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William M Feinberg Award for Excellence in Clinical Stroke: Hemodynamics and Stroke Risk in Carotid Artery Occlusion

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Keywords

Cerebral Hemodynamics; Oxygen Extraction Fraction; Carotid Artery Occlusion; Extracranial-intracranial bypass

Five to 15% of patients with carotid territory transient ischemic attacks or cerebral infarctions have complete occlusion of the internal carotid artery.^{1,2} Their risk of recurrent stroke during the next two years while on medical therapy is 5–9% per year for all stroke and 2–8% per year for ipsilateral ischemic stroke.^{3–6} Debate on the best means to prevent recurrence has centered on whether embolic or hemodynamic mechanisms are most important. In the late 1970s and early 1980s, embolism of atherothrombotic material from the persisting proximal stump of the occluded internal carotid artery through external carotid artery collaterals was put forward as the most common cause for recurrent cerebral ischemic events.^{7,8} At this same time, extracranial-intracranial (EC-IC) bypass was increasingly used to try to prevent recurrent stroke by improving the hemodynamic status of the cerebral circulation distal to the occluded vessel.^{9,10} From 1977–1985, an international, multicenter, randomized trial was conducted to determine the efficacy of EC-IC bypass for the prevention of subsequent stroke. Among 808 randomized patients with symptomatic carotid occlusion, no benefit of surgery was demonstrated.¹¹ Some concluded that the reason for the negative results was that the majority of strokes were due to emboli whereas others criticized the trial for failing to identify patients with hemodynamic cerebral ischemia due to poor collateral circulation for whom surgical revascularization would be of benefit.^{12,13} However, the pattern of arteriographic collaterals failed to identify a subgroup who benefitted from surgery.¹⁴

At the time of the EC-IC Bypass Study, there was no reliable method for assessing the hemodynamic effects of carotid artery occlusion on the cerebral circulation. While direct measurements of arterial-jugular venous oxygen differences had demonstrated that reductions in whole brain cerebral blood flow (CBF) by induced systemic hypotension led to an increase in cerebral oxygen extraction fraction (OEF), jugular sampling was not useful for assessing the hemodynamic effects of unilateral carotid occlusion.^{15,16}

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DISCLOSURES

None

$$\text{OEF} = \text{CMRO}_2 / (\text{CBF} \times \text{CaO}_2)$$

where CMRO₂ is the cerebral metabolic rate of oxygen, CBF is the cerebral blood flow and CaO₂ is the arterial oxygen content.

OEF reflects the balance between oxygen utilization (CMRO₂) and oxygen delivery (CBF x CaO₂). Normal OEF is 30–40%. When whole brain CBF decreases, OEF increases as much as two-fold. The invention of positron emission tomography (PET) in the early 1980s made it possible to measure regional cerebral OEF in vivo. Because of the close coupling between regional flow and metabolism in the resting brain, OEF is normally quite uniform (Figure 1).^{17–19} In 1981, Jean-Claude Baron and colleagues described a patient with carotid artery occlusion and focally increased OEF in the ipsilateral cerebral hemisphere. They proposed the term “misery perfusion” to describe this condition.²⁰

At Washington University in the early 1980s, we began to study patients with carotid artery occlusion using PET measurements of OEF to assess the hemodynamic status of the cerebral circulation in the ipsilateral middle cerebral artery (MCA) territory. In some, OEF in the MCA territory distal to the occlusion was normal indicating collateral circulation maintained the normal balance between oxygen delivery and metabolism. In others, a regional increase in OEF indicated poor collateral circulation with chronically reduced CBF relative to CMRO₂ (Figure 1).²¹

From 1992–1997, we carried out the St. Louis Carotid Occlusion Study to determine if increased OEF in the cerebral hemisphere distal to symptomatic carotid artery occlusion was an independent predictor of the subsequent stroke in medically treated patients.⁵ Major eligibility criteria were: (1) Occlusion of one or both common or internal carotid arteries and (2) Transient ischemic neurological deficits (including transient monocular blindness) or mild to moderate stroke in the appropriate carotid artery territory. Just prior to PET, each subject underwent neurological evaluation and assessment of the baseline risk factors.

Quantitative regional OEF was measured by PET.²² When technical difficulties precluded collection of the arterial time activity curves necessary to determine quantitative OEF, the ratio image of the counts in the unprocessed images of O¹⁵O and H₂¹⁵O was substituted. The left/right MCA OEF ratio was calculated from non-infarcted tissue. Ratios from 18 normal control subjects defined the normal range for OEF. A separate normal range for count-based O¹⁵O/H₂¹⁵O ratio images was determined. No information regarding the PET results was provided to patients, treating physicians or the investigator responsible for determining endpoints

The primary endpoint was ischemic stroke defined clinically as a neurological deficit of presumed ischemic cerebrovascular cause lasting greater than 24 hours in any cerebrovascular territory. Secondary endpoints were ipsilateral ischemic stroke and death. Patients with subsequent cerebrovascular surgery were censored at the time of surgery.

