Improvement of cerebrovascular reserve capacity by EC-IC arterial bypass surgery in patients with ICA occlusion and hemodynamic cerebral ischemia

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Since the negative results of the international Bypass Study, extracranial-intracranial (EC-IC) bypass surgery is infrequently employed in the treatment of patients with cerebral ischemia. Newly acquired evidence concerning the pathophysiology of cerebral ischemia, however, has facilitated the identification of a small subgroup of patients with "hemodynamic" cerebral ischemia. Characteristically, these patients demonstrate severely impaired cerebrovascular reserve capacity due to occlusive disease and insufficient collateral blood supply.

Over an 8-year period, 28 patients were defined by clinical and laboratory criteria as suffering from hemodynamic cerebral ischemia. All patients had recurring episodes of focal cerebral ischemia due to unilateral internal carotid artery occlusion. Computerized tomography (CT) scans either were normal or showed evidence of border zone infarction. The cerebrovascular reserve capacity was studied using $^{133}$Xe single-photon emission CT and acetazolamide challenge and was found to be significantly impaired in all patients. Based on these criteria, superficial temporal artery-middle cerebral artery anastomosis was performed to augment collateral flow to the ischemic hemispheres. Two patients died from myocardial infarction, one 4 days and the other 2 months postoperatively. One patient died from massive brain infarction and another suffered a postoperative stroke with incomplete recovery, resulting in a major morbidity and mortality rate of 14%. Minor morbidity included one patient with a subdural hematoma who subsequently recovered completely. The postoperative course was uneventful in 22 patients (82%). Over a mean follow-up period of almost 3 years, no patient had another episode of brain ischemia. Bypass patency was confirmed by postoperative angiography in 26 patients.

Follow-up studies of cerebral blood flow (CBF) and cerebrovascular reserve capacity showed significant improvement of the latter while the resting CBF was essentially unchanged. In view of these findings, the authors conclude that EC-IC bypass surgery constitutes appropriate therapy for a subgroup of patients with recurrent focal cerebral ischemia, defined using the strict selection criteria employed in this study.

KEY WORDS: extracranial-intracranial bypass surgery • cerebral ischemia • internal carotid artery occlusion • cerebrovascular reserve capacity • cerebral blood flow • acetazolamide

STROKE remains a leading cause of mortality and permanent disability despite manifold attempts at treating or preventing cerebral ischemia using various medical and surgical means, many with either unproven efficacy or proven inefficacy. Among these techniques is extracranial-intracranial (EC-IC) arterial bypass surgery using anastomosis of the superficial temporal artery (STA) to the middle cerebral artery (MCA). Following its introduction by Yaşargil in 1969, this procedure was used to treat numerous patients with carotid artery or MCA stenosis or internal carotid artery (ICA) occlusion, with the intent of increasing collateral cerebral blood flow (CBF) distal to the occlusive or stenosing lesion. Although attractive from a conceptual point of view, EC-IC bypass surgery was shown in an international randomized trial to be ineffective in preventing stroke. This study, published in 1985, failed to demonstrate any benefit to surgically treated patients compared to patients receiving medical treatment alone. Criticisms were raised concerning the trial methodology and the large amount of data that came from in-
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stitions not directly affiliated with the study. Also, the inclusion criteria for the study population were excessively broad and did not provide for identification and selection of those patients at maximum risk for subsequent cerebral infarction. Admittedly, the patients included in the study were representative of those who were generally being accepted as EC-IC bypass candidates at that time. The study results showed no evidence of stroke prevention from this procedure, resulting in the near abandonment of EC-IC bypass surgery for the treatment of patients with cerebral ischemia. Since then, only a few reports have been published on the potential beneficial effect of EC-IC bypass surgery in selected patients.

