic cause: limb shaking in 6 patients, symptoms subsequent to rising to the upright position in 4, and symptoms precipitated by exercise in 3. Most patients had multiple vascular risk factors. In about half of the patients, the angiogram showed a stenosis of 1 of the 3 other cerebrovascular vessels. One patient (patient 14) had undergone endarterectomy of a 71% stenosis of the contralateral ICA before the EC/IC bypass procedure, after which he continued to have TIAs. In all patients, collateral flow via at least 1 of the so-called secondary pathways (OphthA or leptomeningeal vessels) was seen. CO2 reactivity could not be determined in 2 patients and was low in all other 13. In 1 of the 13 patients, CO2 reactivity was completely absent, and in 5 patients, CO2 reactivity was negative, indicating a steal phenomenon with redistribution of blood toward the symp-
In 13 patients, the saphenous vein was used as the donor vessel; in 2 patients, the donor vessel was the radial artery (patients 13 and 14). The distal anastomosis was made at the distal intracranial part of the ICA in 11 patients and at the proximal part of the MCA in 4 patients (patients 2, 4, 5, and 15).

In 3 of the 15 patients (patients 3, 7, and 15), an ipsilateral ischemic stroke occurred in the postoperative period, and 1 patient (patient 4) died of myocardial infarction. In patient 3, the TIAs that had occurred daily before the operation stopped completely for the first 10 days after the operation. On day 11 after the operation, this patient developed fluctuating symptoms of dysphasia and right-sided weakness, particularly on rising. The pulsations of the EC/IC bypass, which clearly had been present until day 11, could not be recorded any longer, and reoperation showed thrombosis over the full length of the bypass. During this second operation, a possible cause (such as kinking) of thrombosis of the bypass was searched for but could not be established. A conventional STA-MCA bypass was made, but the dysphasia and hemiparesis remained due to a new infarct in the ipsilateral MCA territory. This patient was no longer independent in her daily activities (Rankin grade 4). In patient 7, the proximal portion of the ACA was chosen as the recipient artery because the distal part of the ICA and the proximal MCA were extremely atherosclerotic. During application of the platinum ring at the very thin wall of the ACA, a bleeding occurred, which made it necessary to choose a new location at the ICA. Because no punched-out part of this second recipient vessel was removed on retraction of the laser catheter, construction of a high-flow EC/IC bypass was abandoned, and a conventional anastomosis with 1 of the cortical branches of the MCA was established. Postoperatively, the patient had weakness of her leg, which worsened her Rankin grade from 2 to 3. CT showed a new infarct in the territory of the MCA and a border-zone infarct between the territories of the ACA, MCA, and posterior cerebral artery, both on the side of the ICA occlusion. In patient 15, again the punched-out part of the recipient vessel was not seen. Subsequently, a bypass was made with a third-generation branch of the MCA by means of a conventional end-to-side technique with temporary (≈25 minutes)
clipping of this branch. At the start of the operation, blood pressure had been as low as 75/40 mm Hg. The patient awoke from anesthesia with dysphasia and right-sided hemiplegia. The median follow-up time of the 14 patients who survived the operation was 27 months (range, 14 to 48 months). Two patients (patients 3 and 7) died after sudden death within the postoperative period (patients 2, 3, and 7). In none of the 14 patients who survived the operation show clinically silent infarcts.

Patient 4 experienced not only frequent left hemispheric TIAs but also frequent attacks of polyneuropathy, including rising† and limb shaking. Patient 5 developed transient dysphasia and right-sided weakness 5 days after the procedure. On the basis of an evident decrease in pulsations of the bypass, kinking through changes in volume was suspected and in fact found at reoperation. Subsequently, a second excimer laser–assisted procedure was carried out in which an anastomosis was made between the external lumbar drainage was provided in 2 patients (patients 6 and 13), bone flap infection 2 months after craniotomy (patient 14), wound infection (patient 7), pneumonia (patient 13), urinary tract infection (patient 15), and transient delirium (patients 2, 3, and 7). In none of the 14 patients who survived the postoperative period did MRI of the brain 6 months after the operation show clinically silent infarcts.

