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The EC-IC Bypass Study: Does it Answer the Question?

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The procedure of cerebral revascularization was introduced to the management of patients with cerebrovascular occlusive disease as a surgical option. Cerebral revascularization is intended to reestablish cerebral perfusion to brain areas which may be deficient in blood flow because of proximal arterial occlusive lesions. These lesions are not accessible by any other surgical approach.

Cerebral revascularization was introduced in 1967 by Yasargil and Donaghy (1), and many operations have since been performed. An international cooperative study (2,3) was designed to determine whether the anastomosis of an extracranial to an intracranial artery (superficial temporal to middle cerebral artery STA-MCA) would be effective in reducing the development of cerebral infarction or death in patients with otherwise inaccessible carotid circulation lesions. Patients who had been symptomatic within three months before evaluation and who had angiographically demonstrable lesions in the appropriate location were entered and randomized into either a medical group receiving acetylsalicylic acid 325 mg four times a day throughout the trial or a surgical group undergoing an STA-MCA anastomosis in addition to the medication. A careful follow-up was completed for all these patients, and a commendable statistical study was performed on the results.

The international cooperative study (2,3) found no demonstrable difference in the development of stroke or death in patients treated either medically or surgically. In fact, in patients with unilateral internal carotid artery occlusion or with middle cerebral artery stenosis, the patients in the surgical group had a worse outcome. Conclusions of the study were: "...fatal and nonfatal strokes were not prevented by anastomosis of the superficial temporal to the middle cerebral artery...This negative result held for all patients and for individual subgroups, whether the patients had transient ischemic attacks or minor strokes, whether their lesions were occlusive or stenotic, and whether they involved the internal carotid artery, the middle cerebral artery or both."

The only scientific conclusion that can be made from the hypothesis tested in the extracranial-intracranial bypass study is as follows: EC-IC bypass surgery, primarily superficial temporal to middle cerebral artery anastomosis, was not shown to reduce stroke or stroke-related deaths more than the aspirin prescribed for the population of patients selected, who were evaluated in the manner detailed and analyzed with the methods described in the study. No valid scientific conclusion can be made that the study definitely proves bypass surgery to be of no value because the hypothesis did not test that in the study.

We do not believe that the EC/IC bypass study has been specific enough to answer whether cerebral revascularization by anastomosis of the superficial temporal artery to middle cerebral artery effectively prevents cerebral infarction or death in patients with a demonstrated perfusion deficit referable to a specific territory in the carotid circulation and who have an area of inactive but viable cerebral tissue. Evidence from the study would suggest that it contained a large percentage, probably over 40% of its patients who in fact did not have a blood flow deficit to the brain and who had no need for the surgery. Proponents of the study will argue that the study was based on the methods of selection used by neurosurgeons who have published articles on the procedure claiming its benefit. This is true but relates to published work done in the past ten years. It does not reflect the changing practice of those accomplished in the procedure who no longer follow the indications upon which this study was initially based. At present, these criteria have matured to select those patients who are clinically unstable with continuing evidence of cerebral ischemia, with evidence of impaired collateral circulation to the brain by examination of all the blood vessels supplying the brain with four vessel cerebral angiography (the study required only two major vessels to be studied) and by evaluation and selection of patients on the basis of cerebral blood flow testing.

The pathophysiological mechanisms responsible for the development of cerebral ischemia include: 1) an embolic process from a distant source with the passage of artery to artery emboli and the occlusion of a cerebral vessel, 2) a regional cerebral perfusion deficit that results from the existence of a proximal arterial occlusion or a hemodynamically significant stenosis, and 3) a local cerebral perfusion deficit secondary to the occlusion of a small intraparenchymal cerebral artery. Of these mechanisms, the only one that could benefit from the procedure of cerebral revascularization by an extracranial to intracranial anastomosis is the perfusion deficit that results from a major proximal occlusive arterial lesion. Furthermore, not all proximal occlusive lesions result in a perfusion deficit, and not all areas with decreased cerebral perfusion have viable tissue that would benefit from a cerebral reconstructive vascular procedure. The methodology in the EC/IC bypass study did not provide a means of selection or separation of patients with a perfusion deficit who have inactive yet viable tissue. Furthermore, the EC/IC bypass study methods did not require full evaluation of collateral circulation in patients entered in the study. The group reported that ". . . bilateral common carotid arteriograms have been requested on all patients, and angiography of the vertebrobasilar circulation has been optional" (3). Full understanding of the collateral circulation to the area of occlusive disease cannot be gained without a selective four-vessel cerebral angiogram.

The control group was treated with acetylsalicylic acid and compared to the surgical group. The choice of medical treatment was based on the findings of the Canadian Cooperative Study Group (4), who compared the effect of aspirin, sulfinpyrazone, and aspirin and sulfinpyrazone and placebo in patients who by clinical criteria alone ". . . had experienced at least one cerebral or retinal ischemic attack in the three months before entry."