Our own continued interest in EC-IC bypass surgery results from newly accepted evidence regarding the pathophysiology of cerebral ischemia. In addition to standard clinical and angiographic studies, it is now possible to identify from within the extremely diverse population of patients with cerebral ischemia a small subgroup exhibiting a characteristic deficit, namely impairment of the cerebrovascular reserve capacity. Using refined techniques for measuring basal CBF and CBF under stimulated conditions. This impairment is due to poorly developed natural collateral vessels and the presence of underlying cerebrovascular occlusive disease, and may result in what we term “hemodynamic” cerebral ischemia. Recent evidence suggests that these patients are at particular risk for subsequent stroke compared to those with similar occlusive lesions but intact cerebrovascular reserve capacity. In view of these pathophysiological considerations, we used EC-IC bypass surgery to increase collateral blood flow to the brain with the expectation of restoring the cerebrovascular reserve capacity. In this report we present our clinical experience with a group of these patients treated with EC-IC bypass surgery, with particular emphasis on long-term follow-up data.

Clinical Material and Methods

Patient Population

From January, 1985, to December, 1992, approximately 350 patients with symptoms of cerebral ischemia were evaluated as potential candidates for EC-IC bypass surgery. Of these, 37 patients were selected for surgical treatment. Nine had bilateral ICA occlusion and will be reported separately. In this communication we report 28 patients who had unilateral ICA occlusion, 13 on the right and 15 on the left. There were four women and 24 men, with an age range of 37 to 74 years (mean 55.5 years). All patients had a history of recurrent focal cerebral or retinal ischemic episodes, either in the form of transient ischemic attacks (TIAs) or a combination of TIAs with symptoms of prolonged reversible ischemic neurological deficits. Six patients had transient visual disturbances in the form of amaurosis fugax that affected the eye ipsilateral to the ICA occlusion. Preoperatively, 13 patients were neurologically normal whereas 15 had minor deficits, typically limb paresis, related to previous cerebrovascular at-tacks. Nineteen patients had significant vascular risk factors such as arterial hypertension or diabetes mellitus, and four had experienced previous myocardial infarction. Table 1 summarizes patient age, sex, clinical and diagnostic findings, risk factors, surgical mortality and morbidity, and postoperative outcome.

Diagnostic Findings

All patients underwent diagnostic studies including computerized tomography (CT) of the head, four-vessel cerebral angiography, and measurement of CBF. The CT studies were found to be normal in three patients, and in 25 patients there were areas of low density in the transition zone between the territories of the anterior and middle cerebral arteries, so-called “border zone infarction” (Fig. 1A), suggestive of hemodynamic cerebral ischemia. Patients having major infarcts within the MCA territory were excluded. Unilateral occlusion of the cervical ICA due to arteriosclerosis was demonstrated angiographically in all patients. Although additional vascular abnormalities such as minor stenoses in the contralateral carotid artery or the vertebralbasilar system were found, these findings were not of hemodynamic significance.

Cerebral Blood Flow Measurements

Pre- and postoperative studies of CBF were performed in all patients using 133Xe inhalation single-photon emission CT (Fig. 1B). This method has been described in detail previously. Briefly, it allows quantitative evaluation of regional CBF using three tomographic brain slices, each 2 cm thick and with an interslice distance of 2 cm. Mean regional CBF (rCBF) values were calculated for both hemispheres and, using a “region of interest” technique, sections were further divided according to the underlying vascular territories. Because bypass surgery in this study primarily affected blood flow within the MCA distribution, only CBF values from the second slice, predominantly representing CBF within the MCA territory, were used. With each test, measurements of blood pressure and arterial pCO2 were performed; however, CBF values were not corrected for pCO2.

Following measurement of basal rCBF, 1 gm acetazolamide was administered intravenously and CBF measurement was repeated 20 minutes later. These two measurements were used to determine the cerebrovascular reserve capacity, which was calculated as the difference between the two rCBF studies and expressed in ml/100 gm/min. Using normative data from our laboratory, we distinguished the following subgroups of cerebrovascular reserve capacity: normal, moderately impaired, severely impaired, absent, and paradoxically decreased CBF consistent with the so-called “intracerebral steal phenomenon.” According to our protocol, only patients having severely impaired, absent, or paradoxically decreased cerebrovascular reserve capacity in response to acetazolamide challenge were considered candidates for bypass surgery.