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coma 24 and 14 months after surgery. In patient 3, the presumed cause of death was a brainstem stroke, but the precise nature remained unclear because neither imaging of the brain nor autopsy was performed. Patient 7 had an ischemic stroke in the hemisphere contralateral to the CAO; hemorrhage was excluded by imaging of the brain. A third patient (patient 14) died 17 months after uncomplicated excimer laser–assisted EC/IC bypass surgery, most likely because of a brainstem infarct; neither imaging of the brain nor autopsy was performed. Patient 8 had a small infarct in the territory of the MCA ipsilateral to the ICA occlusion 10 months after the operation, but this did not change his Rankin grade. His bypass was patent as assessed by TCD. The other 10 patients (patients 1, 2, 5, 6, 9 through 13, and 15) did not have any recurrent cerebral, retinal, or cardiac event. The annual rate of major disabling stroke (Rankin grade 4 or 5) or vascular death (including 4 perioperative complications) was 22.2% per year (95% CI, 8.2 to 48.4).

TCD 6 months after the operation showed a patent bypass in 10 of the 14 patients alive; the bypass could not be detected in 1 patient (patient 7) and was not specifically assessed in 3 others (patients 4, 14, and 15). CO2 reactivity had improved in most patients. On average, the median CO2 reactivity was 6% (25th to 75th percentiles, 7% to 12%) before the operation and 22% (25th to 75th percentile, 8% to 39%) after surgery ($P=0.005$, Wilcoxon 2 related samples). CO2 reactivity values for individual patients are shown in the Table.

### Discussion

This study reports the first prospective case series of patients ($n=15$) to undergo excimer laser–assisted high-flow EC/IC bypass surgery because of recurrent cerebral ischemic events associated with CAO, probably of hemodynamic origin.
Patients were selected from a consecutive series of 103 patients with symptomatic CAO by means of predefined selection criteria and were considered at particularly high risk of recurrent stroke by a team of neurologists and neurosurgeons. In the perioperative period, 3 of the 15 operated patients had an ipsilateral ischemic stroke, and 1 patient died of myocardial infarction.

Although the number of patients reported is small, we believe that it is important to report the results of this case series in light of planning future studies on the efficacy of EC/IC bypass surgery for the prevention of recurrent stroke in a subgroup of patients with symptomatic CAO who are at high risk without surgery. The interpretation of the present case series must take into account that the selected patients had frequent (in 11 patients even more than 10) episodes of ischemia attributable to CAO despite antithrombotic treatment. Each of them was considered at high risk of stroke without surgery and fulfilled predefined but admittedly arbitrary criteria that are mentioned in the Patients and Methods section. In a recent series of 39 patients with hemodynamic compromise shown by high oxygen extraction fraction on PET, the 2-year rate of ipsilateral ischemic stroke was 26.5%.6 It is a recognized clinical dilemma that patients who in theory have the most to gain from EC/IC bypass surgery also carry the highest perioperative risk.28,29 One study reported a complication rate of conventional STA-MCA bypass surgery close to 12% in patients who were considered neurologically unstable.28 Another study found a complication rate of 14% (major morbidity or death in 4 of 28 patients) of the conventional STA-MCA operation in patients with unilateral ICA occlusion who had recurrent symptoms and were hemodynamically compromised on the basis of 133Xe-SPECT measurements before and after acetazolamide challenge.30 When a new EC/IC bypass trial is planned in patients at high risk of recurrent stroke, power estimates should probably take into account a potentially higher complication rate of the operation, either the STA-MCA or excimer laser–assisted type, than the 3.1% to 4.5% (major or fatal stroke, respectively, excluding and including stroke that occurred between the time of randomization and the operation) reported in the EC/IC bypass study in 1985.2 Several different factors may add to the risk of operation. Fluctuations in blood pressure during anesthesia are not rare and are difficult to prevent in these patients with generalized atherosclerosis (patient 15). We are currently addressing the technical aspects of the excimer laser–assisted procedure that may give rise to complications. Kinking of the bypass may occur subsequent to elongation after the bypass has become functional, as observed in patient 8 (and probably in patient 3). To reduce the chance of kinking, we have modified the procedure in that we now perform a 90° end-to-end anastomosis of the venous transplant at the transition from the extracranial to intracranial course (Figure 1c). Furthermore, we have learned from our animal experiments that if the cutout portion of the recipient vessel is not retrieved but the bypass shows abundant flow, it is probably not necessary to clip the bypass and establish a new anastomosis, as was done in patients 2, 7, and 15. Laboratory experiments have shown that the partially cutout portion remains attached to the vessel wall and does

