Extracranial-Intracranial Bypass in Cerebral Ischemia

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While the utility of extracranial-intracranial (EC-IC) bypass versus medical therapy for typical stroke indications was cast in doubt in the mid-1980s, EC-IC bypass has continued to be useful for maintaining cerebral circulation in specific cases. A case report demonstrates the utility of EC-IC bypass using PET and SPECT scanning technologies to assess cerebral hemodynamics. While further studies will better define the patient population, there is a subset of stroke patients that benefit from cerebral revascularization.

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For many years it was assumed that most stroke was a consequence of "cerebral thrombosis" similar to coronary artery thrombosis associated with myocardial infarction. However, pathological investigation and increasing use of angiography led Fisher, a pioneer in stroke research, to propose that the major etiology of cerebral infarction was atherosclerotic disease in the extracranial cerebral vessels (1). Following the work of DeBakey (2) and Eastcott et al (3), carotid endarterectomy became one of the most commonly performed procedures in the United States. It was recognized, however, that many patients presenting with cerebral ischemia had either carotid artery occlusion or intracranial arterial occlusive disease that was not amenable to carotid endarterectomy. Longitudinal studies provided evidence that these patients remained at risk for subsequent stroke despite medical treatment.

The original report by Yasargil and Donaghy in 1969 (4) of successful extracranial-intracranial arterial bypass (EC-IC bypass) creating an anastomosis between the superficial temporal artery (STA) and a branch of the middle cerebral artery (MCA) using microsurgical techniques was therefore greeted with considerable enthusiasm. In the subsequent 2 decades, thousands of patients underwent a variety of EC-IC bypass procedures for cerebral ischemic symptoms and stroke prevention with seemingly excellent results. Graft patency rates were above 90%, morbidity was low, studies of cerebral perfusion seemed to confirm improved circulation, and patients were noted to do well clinically. However, the procedure was subjected to an international randomized trial against best medical therapy between l977 and l985 and not found to provide stroke protection for the typical indications, including internal carotid artery (ICA) occlusion, intracranial carotid and middle cerebral artery stenosis, and middle cerebral artery occlusion (5). This study has been criticized on several fronts (6-8), primarily the failure to assess collateral circulation and cerebrovascular reserve thereby lumping patients at high risk of further stroke with patients at lower risk, and the exclusion of many patients from the study who underwent surgery because they were felt to be at too great a risk for medical treatment. Nevertheless, the impact of the study was to essentially remove EC-IC bypass from the armamentarium of stroke management and prevention treatment modalities.

EC-IC bypass has continued to be useful for maintaining cerebral circulation where a major artery must be sacrificed for aneurysm or tumor, and in some cases of traumatic dissections and idiopathic arterial occlusion (moyamoya disease), but these maladies are fairly infrequent, and fewer neurosurgeons are maintaining the skills to perform microsurgical anastomoses. Endovascular techniques have been developed in the last 20 years to help manage intracranial

occlusive disease, and newer thrombolytic agents are being used to manage acute stroke. Does there remain a place for EC-IC bypass procedures in the treatment of cerebral ischemic disease?

CASE REPORT

A 65-year-old man presented to Ochsner Neurology Clinic in February 2002 with a history of recurrent symptoms consistent with cerebral ischemia. He had a history of hypertension and hypercholesterolemia. Two years earlier, he had experienced transient blurring of vision in the left eye and in July 2001 suffered a stroke with right-sided weakness. He presented with aphasia and right hemiparesis, which cleared, and was found to have occlusion of the left ICA. He was treated with clopidogrel, aspirin, and divalaproex sodium, but he continued to complain of "spells" characterized by speech difficulty, right upper extremity numbness, clumsiness, and uncontrolled movements with dragging of the right leg. Ramipril and pentoxifylline were added to his medications, and when seen 1 month later his spells had decreased from 10-14 per week to 2-3 per week. These episodes lasted from 15 minutes to 3-5 hours and remained quite disabling to him.

In April 2002, he was admitted to Ochsner Foundation Hospital with a 3-day history of headache, confusion, and generalized weakness. He was found to have slurred speech and right facial weakness, which cleared over the next day. He then remained neurologically stable. Initial CT scan of the brain showed a small intraventricular hemorrhage without a new parenchymal lesion. MRI of the brain showed multiple areas of infarction in the watershed parietal and temporal areas and white matter ischemic change in the posterior periventricular area of the left hemisphere (Figure 1). Tc99m-Neurolite SPECT scan of the brain showed mild hypoperfusion of the left hemisphere with marked decrease in left hemisphere perfusion following intravenous administration of acetazolamide suggesting poor cerebrovascular reserve. Cerebral angiography demonstrated complete occlusion of the left ICA (Figure 2). There was some reconstitution of the supraclinoid ICA through the left ophthalmic artery, which itself showed stenosis at its origin. The right ICA injection showed poor filling of left MCA branches through a small anterior communicating artery (Figure 3), and the vertebral injection showed retrograde filling of the MCA branches through leptomeningeal anastomoses with the left posterior cerebral artery.

