The Once and Future Treatment: Reconsidering EC/IC Arterial Bypass

Taking a second look at a once disregarded surgical method may help the fight against carotid occlusion.

By William J. Powers, MD

The more we learn, the less we know — at least with any satisfying degree of certainty. This is the paradox that frustrates physicians in many endeavours, and a prime example is management of carotid occlusion. Research concerning the disease often seems to highlight controversies rather than resolve them. A new study now underway at my institution, Washington University School of Medicine, is attempting to provide a few concrete answers concerning surgical intervention in symptomatic patients.

The Carotid Occlusion Surgery Study (COSS) set forth to test the hypothesis that extracranial-intracranial arterial bypass surgery (EC/IC), a procedure first attempted in the 1970s, will reduce the subsequent risk of stroke in patients with symptomatic carotid artery occlusion who are at high-risk due to poor collateral circulation. COSS is an NIH-funded, randomized, partially blinded, multi-center, controlled clinical trial.

Ten to 15 percent of patients presenting with carotid territory stroke or transient ischemic attacks (TIA) are found to have carotid occlusion.[1-3] This results in an estimated 61,000 first-ever strokes and 19,000 TIAs per year.[4] The task at hand, preventing further stroke in these 80,000 patients, remains a difficult challenge: The overall rate of subsequent stroke at two years on medical therapy is 19 percent for all stroke and 16 percent for ischemic stroke ipsilateral to the occluded carotid artery.[5]

Old School

The technique of extracranial-intracranial arterial bypass was developed for symptomatic patients with carotid occlusion in an attempt to prevent subsequent stroke by improving collateral circulation distal to the occluded vessel. In 1977, an international, multi-center, randomized trial was begun to determine the efficacy of EC/IC bypass for the prevention of subsequent stroke.[6] Among 808 participants with symptomatic carotid occlusion who were randomized, no benefit of the surgery could be demonstrated. Based on the results of this well-conducted trial, EC/IC bypass was generally abandoned as a treatment for symptomatic carotid occlusion.

This trial has, however, been criticized. The study failed to identify and separately analyze the subgroup of participants with poor collateral circulation leading to hemodynamic compromise in those who might have benefited from surgical revascularization. Unfortunately, at the time this trial was conducted, there was no reliable and proven method for identifying a subgroup of participants in whom cerebral hemodynamic factors were of primary importance in causing subsequent stroke.

Fortunately, what was in the dark in 1977 has been brought to light in 2007. Modern neuroimaging techniques have now made it possible to evaluate cerebral hemodynamics in patients with carotid occlusion. The adequacy of collateral circulatory pathways to provide normal blood flow to the brain varies among different individuals. Arteriographic assessment of collateral pathways only shows their presence, not their functional ability to restore normal blood flow.[5] Simple measurements of regional cerebral blood flow (CBF) alone are likewise inadequate to assess the hemodynamic effects of carotid artery occlusion because they cannot differentiate low blood flow due to a primary restriction in supply from low blood flow due to reduced metabolic demand.

Fresh Air

The oxygen extraction fraction (OEF) is a measure of the balance between oxygen supplied to the brain (CBF x arterial oxygen content) and the oxygen utilized by the brain. Normally, the brain utilizes 30-40 percent of the available oxygen. When oxygen utilization decreases due to underlying ischemic brain damage, blood flow will decrease in proportion and the OEF will remain 30-40 percent. However, if there is a primary restriction in blood supply, OEF will increase to meet the oxygen needs of the brain. Thus, the measurement of OEF can be used to determine the functional adequacy of the collateral circulation in individual patients with carotid artery occlusion, even in those with pre-existing infarction.[5,7] Studies with positron emission tomography (PET) have shown patients with carotid occlusion may have normal or elevated OEF distal to the occlusion.[8-10]

