The Extracranial–Intracranial Bypass Trial: implications for future investigations

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✓The 1985 International Extracranial–Intracranial (EC-IC) Bypass Trial failed to show a surgical benefit of EC-IC bypass in patients with varying degrees of angiographic stenosis. This study was limited by the technology available at the time it was conducted. In the 20 years since, there has been considerable progress in imaging techniques that now enable the identification of a subset of stroke patients with hemodynamic ischemia. In the present study, the authors review the relevant literature and propose a reevaluation of the benefits of the EC-IC bypass procedure using these new imaging techniques.

The authors reviewed the admission criteria for the EC-IC Bypass Trial in the light of more recently discovered neurovascular physiology and showed that the imaging criteria used in that trial are not physiologically adequate. A MEDLINE (1985–2007) database search for EC-IC case studies was conducted, and additional studies were identified manually by scrutinizing references from identified manuscripts, major neurosurgical journals and texts, and personal files. (DOI: 10.3171/FOC/2008/24/2/E4)

KEY WORDS • carotid angiography • extracranial–intracranial bypass • hemodynamic failure

CAROTID artery stenosis has been shown to be highly predictive of stroke. Carotid endarterectomy was designed to treat these patients and has Class 1 evidence to support its efficacy in preventing strokes, but many occlusive lesions are too distal to be accessible.^{2,4,36} In 1969 Yaşargil¹⁸ first described the STA-MCA bypass procedure in which the STA is anastomosed to the MCA. This procedure offered a new hope of treating those with inaccessible carotid and MCA lesions. Proponents of the surgery believed that its anatomical and physiological rationale, in conjunction with the relatively low rates of surgical complications and high patency rates provided sufficient justification for its use. As the procedure was increasingly performed, reports appeared in the literature describing its successful application. Only a few of these case studies had control groups, and none were randomized. Thus, there was a need for a large scale, randomized controlled trial to prove the efficacy of this surgery.

Results of the EC-IC Bypass Study

Methodology and Findings

In 1985, the International EC-IC Bypass Trial was published. The entrance criteria included: 1) a history of TIAs or 1 or more minor or completed strokes in the carotid distribution; and 2) the presence of at least 1 of several atherosclerotic angiographic lesions, such as stenosis or occlusion of the trunk or major branches before the bi- or trifurcation of the MCA, stenosis of the internal carotid artery at or above the C-2 vertebral body, or occlusion of the internal carotid artery. The study included 1377 patients who were randomized to surgical or medical therapy. The study hypothesis was that there would be a one third decrease in the stroke rate in those treated with surgery. However, the results rejected this hypothesis with over 99% power. No patients were lost to follow-up, and none were withdrawn. The average duration of follow-up for surviving patients was 55.8 months, during which period 29% of patients treated medically experienced 1 or more strokes compared with 31% in the surgical group (this result did not quite reach statistical significance).³

Limitations in Patient Selection

Critics and the authors of the trial noted 3 major prob-

Abbreviations used in this paper: CBF = cerebral blood flow; EC-IC = extracranial–intracranial; MCA = middle cerebral artery; PET = positron emission tomography; STA = superficial temporal artery; TIA = transient ischemic attack.

TABLE 1
Review of outcome studies with follow-up of patients after EC-IC bypass surgery*