With the history of recurrent TIAs despite intensive medical therapy, MRI showing chronic ischemic changes, SPECT scan showing poor left hemispheral cerebrovascular reserve, and angiography showing marginal collateral circulation, a decision was made to proceed with EC-IC bypass. A microsurgical anastomosis of the STA to a branch of MCA was performed. Postoperatively systemic blood pressure remained quite low and required vasopressor support. On two occasions when systolic blood pressure

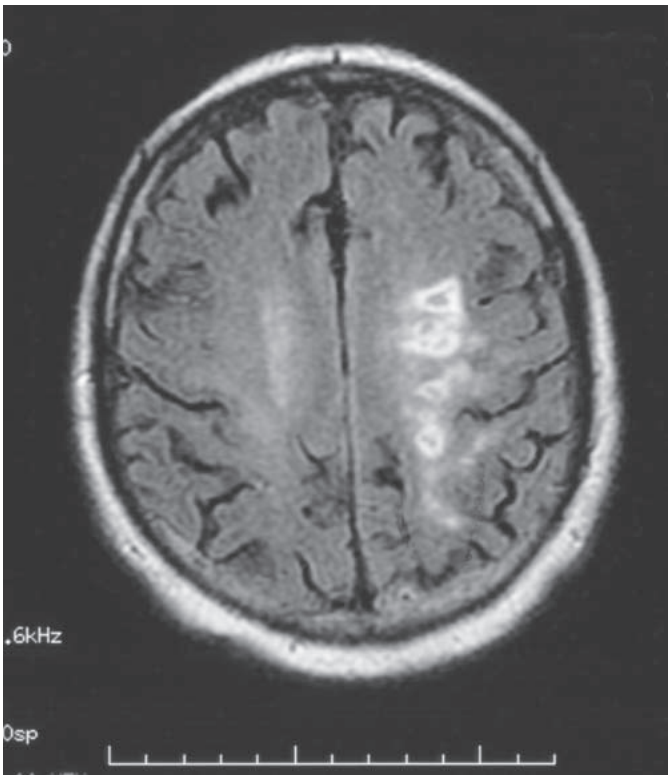

Figure 1. MRI Fluid Attenuation Inversion Recovery (FLAIR) image showing signal intense changes in the watershed areas of the left cerebral hemisphere.

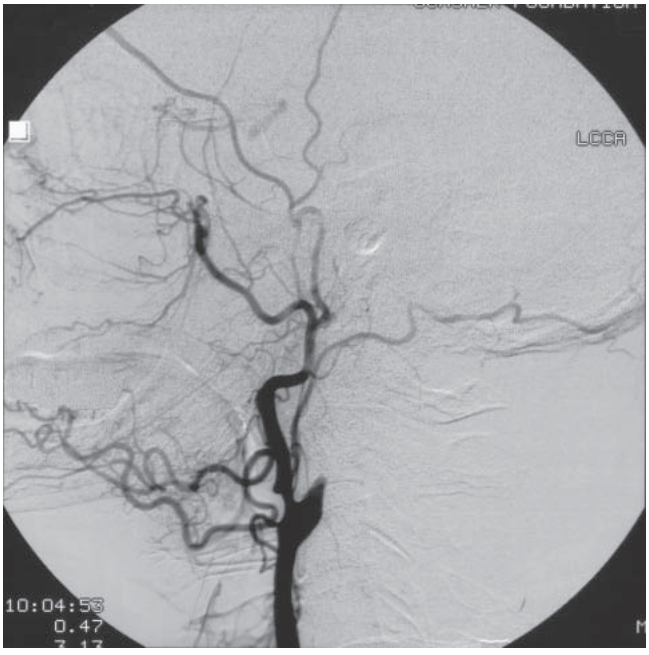

Figure 2. Left carotid angiogram showing left ICA occlusion with slight reconstitution of the intracranial ICA through the ophthalmic artery.

