Future of extracranial–intracranial bypass

Murali Guthikonda, Lisa L. Guyot and Fernando G. Diaz

Department of Neurological Surgery, Wayne State University, Detroit, MI, USA

Total occlusion of internal carotid artery in the cervical region is an end result of progressive occlusive vascular disease. A small proportion of these patients will have symptoms of cerebral ischemia due to cerebral hypoperfusion in a delayed fashion. Identification of those individuals who are at risk of developing symptoms and prophylactically treating with a revascularization procedure will prevent such catastrophic events. With the co-operative study for bypass not supporting the bypass procedure and trial being questioned for its design and conclusions, a new trial of extracranial–intracranial bypass, The Carotid Occlusion Surgery Study, using the currently available technology will be undertaken to verify that the bypass will decrease the future stroke rate by at least 40% in patients with total carotid occlusion. A subset of patients with skull base pathology including tumors and aneurysms who may have to undergo carotid sacrifice as part of the surgical procedure are at risk of peri-operative and delayed stroke. Identification of these patients at risk by pre-operative tests may allow performance of extracranial–intracranial bypass prior to undertaking complex skull base procedures. The new imaging technology will guide management of these patients at risk and help identify patients who may need a bypass procedure. [Neurology 2002; 24: S80–S83]

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INTRODUCTION
The conclusions from the extracranial–intracranial bypass study were instrumental in total abandonment of the procedure in 1985. Unfortunately the patients enrolled in the study did not undergo certain metabolic studies that are available to date and known to have better correlation with ischemic manifestations. The potential benefit of the bypass procedure can only be determined by future trials that will utilize newer techniques known to have better correlation with ischemic manifestations as measurement of Oxygen Extraction Fraction. Identification of those patients with carotid occlusion and at risk of ischemic stroke will help identify this small group who most likely will benefit by the bypass procedure.

HISTORICAL BACKGROUND
Bypass procedures to augment the blood flow to the brain have been conceptualized from observing cardiac surgical colleagues. The first attempts included bringing vascularized tissue into contact with brain tissue with the idea that vascular growth would develop between these two structures and thereby increase blood flow to the brain1. Subsequent attempts to increase the blood flow resulted in techniques using the superficial temporal artery (STA) as the donor vessel and the middle cerebral artery (MCA) or its branches as the recipient. The first successful anastomosis of the STA to the MCA was performed on a dog by Yasargil in Donaghy's laboratory at University of Vermont2.

This surgical technique became popular in 1970s and 1980s to the extent that an international multicenter randomized trial was undertaken with 71 centers participating from US, Canada, Japan and Europe. Qualifying lesions included middle cerebral artery stenosis or occlusion, cervical carotid stenosis above the C2 level and total ICA occlusion. Patients were followed for five years and primary endpoints were designated as fatal or nonfatal stroke in any vascular distribution. Out of the 1,377 patients admitted to the study, 714 were assigned to the best medical therapy and 663 were treated with the same medical therapy along with superficial temporal artery–middle cerebral artery (STA–MCA) bypass3. All patients were followed for an average of 55.8 months. In spite of high technical excellence with a 96% patency rate, nonfatal and fatal strokes occurred both more frequently and earlier in the surgical group. By 60 months there was no significant difference in the stroke rate between surgical (20%) and the nonsurgical (18%) groups.

Shocked by the results of the study multiple critical analyses of the study were undertaken and new information came to light. In 57 out of 71 centers 601 patients were randomized when an additional 2,572 patients underwent bypass procedure outside the study. This finding raised questions about the validity of the study and its conclusions. Also included in this group were patients with asymptomatic ICA occlusion, representing 38% of cases entered into the trial. The natural history of patients with carotid occlusion has been quite controversial in regards to the incidence of stroke in their life time. Klijn4 summarized all the studies published.
newer and detailed metabolic and blood flow measurement techniques will probably guide decision process in rationally deciding the indications for a bypass procedure in a given patient rather than the techniques used in the earlier conducted EC-IC bypass study.

TESTS TO STUDY THE rCBF

The rCBF studies can be done to assess the baseline measurements or subject the patient to additional provocative measures to increase the need for additional blood flow by increasing the metabolism or by testing the ability for additional vasodilatation. The tests can also be done to check for rCBF with temporary Balloon Test Occlusion (BTO) of the ICA and check for the adequacy of the collateral circulation.