Authors, Year	No. of Patients	Imaging Modality	Follow-Up Duration	Outcome
Ma et al., 2007	12	SPECT w/ ACZ	NA	Surgery Group: 4 w/ improved neurological status; 1 patient w/ a new ischemic lesion (worsened dysphagia); Medical Group: 6 w/ stable neurological status
Hirai et al., 2005	40	SPECT w/ ACZ	14 days	rCBF & ACZ reactivity improved
Tummala et al., 2003	44	CT/Xe	NA	all had preoperative TIAs; 95.4% had no further ischemic events
Neff et al., 2004	25	CT/Xe w/ ACZ	NA	CBF increased after surgery
Murata et al., 2003	30	CT/Xe	12 mos	18/30 patients experienced desaturation on temporal pressure
Sasoh et al., 2003	5	PET	5 mos	13 had better cognitive improvement; 5 had higher FSIQ score
Przbylski et al., 1998	42	Xe/CT w/ ACZ	18–29 mos	9 patients (30%) had stroke prior to surgery; no strokes postsurgery
Kuwabara et al., 1998	7	PET w/ ACZ	NA	improved reactivity postoperatively
Takagi et al., 1997	12	PET	36 mos	no strokes
Schick et al., 1996	40	CT/SPECT w/ ACZ	67.2 mos	23% improved neurological status, 22% worsened w/ further ischemic events
Ishikawa et al., 1995	28	SPECT/Xe w/ ACZ	27–115 mos	reactivity was increased in all but 1; 4 w/ lower CBF had strokes ($p < 0.03$)
Schmiedek et al., 1994	28	SPECT/Xe w/ ACZ	NA	82% had improved CBF & reactivity
Muraishi et al., 1993	6	PET	NA	improved CBF & OEF
Yamashita et al., 1991	15	CT/Xe w/ ACZ	NA	6/9 with low reactivity preoperatively had improved neurological status
Holzschuh et al., 1991	18	CT/Xe w/ ACZ	NA	surgical group had improved reactivity over 29 control patients
Kuroda et al., 1991	5	SPECT/Xe w/ ACZ	NA	improved reactivity
Pavics et al., 1990	32	99mTc-SPECT	NA	CBF: 19 unchanged, 7 increased, 6 decreased
Kuroda et al., 1990	13	SPECT/Xe w/ ACZ	NA	4 patients had increased reactivity
Sunada, 1989	9	CT/Xe	NA	no significant change in CBF
Leinsinger et al., 1988	31	SPECT/Xe	NA	increased CBF
Bishop et al., 1987	8	CT/Xe w/ hypercapnia	NA	CBF unchanged, reactivity improved
Di Piero et al., 1987	14	SPECT	12 mos	CBF improved after surgery but no difference at 6 & 12 months
Vorstrup et al., 1985	22	CT/Xe	NA	20 patients had no increase in CBF

* ACZ = acetazolamide; FSIQ = Full Scale Intelligence Quotient; NA = not available; OEF = oxygen extraction fraction; SPECT = single photon emission computed tomography.

lems with the entrance criteria. First, the cerebral and retinal ischemic events experienced by the patients in the trial could be of either hemodynamic origin (resulting from poor circulatory perfusion and inadequate collateral vessels) or thromboembolic origin, and it was not possible with angiography to determine which mechanism was responsible.^{3,6} Secondly, angiographic lesions are static representations and do not capture the complex hemodynamics of cerebral circulation. Arterial stenosis or occlusion can cause a reduction in the pressure of distal arterial vessels, but the degree of stenosis or the presence of arterial occlusion does not accurately predict the hemodynamic status of the distal circulation.³³ Although stenoses of the extracranial carotid artery resulting in reductions in luminal diameter ≥ 50 –70% are known to reduce the distal pressure in some cases,¹⁰ collateral circulation can maintain normal cerebral perfusion pressure and normal flow in many of these patients. Up to 60% of patients with complete occlusion of the carotid artery may have no evidence of hemodynamic compromise in the distal circulation.³² Third, the study included patients with cerebral ischemia as well those with completed infarctions. Positron emission tomography studies have shown that as CBF falls, oxygen extraction rises to 100% so that cerebral metabolism becomes totally flow dependent. This is the ideal state for bypass graft placement to increase flow. However, once an acute infarction has occurred, both cerebral oxygen metabolism and arterial oxygen extraction fall to low levels while blood flow paradoxically rises—a state known as “luxury perfusion.” Once luxury perfusion becomes established, the use of surgical intervention to increase CBF is inappropriate

because the tissue is not salvageable, and ineffective because the system is no longer low flow.

Implications for Future Investigations

Better techniques are needed to identify patients with hemodynamic failure. Over the last 20 years, investigators have found 2 different testing methodologies to identify these patients. The first is to evaluate a patient's dilation state with an acetazolamide challenge test. This test involves determining CBF via xenon-enhanced computed tomography,⁴⁴ transcranial Doppler ultrasonography,⁹ single photon emission computed tomography (¹²³I),¹⁶ infrared spectroscopy, or magnetic resonance imaging¹⁴ before and after administration of acetazolamide (similar methods include breath-holding or CO₂ inhalation). Acetazolamide acts as a potent vasodilator of the cerebral vasculature and globally increases CBF. Vessels that are already maximally dilated are less reactive and show a smaller increase or no increase in blood flow. In extreme cases, nonselective global vasodilation can act to decrease the blood flow through the strained vasculature, causing a “steal” effect.⁴⁴ The second methodology involves using PET scanning to measure oxygen extraction fraction. When the capacity of vasodilation is insufficient to meet cerebral demand, the brain can increase the amount of oxygen extracted from the blood.