Eighty-one subjects were enrolled and followed through telephone contact every six months. Medical treatment on a monthly basis was recorded. Symptoms suggesting a stroke were evaluated by the designated blinded investigator using history from the patient or eyewitness and review of medical records. If necessary, follow-up examination and brain imaging were arranged. All living patients were followed for the duration of the study. Mean follow-up was 31.5 months.

Of the 81 patients, 39 had ipsilateral increased OEF and 42 did not. The two groups were well matched for baseline risk factors except that retinal symptoms were less common in the high OEF group. Arteriographic collateral circulation did not permit identification of the high OEF group. In the 39 high OEF subjects, 12 total and 11 ipsilateral strokes occurred. In the 42 subjects with normal OEF, there were 3 total and 2 ipsilateral strokes. The rates for all stroke and ipsilateral ischemic stroke in high OEF subjects were significantly higher than in those with normal OEF ($p=.005$ and $p=.004$, respectively). (Table 1, Figure 2) After adjustment for 17 baseline patient characteristics and interval medical treatment, the relative risk conferred by high 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.

Arterial time-activity data was not available in 13 of 81 subjects and the count-based ratio was substituted. Subsequently, we analyzed the count-based method ratio for all 81 patients. All 13 ipsilateral ischemic strokes occurred in the 50 patients with increased count-based OEF ($p = .002$) The count-based ratio method was a better predictor of subsequent stroke than ipsilateral quantitative OEF measurements or quantitative ratios.²³ The quantitative and count-based OEF ratio methods were each significant predictors of stroke risk when analyzed as a continuous variable (both $p < .02$).²⁴

Four additional published studies in symptomatic patients with carotid occlusion or intracranial stenosis/occlusion have confirmed that PET measurements of OEF identify patients at high risk for subsequent ipsilateral ischemic stroke while on medical therapy (Table 2).^{25–28}

Concurrently with the EC-IC Bypass Study, we and others demonstrated that EC-IC bypass in patients with carotid occlusion and increased OEF could improve OEF and sometimes return it to normal (Figure 1).^{20,21,29,30} In the absence of an empiric trial, however, it could not be assumed that EC-IC bypass surgery would reduce the risk of subsequent stroke in this group of patients. The morbidity and mortality due to surgery and the long-term stroke risk in operated patients were not known.

The Carotid Occlusion Surgery Study (COSS) was a prospective, randomized, controlled, blinded end-point clinical trial designed to determine whether EC-IC bypass could reduce subsequent ipsilateral ischemic stroke at two years in participants with recent (< 120 days) hemispheric symptoms from internal carotid artery occlusion and hemodynamic cerebral ischemia identified by an ipsilateral increased OEF measured by PET.²⁸ It was conducted at 49 clinical centers and 18 PET centers in the United States and Canada from 2002–2010. The PET eligibility criterion was an ipsilateral-to-contralateral count-based OEF ratio >1.130 . Intra-arterial catheter arteriography documenting (1) occlusion of the symptomatic

internal carotid artery and (2) intracranial and extracranial arteries suitable for anastomosis was required. Peri-operative anti-thrombotic treatment for the surgical group was determined by the COSS neurosurgeon. Otherwise all subjects remained on the anti-thrombotic treatment preferred by their physicians. Target goals for risk factor control were: 130/85 mm Hg for blood pressure, 100 mg/dL for low density lipoprotein (LDL)-cholesterol, 150 mg/dL for triglycerides and 7% for hemoglobin A1C. Referral to primary physicians or directly to smoking cessation programs was encouraged.

The first follow-up visit was 30–35 days after randomization. All surgical participants received a repeat PET scan 30–60 days post-operatively. Subsequent follow-up visits were at three-month intervals after randomization until 24 months or the end of the trial.

The primary endpoint for all who were assigned to surgery and received surgery was the combination of: (1) all stroke and death from surgery through 30 days post-surgery and (2) ipsilateral ischemic stroke within two years of randomization. The primary endpoint in the non-surgical group and for those assigned to surgery who did not receive surgery was the combination of: (1) all stroke and death from randomization to randomization plus 30 days and (2) ipsilateral ischemic stroke within two years of randomization. Ipsilateral ischemic stroke was defined as the clinical diagnosis of a focal neurological deficit due to cerebral ischemia clinically localizable within the territory of the symptomatic occluded internal carotid artery that lasted for more than 24 hours. Final determination of stroke endpoints was by a 3-person blinded Adjudication Committee.

