Revascularization of Collaterals for Hemodynamic Stroke
Insight on Pathophysiology From the Carotid Occlusion Surgery Study

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Carotid atherosclerosis accounts for up to 15% of all strokes and approximately 15,000 to 20,000 have symptomatic carotid occlusions in the United States each year. Furthermore, recurrent ipsilateral stroke in unselected patients with carotid occlusion affects 2.1% to 3.8% on an annual basis. The pathophysiology of stroke due to atherosclerotic plaque of the internal carotid artery may be distinct once the stenotic or narrowed vessel progresses to occlusion. Various mechanisms for cerebral ischemia in carotid occlusion have been described, including downstream clot propagation and stump embolism; however, impaired perfusion plays a major role, particularly once the distal stump of the occlusion develops mature endothelium. A combined effect of hypoperfusion and poor clearance of embolic material has also been described. Perfusion through collaterals to downstream territories of the brain is therefore pivotal. In fact, collaterals largely determine recurrence of symptomatic ischemia after hemodynamic stroke in carotid occlusion. The clinical observation of stereotypical events and those that occur with hypotension and initiation of antihypertensive agents, after a hot bath, or even with the upright position, support a hemodynamic process. Imaging reveals a hemodynamic pattern of ischemia with border zone infarcts as an initial presentation of carotid occlusion in 5% to 13% and in 44% to 72% of recurrent strokes. As perfusion pressure is reduced, cerebral blood flow determined by collaterals is maintained by dilatation of the resistance arterioles (Stage 1 hemodynamic impairment). Further reduction of perfusion pressure may exhaust this autoregulatory capacity and blood flow decreases proportionally to the perfusion pressure. Initially, increased oxygen extraction fraction will maintain tissue metabolism (Stage 2 hemodynamic impairment). Thereafter, insufficient flow and oxygen delivery may result in energetic failure and infarction.

The Carotid Occlusion Surgery Study (COSS) provides important data on the role of collaterals in ischemic stroke. COSS directly studied the role of collaterals in stroke. Although collateral flow is a beneficial compensatory mechanism against ischemia, the ischemic insult itself can lead to collateral recruitment. Thus, individuals with robust collaterals may remain asymptomatic, whereas insufficient collaterals or hypoperfusion may trigger arteriogenesis. Symptomatic carotid occlusion reflects some degree of collateral failure in the setting of progressive atherosclerotic disease. The degree of initial infarction and residual perfusion is determined by complementary sources of collateral circulation; these include the ipsilateral extracranial carotid anastomoses, contralateral carotid flow, and the posterior circulation. Surgical revascularization of collaterals is a rational therapeutic strategy, although the effect of the revascularization on baseline collateral flow may differ. The effect of various medical treatments such as statin administration may also impact collateral status. In sum, both medical and surgical interventions in symptomatic carotid occlusion may affect collaterals and recurrent ischemia due to carotid occlusion by various mechanisms.

Extracranial to intracranial carotid artery (EC-IC) bypass surgery with anastomosis of the superficial temporal artery branch to cortical branch of the middle cerebral artery was designed to augment flow to the anterior circulation in those with carotid occlusion. The EC-IC bypass surgery trial randomized 1377 patients to surgery or medical therapy. No benefit from the procedure was detected with recurrent stroke occurring in 31% in the surgical arm and 29% in the medical arm. Indeed, systematic analysis confirmed these findings; among 21 trials and 2591 patients, no benefit in stroke, death, and dependency was noted for the procedure. However, a number of smaller studies and series reported a high risk of stroke in patients with observed impaired hemodynamics tested with various techniques with an overall estimated annual risk of ipsilateral stroke of 9.5%. Moreover, small nonrandomized studies suggested a benefit of EC-IC bypass surgery in those with impaired hemodynamic distal to the occlusion. The Japanese EC-IC Trial (JET) randomized patients with hemodynamic impairment diagnosed by single photon emission CT cerebral blood flow with an acetazolamide challenge to EC-IC bypass or medical therapy; an interim analysis reported more ischemic events in the medical arm.