Literature Review

A MEDLINE (1985–2007) database search was conducted using the following keywords, singly and in combination: EC-IC bypass, hemodynamic failure, and misery

perfusion; 23 unique EC-IC bypass case series involving 486 patients were found (Table 1).^{7,11,17,19,23–31,34,37–39,42–44,47} The authors of 15 of these studies used improved resting CBF and/or improved reactivity as an outcome. Of the 10 studies in which postsurgical resting CBF was reported, there was an increase in 5 studies^{17,26,28,30,39} and an unchanged or decreased resting CBF in the other 5,^{7,31,41,45} for a combined rate of 30% (34/113) of patients showing increased resting CBF. All 8 the studies in which postsurgical reactivity was reported noted a significant increase in reactivity for a combined rate of 80% (68/86).^{17,19,20,23–25,39}

However, the original authors of the 1985 trial raised 3 objections to these case series. First, in the majority of these studies surrogate markers were used (such as blood flow and dilation response) instead of stroke and mortality rates. Improved postoperative stroke rates were reported in only 4 of these case series, and each used the preoperative stroke rate as a control. The second objection was the lack of an appropriate control group. Using pre- and postoperative data is unreliable because the natural course of cerebrovascular reactivity is highly variable, and numerous investigators have reported spontaneous improvement in many patients with impaired cerebrovascular reactivity.^{16,46,50} Third, case studies carry a strong publication bias with many surgeons being motivated to publish neurological improvement over decline.

To address these difficulties, 2 randomized clinical trials were initiated using these new diagnostic modalities. The Japanese EC-IC Bypass Trial²¹ included 206 patients who met the following entrance criteria: 1) symptomatic internal carotid artery/MCA stenosis $\geq 70\%$ in diameter or an occlusion; 2) independent in daily life (modified Rankin scale ≤ 2); 3) small or no brain infarct, and 4) regional CBF of the ipsilateral MCA territory $< 80\%$ of the control value and acetazolamide reactivity $< 10\%$. Patients were randomly allocated to EC-IC bypass surgery or medical treatment, and continued with best medical management for 2 years. The authors concluded that the patients in the surgical group showed a statistically significant decrease in stroke rate at 2 years. A second trial (the Carotid Occlusion Surgery Study trial)¹ is being conducted in the United States using increased oxygen extraction fraction as measured on PET scanning. The specific aim of this second trial is to see if patients identified to have increased oxygen extraction fraction on PET will have better neurocognitive outcomes after EC-IC bypass compared with a medically treated group. Although this trial has flaws (notably using PET, which is scarcely available), if there is a demonstrated benefit it may lead to a resurgence in this procedure.

Given the high cost and great effort involved in these imaging studies, much work has been done to identify clinical features that might aid in identifying these patients. Two classic presentations have been proposed in the literature. The first presentation is TIAs during periods of hypotension either from coughing or standing.^{8,12,40} A more specific type of TIA that has been documented in a few case reports is “orthostatic limb shaking”¹³ which occurs on standing or neck-bending in 1 or more extremities, and is without electroencephalography correlate.^{5,48,49,51} In the 3 most notable studies, 5 patients with limb-shaking were also shown to have decreased reactivity after inhaling CO₂,⁴⁸ and another patient’s symptoms resolved after endarterectomy.⁵¹ In a study in which patients with this presen-

tation were followed up over 2 years, the authors found that there was a 5- to 6-fold increased risk of stroke in these patients over those with carotid stenosis only.²² Although thought provoking, this is probably a rare presentation (21 cases reported over 30 years), probably with high specificity but low sensitivity.

Another controversial presentation of hemodynamic insufficiency is unilateral blurry vision when looking at bright lights or going from cold to warm environments.^{15,35} It is suspected that the borderline circulation may be unable to sustain the increased retinal metabolic activity associated with bright light. Notably, when 24 patients with this presentation were followed up over 2 years, no patient experienced any cerebral ischemic symptoms.²² The authors of this study concluded that this clinical presentation should not be an indication for surgical intervention.

Conclusions

For the last 20 years, the 1985 EC-IC Bypass Trial constituted the best available evidence with which to judge the efficacy of EC-IC bypass procedures. However, as the technology has advanced, static angiography images are no longer adequate to evaluate low blood flow states. New clinical trials using more sophisticated methodologies for patient selection are now emerging. It is these new trials that will constitute the best available evidence in the years to come.

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