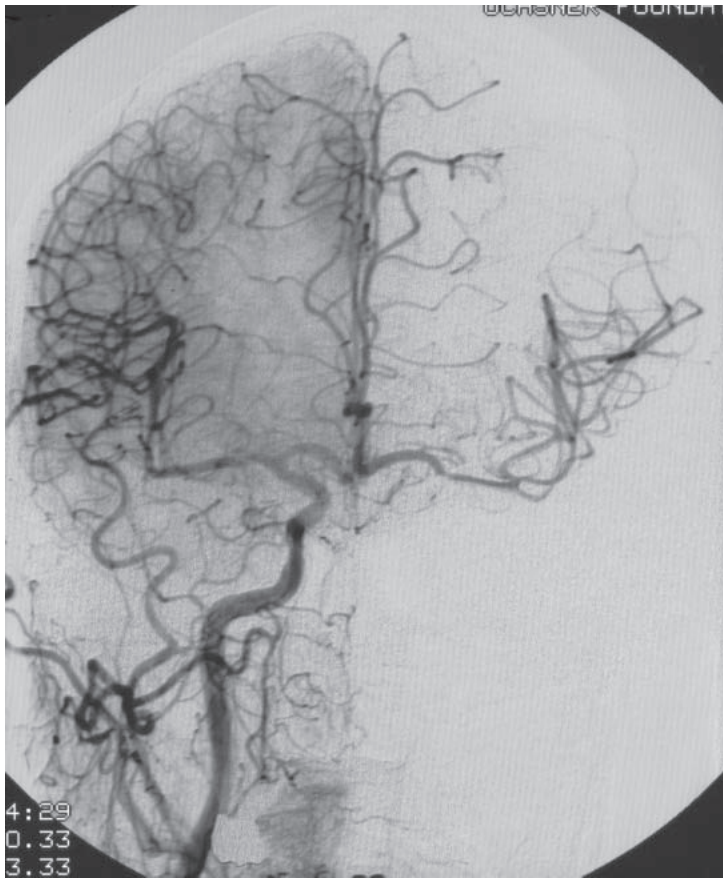

Figure 3. Right carotid angiogram showing some filling of the left middle cerebral artery through the anterior communicating artery. Note middle cerebral artery stenosis.

fell below 90 torr the patient became aphasic, which was reversed by elevating his blood pressure.

By the end of the week he was up and around doing well and was discharged. He has had no further ischemic episodes in the 5 months since discharge, and transcranial Doppler studies (TCDs) show continued patency of the anastomosis. Follow-up angiography and SPECT scans are planned.

DISCUSSION

Ischemic stroke results from a variety of pathological conditions. Cerebral infarction may follow embolization from the heart or cerebrovascular tree, occlusion of major cerebral arteries, occlusion of penetrating arterioles in the brain parenchyma, a variety of coagulopathies, and in a minority of cases loss of perfusion pressure in an area of the brain with marginal circulation. This latter category is most likely to benefit from augmentation of cerebral blood flow through EC-IC arterial anastomosis.

Assessment of Cerebral Hemodynamics

Brain tissue requires continuous delivery of oxygen and glucose to function and survive. Cerebral blood flow (CBF) is dependent on the cerebral perfusion pressure (CPP) (the difference between systemic arterial pressure [SAP] and cerebral venous pressure or intracranial pressure [ICP]) and the resistance provided by arteriolar constriction. Arteriolar caliber varies in response to blood pressure (autoregulation) and to metabolic demand (metabolic coupling) to maintain a constant CBF. Vasodilatation in response to lowered CPP or increased metabolic demand increases cerebral blood volume (CBV). These effects may be global or regional. Therefore, the ratio of CBV to CBF gives a parameter of vasodilatation to compensate for decreased CPP. The cerebral metabolic rate of oxygen ($CMRO_2$) is maintained until CBF drops below a critical level.

It has been noted that an additional buffer to protect $CMRO_2$ is the ability of the tissue to extract a greater fraction of oxygen from the blood when perfusion is poor; that is, the oxygen extraction fraction (OEF) is increased with marginally perfused tissue. When the compensatory mechanisms of vasodilatation and OEF are exceeded by reduced CPP, $CMRO_2$ declines and dysfunction and subsequent infarction occur. With large vessel occlusion, this is most common in the deep white matter and grey matter of the border zones (watershed areas) of vascular territories (9).

PET scanning with the proper isotopes is able to quantitatively measure CBF, CBV, OEF and $CMRO_2$ (10). Grubb and Powers (11) have classified changes in regional cerebral hemodynamics into three stages: normal perfusion, increased CBV and CBV/CBF ratios with normal OEF, and increased CBV and OEF. Since PET scanning has not been readily available to most stroke investigators, other strategies using blood flow and cerebral perfusion measurements with vasodilatatory challenge have been employed. The general concept is to measure regional CBF and then give an agent, which causes general cerebral vasodilatation (12,13). Areas of relative ischemia are presumed to already show vasodilatation and, therefore, CBF should not be increased in these areas.