Two prospective natural history studies have demonstrated that patients with symptomatic carotid artery occlusion who have increased OEF have a higher rate of subsequent stroke within the next two years than those with normal OEF. In their Kyoto study, Yamauchi and co-workers performed PET measurements on 40 medically treated participants with sympto-

Table 1. Stroke Rates in the St. Louis Carotid Occlusion Study

	Total Sample (n=81)	Increased OEF (n=39)	Normal OEF (n=42)
All Stroke:			
1 year	.077	.132	.024
2 years	.190	.292	.090
Ipsilateral Stroke:			
1 year	.064	.106	.024
2 years	.158	.265	.053

matic occlusion or intracranial stenosis of the internal carotid or middle cerebral arterial system.[11] Thirty participants had carotid artery occlusion. At two years following the PET studies, five of seven participants with increased OEF had developed a stroke. Four strokes were ipsilateral and one was contralateral. Six of 33 participants with normal OEF had developed a stroke; three strokes were ipsilateral and three were contralateral. Based on life table analysis, this corresponds to a two-year ipsilateral stroke rate of 0.57 in the high OEF group and 0.15 in the normal OEF group. This difference was significant for both all stroke (p=0.0002) and ipsilateral stroke (p=0.002). The adjusted relative risk conferred by increased OEF was 7.2 (95% CI 2.0-25.5) for all stroke and 6.4 (95% CI 1.6-26.1) for ipsilateral stroke.

The second study, the St. Louis Carotid Occlusion Study, was a prospective, blinded study that addressed the effects of treatment and other risk factors for stroke in 81 participants with symptomatic carotid occlusion. Of these, 39 had increased OEF and 42 did not.[5] The average follow-up was 31.5 months. In the 39 participants with increased OEF, 12 total and 11 ipsilateral strokes occurred. In the 42 participants with normal OEF, there were three total and two ipsilateral strokes. The Kaplan-Meier estimates for the rates of subsequent stroke at one and two years are provided in the table.

The rate of all stroke and ipsilateral ischemic stroke in participants with increased OEF was significantly higher than in those with normal OEF (p=0.005 and p=0.004, respectively). After adjustment for 17 baseline participant characteristics and interval medical treatment, the relative risk conferred by increased OEF was 6.0 (95% CI 1.7-21.6) for all stroke and 7.3 (95% CI 1.6-33.4) for ipsilateral stroke. No ipsilateral strokes occurred in those participants whose most recent symptoms occurred more than 120 days earlier or who had had only retinal symptoms.

Proceed With Caution

Previously, EC/IC bypass has been shown to return areas of increased OEF to normal in participants with carotid artery occlusion.[8-10] However, EC/IC bypass is not without risk. In the original EC/IC bypass study, the 30-day post-operative complication rates were 11 percent stroke and one percent death. The use of PET now allows us to identify a subgroup of patients with carotid artery occlusion with increased OEF who are at high risk for stroke within two years. Even with the surgical morbidity and mortality taken into account, EC/IC bypass offers the promise to substantially reduce the occurrence of subsequent stroke by returning OEF to normal.

The National Institutes of Neurological Disorders and Stroke has provided funds to conduct the Carotid Occlusion Surgery Study to test the hypothesis that EC/IC bypass surgical will reduce subsequent ipsilateral ischemic stroke at two years despite peri-operative stroke and death in patients with symptomatic carotid artery occlusion and increased ipsilateral OEF. This randomized, partially-blinded controlled clinical trial is currently underway at 40 centers in the United States and Canada. Major eligibility criteria are: (1) Atherosclerotic occlusion of one or both carotid arteries; (2) Hemispheric TIA or mild-to-moderate stroke (Barthel Index > 60) in the territory of an occluded carotid artery within 120 days; and (3) Increased OEF measured by PET ipsilateral to the symptomatic carotid artery occlusion. The study will pay the costs of PET and of the bypass surgery. Further details and a list of participating centers can be found at www.cosstrial.org or by contacting Carol Hess, the Project Coordinator (carol@npg.wustl.edu). **PN**

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