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<th>Case No.</th>
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* Abbreviations: ICA = internal carotid artery; EC-IC = extracranial-intracranial; CT = computerized tomography; CVRC = cerebrovascular reserve capacity; rec = recurrent; PRIND = prolonged reversible ischemic neurological deficits; WNL = within normal limits; ICA-O = ICA occlusion; BZI = border-zone infarction; diabetes = diabetes mellitus; hypertension = arterial hypertension.

† For classification of by-pass filling see text.
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TABLE 1 (continued) *

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<th>Case</th>
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* Abbreviations: CT = computerized tomography; CVRC = cerebrovascular reserve capacity; rec = recurrent; PRIND = prolonged reversible ischemic neurological deficits; WNL = within normal limits; ICA-O = ICA occlusion; BZI = border-zone infarction; hypertension = arterial hypertension.

† For classification of bypass filling see text.

Surgical Technique

An STA-MCA anastomosis was performed in all cases on the side of ICA occlusion, which was equally divided between the right and left sides. We modified a previously described technique, and used a V-shaped skin incision in the temporal region, which allowed access to either the frontal or parietal branch of the STA. In 26 patients the frontal branch was used because of its larger diameter. Following a linear incision of the temporal muscle, a craniectomy approximately 3 cm in diameter was made over the temporoparietal junction. This overlies the posterior sylvian fissure and provides access to suitably sized proximal cortical branches of the MCA as they arise. Donor and recipient arteries were anastomosed with interrupted 10-0 sutures under the operating microscope.

Fig. 1. A: Case 9. Computerized tomography (CT) scans in a patient with left internal carotid artery (ICA) occlusion showing low-density areas between the anterior and middle cerebral artery territories on the right side. B: Single-photon emission CT findings in Case 5, a patient with left ICA occlusion. Preoperative studies before (upper left) and following acetazolamide (Diamox) administration (upper right) of cerebral blood flow (CBF) shows a paradoxical decrease in the left hemisphere. Six months following anastomosis there is marked improvement in the baseline CBF (lower left) and in CBF response to acetazolamide stimulation (lower right) in the left hemisphere. CBF scale = ml/100 gm/min.
Study Protocol

In addition to preoperative CT, four-vessel cerebral angiography, and both baseline CBF measurements and those following acetazolamide administration, the following postoperative studies were also performed. Cerebrovascular reserve capacity and CBF were measured at the end of the 1st postoperative week, then again 6 to 8 weeks postoperatively, and thereafter at yearly intervals. Angiography for assessment of bypass function was performed 6 to 8 weeks postoperatively. Bypass flow, assessed on this angiogram, was graded as follows: Grade 0, no flow; Grade 1, filling of one or two MCA branches; Grade 2, antegrade filling of multiple MCA branches; and Grade 3, antegrade and retrograde filling of the entire MCA system.

Statistical Analysis

Statistical evaluation of the results was carried out using the Wilcoxon paired-sample test and a Bonferroni correction when necessary. A value of \( \alpha \leq 0.05 \) indicated significant difference.

Results

Clinical Outcome

Of the 28 patients who underwent bypass surgery, 23 had an uneventful postoperative course and experienced no further cerebral ischemic events over a mean postoperative follow-up time of 34.2 months (range 4 to 79 months). Thirteen patients had minor neurological deficits before surgery and five had improved neurological function postoperatively.

Mortality and Morbidity

Major morbidity and mortality occurred in five patients (18%). Two patients (Cases 11 and 23) died suddenly of a myocardial infarction 4 days and 2 months postoperatively, respectively, after an initially uneventful postoperative course. One patient (Case 13) awoke from surgery with right-sided hemiparesis. A CT scan demonstrated a large area of infarction involving the operated left hemisphere. Postoperative angiography demonstrated no flow through the bypass at 5 days postsurgery. Six weeks following a protracted clinical course without sign of improvement, this patient died from pneumonia and sepsis. Another patient (Case 7) developed a progressive stroke during the first few postoperative days. A CT scan revealed new areas of ischemic infarction on the operated side. Although follow-up angiography demonstrated bypass patency with filling of two cortical branches, there was little recovery and the patient remained severely disabled.

One patient (Case 12) developed a right-sided hemiparesis postoperatively. A CT scan of the head showed a subdural hematoma over the operated left hemisphere; this was evacuated and the patient recovered completely.