Many tests are available to study the rCBF including 133Xenon studies administered by inhalation or by intravenous administration, stable Xenon CT, SPECT using 99m-Technitium Hexamethylpropyleneamine (99mTc HMPAO), PET and MR. Benzodiazepine receptor SPECT (BZrSPECT) using 123I-Homazenil (IMZ) was performed before and after bypass procedure and the rCBF was noted to increased only in those patients with preserved BZr after the bypass procedure.

Xenon CT

devries described the technique using stable Xenon. Balloon test occlusion with neurological evaluation is carried out and if successful, the rCBF studies are obtained by means of stable Xenon enhanced CT scanning after inflating the balloon. Patient inhales 28% xenon gas mixed with oxygen for 1–2 min and the CT measures the increase in Hounsfield units. The rCBF is calculated as ml 100 g⁻¹ min⁻¹. The patient is given 1 g of Acetazolamide by i.v. route and this procedure is repeated.

Based on the rCBF values the patients were classified into three groups:

Low-risk group with rCBF values above 30 ml 100 g⁻¹ min⁻¹

Carotid ligation can be undertaken with least likelihood of developing neurological deficits.

Moderate-risk group with rCBF values between 15 and 30 ml 100 g⁻¹ min⁻¹

This group of patients are at risk of developing neurological deficits with carotid ligation and a bypass procedure should be undertaken.

High-risk group with rCBF values lower than 15 ml 100 g⁻¹ min⁻¹

These patients are at high risk for developing ischemic stroke and will not tolerate carotid occlusion. A high-flow bypass is needed before carotid occlusion.

HMPAO SPECT

99mTc HMPAO is a lipophilic tracer and crosses the BBB in the first pass with a maximum uptake in the first
ten minutes. Once in the brain tissue it converts into a hydrophilic form and retained for a few hours so the SPECT can be obtained. A difference of 10% is considered to be positive. HMPAO SPECT provides qualitative assessment of asymmetry in the hemispheres and does not give quantitative measurements. In patients with occlusive disease the test is carried out by injecting the tracer. If Balloon Test Occlusion (BTO) is planned, the tracer is injected after the balloon has been inflated.

PROVOCATIVE TESTS

Acetazolamide challenge

Acetazolamide (Diamox®) produces vasodilatation. If the vessels are already maximally dilated one would not see any additional response following Diamox injection indicating poor vasomotor reserve. Poor reserves indicate higher susceptibility for stroke.

Metabolic tests

By directly measuring the regional oxygen extraction fraction (rOEF) and if found to be increased it gives an indication as to the relative inadequacy of regional blood flow. Powers and associates used PET measurements of rCBV, tCBV and rOEF to classify changes in the regional cerebral hemodynamics into three stages:

Stage 0: rCBV, tCBV: rCBF ratio and rOEF are all normal.

Stage 1: In cases of mild reduction in CPP the cerebral vessels dilate to maintain the blood flow. rCBF is normal or mildly reduced and the rOEF remains normal.

Stage 2: If the CPP falls to further lower levels, the capacity of the cerebral vessels to dilate and maintain blood flow is exceeded, and the rCBF begins to decline. rCBV, tCBV: rCBF ratio and rOEF all increase. Patients whose measurements place them into stage 2 are at higher risk of ischemic brain injury. The term 'misery perfusion' was given to this stage of cerebral ischemia by Baron.

In summary, patients who have low rCBF at rest, with poor vascular reserve and areas of low metabolism are probably the candidates who will benefit from a cerebral revascularization.

Test occlusion as a predictor of ischemia

Standard et al. studied 47 patients with balloon test occlusion along with provocative hypotensive challenge. Occlusion was performed under normotensive condition with distal perfusion of heparinized saline for 20 min, or until a deficit is noted. If 20 min of normotension was tolerated, hypotension was induced to two thirds of mean arterial pressure for 20 min, or until a deficit was noted. Nineteen out of 47 patients who clinically tolerated test occlusion with hypotensive challenge, tolerated the carotid sacrifice without the need for a bypass and did not suffer any neurological sequelae from hypoperfusion.

Balloon Test Occlusion with SPECT

The procedure is very similar to the technique described above but 99mTC HMPAO is injected once the carotid artery is occluded. Large areas of low uptake indicate higher risk of ischemic stroke if the carotid artery is sacrificed as part of the tumor resection.