Figure 2. Angiogram of patient 8 showing filling of the anterior cerebral artery (black arrows) and MCA branches (white arrows) via the excimer laser–assisted bypass between the occipital artery (OA) and the proximal part of the MCA (*). A, Anterior-posterior view; B, lateral view; C, 3-dimensional representation.
not obstruct the bypass, nor will it become unstuck and obstruct 1 of the vessels farther down the vascular tree. In addition, intraoperative flow measurements that we now routinely use allow us to check bypass functionality during the procedure. Despite all this information, it remains extremely difficult to establish in individual patients which factor(s) may have contributed to the perioperative stroke: the fact that we could not retrieve the punched-out part of the recipient artery, the consequent necessary extra manipulation of the arteries with lengthening of the total procedure, the bleeding of the ACA wall in patient 7, the low blood pressure observed in patient 15, the clipping of the third-generation branch of the MCA in patient 15, or dislodging of emboli from the proximal or distal stump of the ICA occlusion possibly resulting from hemodynamic changes after flow was established through the EC/IC bypass.

In search of a more effective EC/IC bypass, some surgeons have connected the STA with a larger branch of the MCA than previously used by means of the conventional technique. Comparative studies have not been performed, but the excimer laser-assisted procedure may be safer than this procedure because temporary clamping of a large branch of the MCA may lead to infarction during the operation. Furthermore, the excimer laser-assisted EC/IC bypass may be more efficient than the conventional STA-MCA bypass because it ensures high flow proximal in the vascular tree.

Many studies have reported improvement in cerebral hemodynamic measurements after a conventional STA-MCA bypass, but comparisons with similar patients who were not operated on are lacking. Others found that improvement in hemodynamic measures did not occur or occurred in only some operated patients. Improvement in hemodynamic measures has been shown most prominently in patients in whom such measures were most disturbed before operation. Furthermore, improvement in cerebral blood flow shortly after STA-MCA bypass surgery may not last over time, and cerebral hemodynamic measures may improve spontaneously. We found that CO2 reactivity had improved 6 months after the excimer laser-assisted bypass operation, but again a control group of similar but unoperated patients was not available.

Evidently, our uncontrolled case series cannot provide evidence for the efficacy of the procedure in preventing recurrent cerebral ischemia in patients with symptomatic ICA occlusion who are at high risk of such events. The feasibility of a new randomized, controlled trial in high-risk patients is currently under investigation. However, cessation of very frequent TIAs immediately after the procedure (as illustrated by patients 3 and 6) suggests that augmentation of the blood flow to the brain with the excimer laser-assisted EC/IC bypass is a potentially valuable treatment option in certain carefully selected patients with CAO who are at high risk of recurrent stroke. In addition, the observation in patient 3 that TIAs recurred immediately when the bypass was no longer functioning can be interpreted as an illustration of the importance of the bypass in this patient.

We conclude that the excimer laser-assisted EC/IC bypass operation is a potentially promising procedure for revascularization of the brain in patients with symptomatic CAO at high risk of recurrent stroke, but preliminary results also show that the procedure carries a substantial risk in these patients. This risk probably is related not only to the procedure itself but also to selection of patients with frequent recurrent episodes of cerebral ischemia despite medical treatment.

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