Stable xenon-enhanced CT scanning has been used for CBF studies before and after administration of intravenous acetazolamide, a cerebral vasodilator causing general increase in CBF (14). In many cases, a steal phenomenon has been observed, with CBF in the affected territory actually going down as blood flow is redirected into other areas of the brain. Stable xenon studies provide a quantitative CBF map and allow anatomical correlation. SPECT scanning using a variety of isotopes provides a picture of cerebral perfusion and requires only standard nuclear medicine equipment, but it gives a qualitative rather than quantitative evaluation of perfusion (15). Transcranial Doppler (TCD) measures velocity of

flow in the intracranial circulation and has been used with inspired CO_2 and acetazolamide as vasodilating agents to measure cerebral vasoreactivity (16,17). More recently, MR techniques of perfusion-weighted imaging and blood flow sequences hold promise for further development (18). Finally, angiography remains a primary modality to identify vascular pathology and assess collateral circulation.

Lowered Cerebral Perfusion Pressure and Stroke Risk

The important question is: Do abnormal cerebral hemodynamics identify a stroke risk? Yonas et al (19) studied 68 patients with carotid stenosis or occlusion using stable xenon CT CBF data and acetazolamide challenge. Stroke incidence was 4.4% in patients with adequate cerebrovascular reserve and 36% in patients with poor cerebrovascular reserve. Kleiser and Widder (20) evaluated 81 patients with unilateral ICA occlusion and 4 patients with bilateral ICA occlusion with TCD and inhaled CO_2 vasoreactivity challenge. Patients with normal cerebrovascular reserve had an 8% incidence of ipsilateral TIA without stroke while those with poor reserve had a 21% incidence of stroke and an 11% incidence of TIA. Those with the most severe hemodynamic impairment had a 45% incidence of stroke. Silvestrini et al (21), using similar methodology, found a 24% incidence of stroke ipsilateral to carotid occlusion with poor reserve over a 2-year period and one stroke in 32 patients with normal reserve. Grubb and colleagues (22) performed a randomized prospective study of 89 patients with unilateral or bilateral ICA occlusion using PET methodology. Patients with increased OEF had a 26.5% incidence of ipsilateral stroke compared to 5.3% with normal OEF. However, two studies from Japan, one using SPECT and acetazolamide challenge (23) and one with PET (24), showed no difference in stroke rate with decreased cerebrovascular reactivity or elevated OEF. In the SPECT study, some patients showed improvement in cerebrovascular reactivity over a 2-year period. In both of these studies a variety of cerebrovascular lesions made interpretation more difficult. Summarizing the studies, the evaluation of cerebrovascular reserve seems to help identify stroke risk in patients with unilateral and bilateral ICA occlusion.

Value of EC-IC Bypass

Does EC-IC bypass offer stroke protection in this setting? Reversal of hemodynamic impairment following EC-IC bypass has been reported by numerous investigators (25-32). Samson et al (33) demonstrated improvement in hemodynamic and metabolic indices by PET scan following EC-IC bypass. Halsey et al (34) showed that EC-IC bypass improves cerebrovascular CO_2 reactivity, and Laurent et al (35) described reversal of intracerebral steal after EC-IC bypass. Anderson and colleagues (25) found improved hemodynamic parameters by xenon-133 studies in 13 patients following EC-IC bypass. Powers et al (31) demonstrated improved hemodynamic and metabolic effects of EC-IC bypass by PET.

It has been more difficult however to show that EC-IC bypass has favorably influenced stroke incidence. Most of these reports are small studies of nonrandomized patients. The 13 patients of Anderson et al (25) showed no additional ischemic events over 30 months follow-up. Nussbaum and Erickson (36) recently reported 20 patients undergoing EC-IC bypass for carotid occlusion, carotid dissection, and moyamoya disease. These patients were all symptomatic with recurrent ischemic episodes. Outcome was considered excellent in 17 and good in 3 with no perioperative or postoperative ischemic complications. Outcomes for rarer ischemic conditions such as vertebrobasilar occlusive disease, intracranial arterial dissection, and moyamoya disease are generally published as smaller case reports. Adams et al (37) have proposed a randomized prospective study limited to ICA occlusion and using PET hemodynamic evaluation to compare EC-IC bypass to medical therapy.

CONCLUSION

Indications for EC-IC arterial bypass surgery are more limited than what was hoped for with the first successful STA-MCA bypass 35 years ago. A randomized international study failed to find benefit from the procedure in prevention of stroke. It seems that there is a subset of stroke patients with ICA or intracranial arterial occlusion and chronic and recurring ischemia that may benefit from cerebral revascularization, but the population remains to be better defined. At present patients must be individually evaluated with clinical history and symptoms, CT and MRI, angiography, hemodynamic evaluation, and associated risk factors, and the risk/benefit of EC-IC bypass must be determined for each patient. Projected studies may further clarify operative indications for the future.

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