In summary there are more techniques available to date that will help assess the hemodynamic status of brain and the risk it is exposed to from ischemia than during the previous co-operative trial period. Using these techniques one may predict the success based on the need for augmenting cerebral perfusion with bypass techniques.

FUTURE ROLE FOR BYPASS PROCEDURE (BASED ON THE DIAGNOSIS)

Patients with known occlusive vascular disease

The vascular occlusion can involve either major vessel like the ICA or the vertebral artery or MCA trunk. Other major sites for intracranial vascular occlusion include basilar artery and posterior cerebral artery at the P1-P2 junction. The natural history of patients with ICA occlusion has been controversial. With this in mind the issue of bypass surgery is being revisited by the Carotid Occlusion Surgery Study which will be starting in early 2002. The study will be randomized, non-blinded controlled trial which will test the hypothesis that STA-MCA bypass, when added to the best medical therapy, can reduce subsequent ipsilateral ischemic stroke by 40% over two years. Patients who will enter into this study should have recent (<3 months) symptomatic atherosclerotic carotid occlusion and Stage II hemodynamic failure (misery perfusion).

Patients with tumors undergoing carotid sacrifice

Bypass procedure may have to be considered in those patients who may have to undergo elective occlusion of major vessels as part of definitive treatment of their underlying disease and who without a bypass may suffer an ischemic insult to their brain. Patients with cancer of head and neck at times followed by radiation therapy and with skull base tumors like meningiomas of the cavernous sinus are the usual candidates.

Patients with giant aneurysms

Patients with giant intracranial aneurysms or with aneurysms in inaccessible areas like high cervical, petrous or intracavernous segments may have to undergo Hunterian ligation of the parent vessel or trapping of the aneurysm with proximal and distal balloon occlusion of the parent vessel preceded by a bypass procedure.

THE CAROTID OCCLUSION SURGERY STUDY

Yonas was 'hopeful that within the second decade after the report of the negative results of the extracranial/intracranial bypass study that there will be an opportunity to re-examine the efficacy of this procedure based on solid physiological selection criteria...by combining such physiological criteria with equally strict clinical criteria can we hope to understand the role of hemodynamics as a cause of stroke as well as the efficacy of...bypass surgery in its treatment'.
The COSS study will begin in the spring of 2002 and has many inclusion criteria and exclusion criteria. The inclusion criteria include a contrast angiography confirming total occlusion of the ICA and less than 50% stenosis of the contralateral ICA. Patients must have had a TIA or ischemic stroke within 120 days. The patient must be aware that he or she has a 50% likelihood of having the bypass operation and that the trial is meant to assess the usefulness of the operation in offering extra protection against stroke. All patients receive best medical treatment for stroke, and purpose of the trial is to see if the bypass will offer any additional protection. The study also takes remedial medical conditions such as uncontrolled diabetes, hypertension, unstable angina, pectors and unstable neurologic deficit into consideration as long as the exclusion criteria no longer apply within 120 days of onset of the most recent qualifying ischemic event. The primary end point of the study is the combination of ipsilateral hemispheric stroke within two years or any stroke within 40 days of entry into the trial. Secondary endpoints include ipsilateral disabling stroke, any fatal or nonfatal stroke, or death.

The new trial would use PET as the screening technique because of the strong correlation established between abnormal OEF and the risk of stroke. The technique has been described by Derdeyn et al. PET is not readily available in most institutions and this may limit the number of centers where the study can be undertaken. Similarly technically skilled surgeons may be present in an institute which does not have PET facility.

CONCLUSION
In summary one may utilize the multitude of tests available to date to determine if a patient who has an existing vascular occlusion or one who may have to undergo elective occlusion to treat the underlying pathology, is indeed at risk of suffering from ischemic injury without vascular augmentation. The newer techniques will help identify those candidates who have altered CBF and OEF and at risk of future stroke. The COSS will hopefully shed light as to the role of extracranial-intracranial bypass. With the advent of gamma knife and other stereotactic radiation therapy (SRT) modalities, many skull base lesions are being treated with subtotal tumor resection followed by SRT and not resorting to vascular sacrifice. The newer endovascular stenting techniques may also decrease the need for bypass procedures in occlusive vascular disease. Fewer microsurgical skilled neurosurgeons will be available in the future who will be able to perform such procedures when indicated. Vascular laboratories where the suturing techniques can be practiced on rats and other animals may play an increasing role to maintain such surgical skills.

REFERENCES