COSS was stopped by the Data, Safety and Monitoring Board based on a futility analysis of 139 patients who had completed two-year follow-up; 195 total participants had been randomized, 97 to the surgical group and 98 to the non-surgical group. Comparison of 24 baseline variables produced 1 difference at the $p < .05$ level as expected, in systolic blood pressure. At last follow-up visit, risk factor control was similar in both groups.

Follow-up for the primary endpoint was 99% complete. All primary endpoints were ipsilateral ischemic strokes, twenty in each group. For the intention-to-treat analysis of the primary endpoint, two-year rates were .210 for the surgical group and .227 for the non-surgical group ($p = 0.78$). (Figure 3A) COSS was designed with 90% power to detect 16% absolute risk reduction. The final results excluded with greater than 95% confidence a benefit for surgery this large.

There was no significant benefit for surgery on any of the COSS secondary outcome measures. The Randomized Evaluation of Carotid Occlusion and Neurocognition (RECON) trial performed on a subset of COSS patients showed no difference in 2-year cognitive change between the surgical and non-surgical groups ($p = .9$). The number of subjects studies for RECON met the pre-study power calculation for detecting a large effect size of a difference of 0.8 SD in composite cognitive change score between treatment arms. It is possible that greater numbers of patients may have demonstrated a small or moderate superiority of one treatment arm or the other, although with the point estimate near zero this would have been unlikely. The 95% confidence interval was -0.5 to 0.5 SD, the limits of a moderate effect size³¹

COSS was designed with a two-year endpoint. Trials of medically treated symptomatic large artery atherosclerosis have shown a major decrease in stroke rate after two years. In the EC-IC Bypass Study, the stroke rate at 2 years was 20% but at 4 years the stroke rate had only increased by an additional 6%.¹¹ In the carotid endarterectomy trials, the stroke rate at two years for 70–99% stenosis was 20% but increased only by an additional 4% by year 4.³² Data reported by Persoon and colleagues from 117 patients with symptomatic internal carotid artery occlusion show a recurrent ischemic stroke rate of 12% at 2 years, increasing to only 14% by 4 years.³³ Continuing COSS for an additional three years with a 1–3%/year rate of stroke in the non-surgical group would not have resulted in a statistically significant benefit for surgery, even if no additional strokes occurred in the surgical group.

A subsequent subgroup analysis of 36 subjects in St. Louis Carotid Occlusion Study who met the clinical eligibility criteria for COSS confirmed the superiority of the count-based ratio OEF method to determine eligibility. The risk of ipsilateral stroke in patients who met the COSS ratio criteria (7/18, 39%) was virtually identical to those with quantitative OEF threshold of 50% (4/10, 40%) but the COSS ratio method identified more patients (7/9) who would go on to develop a stroke than the absolute OEF criteria (4/9).³⁴

In the COSS surgical group, 30-day graft patency was 98% and patency at last follow-up was 96%. Mean OEF ratio improved from 1.258 to 1.109. Of 20 strokes in the surgical group, 14 occurred in the 30 day post-operative period. This peri-operative stroke rate of 15% was not significantly different from the international EC-IC Bypass Trial.¹¹ Twelve of these post-operative strokes occurred within 2 days of surgery. Eliminating these 12 strokes, the subsequent stroke rate in the remainder of the surgical group was .09, significantly less than the non-surgical group ($p=.02$). (Figure 3B)

COSS demonstrated the importance of cerebral hemodynamics in the treatment of carotid occlusion. The pathophysiological hypothesis was correct. Surgical improvement of hemodynamics by EC-IC bypass reduced stroke risk. However, the cure was as bad as the disease. The peri-operative stroke rate was sufficiently high to nullify any benefit. Extensive post-hoc analyses failed to define any patient, procedural or surgeon characteristic that predicted who would have a peri-operative stroke.³⁵

COSS demonstrated that EC-IC bypass provides no benefit over medical management for stroke prevention in patients with symptomatic carotid artery occlusion, even on those with increased OEF. However, disagreement existed whether strict blood pressure control was the best for these patients or if higher blood pressures were needed to preserve cerebral perfusion and prevent subsequent stroke.^{1,36} To address this issue, we analyzed data from the non-surgical group of COSS.³⁷

Of 98 non-surgical participants, 91 were included in the analysis: three had no post-randomization blood pressures recorded, and four had ipsilateral ischemic strokes before the first blood pressure recording at the 30–35 day follow-up visit. We compared the occurrence of ipsilateral ischemic stroke during follow-up in the 41 subjects with mean blood pressures during follow-up who met the COSS target 130/85 mm Hg to the remaining 50 with higher blood pressures. We used only the blood pressures recorded before the stroke

occurred for those who experienced an endpoint ipsilateral ischemic stroke. For all others we used all recorded blood pressure measurements. The groups were well-matched for baseline characteristics and medical management during follow-up except for the time from entry event to randomization, which was not a significant predictor of subsequent stroke in these 91 patients ($p = .32$).