Angiographic Bypass Function

Except for the patient who died from myocardial infarction on the 4th postoperative day, angiographic confirmation of bypass function was obtained in all cases. Using the grading system described above, 18 patients had excellent function of the bypass, with antegrade and retrograde filling of the MCA. Six patients had Grade 2 function, with antegrade filling of the MCA territory. Two patients had only Grade 1 function and in one patient the bypass was occluded. This patient (Case 13) developed a postoperative stroke and died 6 weeks after surgery.

Cerebral Blood Flow

Preoperative measurement of baseline CBF (Fig. 2a and b) revealed a mean value (± standard deviation) of 53.9 ± 8.8 ml/100 gm/min ipsilateral to the ICA occlusion, compared with a mean value of 64.4 ± 13.5 ml/100 gm/min on the contralateral asymptomatic side. Postoperatively, no significant change in resting CBF in either the operated or the contralateral hemisphere was demonstrated, and the difference between the two hemispheres remained essentially unchanged over time.

Cerebrovascular Reserve Capacity

Following preoperative administration of 1 gm acetazolamide, a mean increase in cerebrovascular reserve capacity of only 0.5 ± 3.7 ml/100 gm/min was found ipsilateral to the carotid artery occlusion (Fig. 2c and d). In 13 patients cerebrovascular reserve capacity was found to be severely impaired, with a maximum increase of 7 ml/100 gm/min. In five patients there was no increase and in 10 patients CBF paradoxically decreased in response to acetazolamide. Over the contralateral hemisphere, mean CBF increased from 64.4 ± 13.5 to 82.3 ± 15.2 ml/100 gm/min following acetazolamide stimulation, corresponding to a mean cerebrovascular reserve capacity of 17.9 ± 7.2 ml/100 gm/min.

Postoperative follow-up studies of cerebrovascular reserve capacity showed a significant increase to 4.9 ± 5.1 ml/100 gm/min over the operated side 1 week after surgery. Cerebrovascular reserve capacity gradually improved during the subsequent follow-up period whereas, over the contralateral side, it remained essentially unchanged when pre- and postoperative values were compared.

Discussion

In addition to the more common thromboembolic mechanisms, hemodynamic factors constitute a major determinant in the pathogenesis of cerebral ischemia. The underlying pathophysiological mechanisms of hemodynamic cerebral ischemia have been investigated in considerable detail with the use of positron emission tomography (PET).12,20 From these studies it is known that dilation of cerebral vessels is an important compensatory mechanism in conditions of reduced cerebral perfusion pressure in patients with cerebrovascular occlusive lesions and poorly developed natural collateral vessels. It has also been demonstrated that basal CBF may not necessarily be altered in hemodynamic cerebral ischemia. Additional study of these patients is nec-
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necessary to assess the cerebrovascular ability to increase CBF beyond the resting state and to determine the capacity to respond to a physiological challenge such as CO₂ or acetazolamide. This responsiveness has been termed the "cerebrovascular reserve capacity." As employed in this study, cerebrovascular reserve capacity equals stimulated CBF minus basal CBF. Herold, et al., have shown that the information obtained from these tests strongly agrees with the "oxygen extraction fraction" in PET studies. The main mechanism of action of acetazolamide is a reversible inhibition of carbonic anhydrase that causes extracellular acidosis in the brain, a strong vasodilating stimulus that is most likely responsible for the increase in CBF.

In the present study we have used the acetazolamide test first described by Vorstrup, et al. Since its introduction in 1985, this test has been used in more than 1000 patients in our cerebrovascular laboratory and we have found it to be reliable, well tolerated without significant side effects, and easy to perform.