As a consequence of the finding of higher risk in the presence of impaired hemodynamics, the COSS was designed to test the specific hypothesis that hemodynamic impairment
with increased OEF on positron emission tomography could be used to determine superiority of EC-IC bypass surgery to medical treatment in those with angiographically confirmed carotid occlusion within 120 days of a hemispheric stroke or transient ischemic attack. Based on a prospective series, the surgical arm was anticipated to have a 24% risk of the primary outcome at 2 years (12% perioperative risk and 12% subsequent risk of ipsilateral stroke) versus 40% in the medical arm. However, after 195 patients had been enrolled in COSS, the study was terminated for futility. Although the OEF improved at a follow-up positron emission tomography scan in the surgical group, and grafts remained patent, clinical outcomes did not improve. The 2-year risk of perioperative stroke and death and subsequent ipsilateral stroke was 21% in the surgical arm and 22.7% in the medical arm (P=0.78); the 30-day risk of ipsilateral stroke was higher in the bypass group (14.4% versus 2%). Both groups had similar baseline characteristics, use of antithrombotic therapy, and control of risk factors.

The surgical failure in COSS to demonstrate superior outcomes of EC-IC bypass despite graft patency and improved hemodynamic measurements has prompted numerous avenues of thought and potential future investigation in the role of collateral perfusion and hemodynamic impairment. The selected points discussed subsequently reflect some of the lessons provided by COSS regarding the importance of studying stroke pathophysiology in clinical trials.

**Outcomes in the Medical Arm Were Better Than Expected**

The risk of the primary outcome in COSS was 23% at 2 years compared with an estimated 40% based on previous studies. This is in line with recent trials in which the outcome of medical therapy was superior to the expected rate from preliminary studies. A recent example emanates from the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial, in which the observed rate of 5.8% for stroke and death at 30 days in recently symptomatic intracranial atherosclerotic disease was lower than the estimated 10.7% from a subanalysis of similar patients enrolled in the Warfarin Aspirin Symptomatic Intracranial Disease (WASID) trial. This low event rate led to the early termination of the SAMMPRIS study. Better risk factor control has been invoked as an explanation for this effect. In COSS there was excellent adherence to antithrombotic agents (94%), 68% had good control of low-density lipoprotein cholesterol, and 46% had systolic blood pressure ≤130 mm Hg at last follow-up. The use of statins has been associated with improved vasomotor reactivity and more robust collateral flow. In addition, statins may prevent progression of the contralateral carotid stenosis; it should be noted that contralateral carotid stenosis ≥50% was present in 18% of COSS patients. Blood pressure control may have also played a role. Traditionally, clinicians have been cautious about lowering blood pressure in those with large vessel occlusion or high-grade stenosis to avoid distal hypoperfusion. Subanalysis of the WASID study of patients with intracranial 50% to 99% stenosis revealed that elevated blood pressure >160 mm Hg during the conduct of the trial was associated with a greater risk of ipsilateral risk, whereas levels <120 mm Hg did not increase risk. Thus, it is possible that modern medical management modified the risk of stroke in the medical arm of patients with carotid occlusion. One should also consider that those with lower blood pressure had more robust collaterals, whereas persistent hypertension reflected impaired collaterals.

**Challenges in Patient Selection Through Imaging Studies**

The COSS study used a ratio of OEF between the ipsilateral and contralateral carotid territory >1.13 to select patients. The original study design called for a higher ratio of >1.16, but this was lowered to improve enrollment. This ratio comes from prior studies showing that the upper CI for normal controls was 1.082. Using this threshold to define Stage 2 hemodynamic impairment, a prospective series in carotid occlusion showed ipsilateral recurrent strokes in 11 of 39 patients with impaired OEF versus 2 of 42 with normal OEF. Hemispheric ratios were deemed equivalent to quantitative methods by some investigators. This premise was recently reviewed by Carlson and colleagues; they argue that the OEF ratio method, and the threshold used, does not adequately identify a cohort with hemodynamic compromise. In general, the imaging selection used in COSS provided a simple algorithm for a clinical trial, yet the dichotomous nature of any threshold technique for an entire hemisphere may be flawed because it does not consider regional variations of hypoperfusion that may determine stroke recurrence and severity. Furthermore, hemodynamic impairment may improve as collateral pathways develop. In a select group of 10 individuals with baseline increased OEF who remained stroke-free during follow-up, a subsequent positron emission tomography study found improvement in OEF and cerebral blood flow that was proportional to longer time of follow-up. Therefore, the methodology to identify a high-risk group and the fluctuating nature of the hemodynamic compromise are challenges to any study using a single time point for imaging evaluation.