Of 16 ipsilateral ischemic strokes within two years of randomization, 3 occurred in the 41 subjects with mean follow-up blood pressure of 130/85 compared to 13 in the remaining 50 subjects with mean follow-up blood pressures $>130/85$ (hazard ratio 3.74, 95% CI 1.07–13.15, $p = 0.027$). (Figure 4) The two-year Kaplan-Meier estimated rates were .082 and .304, respectively. In the subgroup of 52 subjects who were always taking at least one antihypertensive drug at every follow-up visit, there were 2 strokes in 23 patients in the 130/85 group and 10 strokes in 32 subjects in the $>130/85$ group (hazard ratio 3.78, 95% CI .83–17.30, $p=0.065$ log-rank). The hazard ratio of 3.78 for this always treated subgroup was essentially identical to that of 3.74 for the primary analysis. There was no evidence of a J-curve.³⁸

This was not a randomized trial of different targets for blood pressure control. Nevertheless, this study provided Class III evidence by American Academy of Neurology criteria that control of hypertension 130/85 mm Hg is associated with a reduced risk of subsequent ipsilateral ischemic stroke in patients with recently symptomatic carotid occlusion and hemodynamic cerebral ischemia (increased OEF).³⁷ COSS patients with increased OEF represent the most extreme case of cerebral hemodynamic compromise. Nevertheless, lower blood pressures were associated with reduced, not increased, stroke risk. This was not simply due to the lower blood pressure group not being hypertensive to begin with as the hazard ratio was the same for the subgroup always treated with anti-hypertensive drugs as for the entire cohort.

This series of studies have demonstrated that the hemodynamic status of the cerebral circulation distal to an occluded carotid artery is the most important predictor of subsequent stroke. Patients with the worst hemodynamic compromise (increased OEF) have a 2-year stroke risk of 20–25%. Surgical improvement of hemodynamics by EC-IC bypass does reduce stroke risk, but the peri-operative stroke rate is sufficiently high to nullify this benefit. Counterintuitively, best medical management for these patients includes strict blood pressure control.

The results of these studies also reinforce the need for empiric data. Conclusions about therapeutic efficacy based on presumed mechanisms for stroke and for stroke therapies have too often proven to be wrong. Research into the pathophysiology of stroke and the biological effects of different treatments can provide the rationale for clinical trials but cannot substitute for the empiric data in choosing individual patient therapy.

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Figure 1.

PET scans of cerebral blood flow (CBF), cerebral metabolic rate of oxygen (CMRO2) and cerebral oxygen extraction fraction (OEF) in a normal subject (top row), a patient with carotid artery occlusion and normal OEF (second row) and a patient with carotid occlusion and high OEF before (third row) and after (bottom row) EC-IC bypass surgery.

Figure 2. Kaplan-Meier cumulative occurrence curves for ipsilateral ischemic stroke from the St. Louis Carotid Occlusion Study. Reprinted from Grubb et al,⁵ with permission from the American Medical Association. Copyright 1998.

Figure 3.

(A) Kaplan-Meier cumulative occurrence curves for the intention-to-treat analysis of the primary end point from the Carotid Occlusion Surgery Study. Reprinted from Powers et al,²⁸ with permission from the American Medical Association. Copyright 2011. (B) Kaplan-Meier cumulative occurrence curves for the on treatment analysis of the primary end point from the Carotid Occlusion Surgery Study with the 12 strokes that occurred within the first two days postoperatively removed from the surgical group.

Figure 4.

Kaplan-Meier cumulative occurrence curves for ipsilateral ischemic stroke for 91 patients from the non-surgical group of the Carotid Occlusion Surgery Study comparing the 41 subjects with mean blood pressures during follow-up who met the COSS target 130/85 mm Hg to the remaining 50 with higher blood pressures. Reprinted from Powers et al,³⁷ with permission from Wolters Kluwer Health. Copyright 2014.

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

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TABLE 2

Two-Year Kaplan-Meier Ipsilateral Stroke Rates from Studies Measuring OEF in Patients with Cerebrovascular Disease

	High OEF (n)	Normal OEF(n)
STLCOS 1998 ⁵	.265(39)	.053(42)
Yamauchi 1999 ²⁵	.714 (7)	.061(33)
Hokari 2009 ²⁷	.375 (9)	.000(11)
COSS 2011 ²⁸	.223 (98)	
Yamauchi 2012 ²⁶	.25 (16)	.03 (114)

STLCOS-St. Louis Carotid Occlusion Study, COSS-Carotid Occlusion Surgery Study.