It should be emphasized that results obtained from PET or stimulated CBF studies were not available at the time the EC-IC Bypass Study Group's trial was initiated. Although there were preliminary published reports indicating that these tests may be particularly applicable to patients being considered for EC-IC bypass, no elaboration on the negative results of EC-IC bypass surgery was given by the Bypass Study Group. It was stated that an extensive subsequent analysis based on clinical data and morphological findings failed to reveal a single subgroup of patients who had benefited from surgery, presumably including those patients who might have had hemodynamic cerebral ischemia. Furthermore, Powers, et al. were unable to demonstrate a beneficial effect of EC-IC bypass surgery in 24 patients who had varying degrees of hemodynamic ce-

![Graphs showing box plots](image)
cardiac infarction early after successful bypass surgery demonstrate that the underlying arteriosclerotic disease affects not only the brain but the heart as well. Therefore, the preoperative workup of potential candidates for bypass surgery should include cardiac monitoring in order to minimize the risk of myocardial infarction. The two cases of ischemic complications in this series were clearly related to surgery. The patient who developed a massive ipsilateral infarction and subsequently died (Case 13) was the only one in this series who had a nonfunctional anastomosis. Another patient (Case 7), who developed a postoperative stroke with incomplete recovery, had a patent bypass, and it remained unclear why he deteriorated postoperatively. However, it should be emphasized that patients with hemodynamic cerebral ischemia have increased operative risk, which can at least in part be explained by the pressure dependency of the cerebral circulation. During surgery and the early postoperative period, careful patient monitoring should alert practitioners to the occurrence of hypotension and the resultant dangerous decrease in cerebral perfusion pressure. On the other hand, the uneventful postoperative course in 23 of our patients seems to prove the effectiveness of the operation, especially since none of these patients had another ischemic episode during a mean follow-up period of almost 3 years. Although authors have speculated that patients with hemodynamic cerebral ischemia are at increased risk for stroke, Powers, et al.,24 were unable to substantiate this in a series of 30 patients with PET-proven hemodynamic cerebral ischemia who did not exhibit an increased stroke rate during a 1-year follow-up period. This is in contrast to more recent studies. Yonas, et al.,38 using acetazolamide-activated stable xenon studies, found a significantly increased risk of stroke during a 3-year follow-up period in patients who had clear evidence of hemodynamic cerebral ischemia. Similar findings were obtained in a prospective study by Kleiser and Widder,15 who found a 32% annual risk of stroke during a 3-year period in patients with ICA occlusion and impaired cerebrovascular reserve capacity as demonstrated by the TCD CO₂ test.

Although the favorable results we obtained in 82% of the operated patients in this series do not prove the efficacy of bypass surgery in these selected cases, there is evidence to support this assumption. All patients were treated surgically because a specific deficit was demonstrated on preoperative CBF studies, namely severely impaired cerebrovascular reserve capacity. Postoperatively, an immediate and lasting significant improvement in cerebrovascular reserve capacity was found. In a previous study, Piepras, et al.,37 did not find significant spontaneous improvement in 14 patients who had obstructive cerebrovascular disease and decreased cerebrovascular reserve capacity. Therefore, the postoperative improvement of cerebrovascular reserve capacity seen in this study must be attributed to the newly established collateral vessel from the extracranial to the cerebral circulation, especially in view of the substantial anastomotic filling of cortical vessels that was demonstrated in the majority of our patients.
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Furthermore, and in contrast to previous studies, no significant effect of bypass surgery was demonstrated with regard to resting CBF. From this finding it can be concluded that, in patients who have hemodynamic cerebral ischemia and a severely impaired cerebrovascular reserve capacity, this deficit can be specifically and successfully treated by EC-IC bypass surgery. In the absence of any medical or other treatment with a proven effect on impaired cerebrovascular reserve capacity, EC-IC bypass surgery therefore may be the only effective way to treat this particular small subgroup of patients who, without treatment, might be at high risk to develop stroke.

Conclusions

We are aware that the results presented in this study cannot be regarded as proof of the beneficial effect of EC-IC bypass surgery in patients with hemodynamic cerebral ischemia. More data are needed on the natural history of these patients and the results in patients who are surgically treated. The ultimate proof depends on the results of another randomized clinical trial. Because of the small percentage of patients eligible for inclusion in such a trial, collaboration of several centers that have access to methods for assessment of cerebrovascular reserve capacity would be ideal. Assessment of cerebrovascular reserve capacity was the most important parameter for inclusion in this study and, in addition to the clinical course, is an essential part of postoperative follow-up studies.

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