**Efficacy of EC-IC Bypass in Improving Flow to the Deep Territories**

It is clear that greater flow and improved cerebral hemodynamic measures are noted after EC-IC bypass. However, the significant risk of ipsilateral events raises the possibility that this flow may not be equally distributed throughout the carotid distribution. The hemispheric ratio improvement does not reflect regional flow changes, particularly in the subcortical areas. By regional mapping with arterial spin labeling, the cerebral territories can be quite variable depending on individual circle of Willis characteristics. In carotid occlusion, improved perfusion from the EC-IC bypass appears to be predominant in the convexity corresponding to the gray matter supplied by the middle cerebral artery. After carotid occlusion, the contributions of other collateral pathways result in altered flow maps of the other major arteries with contributions from the contralateral carotid, the posterior circulation, and the external carotid artery. The effect of the bypass on the altered flow maps has not been well...
defined. Although retrograde flow to the M1 segment of the middle cerebral artery can be visualized angiographically, this depends on the strength of the contrast push and is a poor reflection of actual compensatory flow to the deep white matter. Deep white matter perfusion can be difficult to quantify; similar values have been described for the white matter in the territory of an occluded carotid compared with the contralateral patent territory. Moreover, the normal-appearing white matter may suffer from low-grade ischemic injury in carotid occlusion, as demonstrated by low apparent diffusion coefficient values and associated abnormal cerebrovascular reactivity. These areas may be prone to further ischemic injury with the alteration of flow patterns. It should also be noted that patients with carotid occlusion have significant risk factors and concomitant small vessel disease; indeed, cerebrovascular reactivity is often abnormal in the contralateral hemisphere compared with healthy control subjects. Therefore, it is reasonable to question whether the addition of flow from the bypass adversely modifies flow to the arterial border zones and if it reaches the deep white matter. Detailed imaging analyses of stroke location and patterns in COSS may help clarify these questions and provide further insight.

Risk of the EC-IC Bypass Procedure

COSS certified 30 neurosurgeons to perform EC-IC bypass. Ipsilateral stroke at 30 days occurred in 14 of 93 (15%), and 12 additional patients experienced other serious adverse events. This procedural complication rate is similar to the 12% described in the EC-IC Bypass Trial. The Japanese EC-IC Bypass Trial has not published final results so their perioperative complication rate remains unknown. The early postoperative stroke risk of COSS mirrors the relatively higher risk of recurrent ischemia with other interventions such as intracranial angioplasty and stent placement. Although the risk of ipsilateral stroke in COSS decreased after the perioperative phase with similar rates in both the surgical and medical arms at 2 years, futility analysis suggested that completion of the trial would not provide results favoring EC-IC bypass. Whether higher flow bypass procedures or the less invasive encephaloduroarteriosynangiosis prove safe and effective may be clarified in future studies. However, at this point, given the complications of EC-IC bypass, and medical arms at 2 years, futility analysis suggested that completion of the trial would not provide results favoring EC-IC bypass. Whether higher flow bypass procedures or the less invasive encephaloduroarteriosynangiosis prove safe and effective may be clarified in future studies. However, at this point, given the complications of EC-IC bypass, and the lower event rate with medical management, it is difficult to recommend this procedure on a general basis for those with carotid occlusion.

The COSS trialists are to be commended for applying pathophysiological measures to a defined population. This well-designed study is valuable in confirming the high risk of recurrence and the time course of events in those with hemodynamic compromise from carotid occlusion and in demonstrating the lack of benefit and risks of EC-IC bypass surgery in this positron emission tomography-defined population with increased OEF. This study of carotid occlusion provides a wealth of data regarding collateral circulation and mechanisms of stroke unfortunately absent in most large clinical trials. Detailed analysis in the COSS data set of the patterns of stroke recurrence and their correlation with baseline physiological measures of collaterals, associated perfusion, and metabolic measures will advance the understanding of collateral augmentation in occlusive cerebrovascular disease. Future trials on hemodynamic stroke may benefit from practical imaging applications such as serial CT or MR perfusion techniques that may be readily used in a multicenter setting. Like in other recent trials, a high bar is set for intervention and perhaps the answers are buried in the underlying pathophysiology that only detailed imaging may disclose.

Disclosures

J.G.R. is Site Principal Investigator of the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) study (National Institutes of Health/National Institute of Neurological Disorders and Stroke [NIH/NINDS]); Site Principal Investigator of the Secondary Prevention Of Small Subcortical Strokes (SPS3) Study (NIH/NINDS); and is on the Scientific Advisory Board of NovaVision. D.S.L. is a consultant to Concentric Medical and CoAxia and is supported by NIH/NINDS K23NS054084, P50NS04378, and K24NS072272.

References


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