They reported a 19% reduction in the incidence of stroke or stroke-related deaths in a population treated with acetylsalicylic acid 350 mg four times a day. The treatment was beneficial only in men. When the four groups were analyzed individually, no sufficient number of patients in any group benefited from the treatment to make a statistically valid conclusion. To gain statistical value, those patients treated with aspirin alone and those with aspirin and sulfinpyrazone were added, assuming that sulfinpyrazone had no effect whatsoever on the treatment. Neither the source of the symptoms nor the benefit of aspirin alone in reducing the incidence of stroke or stroke-related death in this population were demonstrated.

Other aspirin studies have shown conflicting results. The American, Italian, and Danish studies (5-7) showed no benefit for patients treated with aspirin. The French aspirin study (8), which included both men and women, found a benefit for patients treated with aspirin. The benefit of aspirin in managing patients with cerebral ischemic symptoms referable to specific angiographic lesions in the carotid circulation has not been demonstrated.

Three major premises in the EC/IC bypass study used to establish its statistical validity were "...a large number of patients with a long period of follow-up,...a uniformity of disease process in the population studied,...and...the achievement of effective anastomoses...." The large number of patients was reached through the collection of cases throughout the world from 71 centers. An unproven assumption is that all people from different parts of the world can be considered to have the same behavior and can be treated equally when dealing with cerebrovascular occlusive disease. Furthermore, not all 71 centers contributed the patients whom they saw to this study and thus a certain preselection process occurred, leaving the study to evaluate a prescreened population of patients. Evidence from two of the 71 centers involved alone indicates that over 90 patients in those two centers were not included in the study. Since we could not enter all of our patients in a consistent manner, we withdrew early from the study.

Five groups or patterns of atherosclerotic carotid arterial disease were observed initially in the EC/IC bypass study: "isolated MCA stenosis, isolated MCA occlusion, isolated ICA stenosis (surgically inaccessible), isolated ICA occlusion, and tandem lesions." When these groups were preserved as initially presented, only the group with unilateral internal carotid artery occlusion had enough numbers to reach statistical power. In the group's final report, the tandem lesion group was not mentioned, and the numbers in all groups excluding the internal carotid artery occlusion group were all different. Reported in the methodology was "when tandem lesions (two lesions in the same vessel or sequence of vessels, one proximal to the other) have existed, and both lesions have fulfilled entry criteria, the patient has been entered for the most distal lesion" (3). Apparently, the patients initially reported in the tandem group were later reallocated to the other groups based on the most distal lesion. Even though this may be a statistically valid maneuver through which all groups were brought to have enough numbers to reach statistical power, the assumption must be made for scientific acceptibility that patients with a single lesion have the same pathophysiological behavior as those patients with tandem lesions. When these groups are combined, one can no longer assume that the groups are uniform because other factors such as embolic phenomena would not be equally distributed.

The achievement of effective anastomoses was determined by a postoperative angiogram obtained "three to six months following bypass." However, the final functional status of the patients at the end of the study was not determined until five years later. This method assumes that the angiographic observations made at the postoperative angiogram in the surgical group and in the initial angiogram in the medical group have remained unchanged. Cerebrovascular occlusive disease is a dynamic process that cannot be expected to remain unchanged throughout time. The final functional outcome, therefore, cannot be correlated with earlier angiographic procedures. Possibly other intervening occlusive events, different from those originally observed, developed in the interim. Without angiographic correlation at the time of final evaluation, one cannot reach a cause and effect conclusion.

The paper by Robertson et al (9) in this issue points out the changes observed in a select population of patients with cerebral ischemic events with full angiographic evaluation and with cerebral blood flow studies. The authors conclude that in this population "...STA-MCA bypass surgery is effective in increasing CBF in a focal area of maximal ischemia."

It is unknown whether cerebral revascularization by anastomosis of the superficial temporal artery to the middle cerebral artery prevents cerebral infarction or death in patients with a demonstrated cerebral perfusion deficit and with viable residual cerebral tissue in the area of ischemia. A randomized study must be conducted to identify persons among the population with cerebral ischemic symptoms who have both a perfusion deficit and preserved cerebral tissue. The random allocation to a surgical and medical group with adequate follow-up by clinical, angiographic, blood flow, and metabolic criteria would then allow one to determine the value of EC/IC bypass. Until then, the EC/IC bypass study indicates that not all patients seen in the daily clinical practice who have a unilateral internal carotid or middle cerebral artery occlusive lesion should be subjected to cerebral revascularization. However, the EC/IC bypass study does not yet exclude the value of cerebral revascularization for patients with a focal cerebral perfusion deficit associated with viable cerebral tissue. Furthermore, the findings of the EC/IC bypass study cannot be generalized to other bypass procedures such as proximal MCA anastomosis or posterior fossa revascularization.

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