Five percent 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 2 years while on medical therapy is 5% to 9% per year for all stroke and 2% to 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 prevent recurrent stroke by improving the hemodynamic status of the cerebral circulation distal to the occluded vessel.9,10 From 1977 to 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 because of emboli, whereas others criticized the trial for failing to identify patients with hemodynamic cerebral ischemia because of 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 cerebral circulation. Although 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

\[
\text{OEF} = \frac{\text{CMRO}_2}{(\text{CBF} \times \text{CaO}_2)}
\]

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

OEF reflects the balance between oxygen use (CMRO2) and oxygen delivery (CBF×CaO2). Normal OEF is 30% to 40%. When whole-brain CBF decreases, OEF increases as much as 2-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 uniform (Figure 1).17–19 In 1981, Baron et al20 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.

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 to 1997, we performed the St Louis Carotid Occlusion Study to determine whether increased OEF in the cerebral hemisphere distal to symptomatic carotid artery occlusion was an independent predictor of the subsequent stroke in medically treated patients.3 Major eligibility criteria were (1) occlusion of 1 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 before 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 H218O was substituted. The left/right MCA OEF ratio was calculated from noninfarcted tissue. Ratios from 18 normal control subjects defined the normal range for OEF. A separate normal range for count-based O15O/H218O ratio images was determined. No information regarding the PET results was...
provided to patients, treating physicians, or the investigator responsible for determining end points.

The primary end point was ischemic stroke defined clinically as a neurological deficit of presumed ischemic cerebrovascular cause lasting >24 hours in any cerebrovascular territory. Secondary end points 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 6 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 up 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 2 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=0.005 and 0.004, 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% confidence interval [CI], 1.7–21.6) for all stroke and 7.3 (95% CI, 1.6–33.4) for ipsilateral stroke.

Arterial time–activity data were not available in 13 of 81 subjects, and the count-based ratio was substituted. Subsequently, we analyzed the count-based ratio for all 81 patients. All 13 ipsilateral ischemic strokes occurred in the 50 patients with increased count-based OEF (P=0.002). The count-based ratio was a better predictor of subsequent stroke compared with 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<0.02).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 empirical 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 because of 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 2 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.24 It was conducted at 49 clinical centers and 18 PET centers in the United States and Canada from 2002 to 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. Perioperative antithrombotic treatment for the surgical group was determined by the COSS neurosurgeon. Otherwise all subjects remained on the antithrombotic 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 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 to 35 days after randomization. All surgical participants received a repeat PET scan 30 to

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

<table>
<thead>
<tr>
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<th>Total Sample (n=81)</th>
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<th>Normal OEF (n=42)</th>
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OEF indicates oxygen extraction fraction. Reprinted from Grubb et al5 with permission of the publisher. Copyright ©1998, the American Medical Association.

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**Figure 1.** Positron emission tomographic 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) extracranial–intracranial (EC-IC) bypass surgery.
60 days postoperatively. Subsequent follow-up visits were at 3-month intervals after randomization until 24 months or the end of the trial.

The primary end point for all who were assigned to surgery and received surgery was the combination of (1) all stroke and death from surgery through 30 days postsurgery and (2) ipsilateral ischemic stroke <2 years of randomization. The primary end point in the nonsurgical 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 <2 years of randomization. Ipsilateral ischemic stroke was defined as the clinical diagnosis of a focal neurological deficit because of cerebral ischemia clinically localizable within the territory of the symptomatic occluded internal carotid artery that lasted >24 hours. Final determination of stroke end points 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 2-year follow-up; 195 total participants had been randomized, 97 to the surgical group and 98 to the nonsurgical group. Comparison of 24 baseline variables produced 1 difference at the \( P < 0.05 \) 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 end point was 99% complete. All primary end points were ipsilateral ischemic strokes, 20 in each group. For the intention-to-treat analysis of the primary end point, 2-year rates were 0.210 for the surgical group and 0.227 for the nonsurgical group (\( P = 0.78 \); Figure 3A). COSS was designed with 90% power to detect 16% absolute risk reduction. The final results excluded with >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 nonsurgical groups (\( P = 0.9 \)). The number of subjects enrolled in RECON met the prestudy power calculation for detecting a large effect size of a difference of 0.8 SD in composite cognitive change score between treatment arms. The 95% CI was −0.5 to 0.5 SD, the limits of a moderate effect size.31 It is possible that greater numbers of patients may have demonstrated a small or moderate superiority of 1 treatment arm or the other, although with the point estimate near zero this would have been unlikely.

COSS was designed with a 2-year end point. Trials of medically treated symptomatic large artery atherosclerosis have shown a major decrease in stroke rate after 2 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 2 years for 70% to 99% stenosis was 20% but increased only by an additional 4% by year 4.32 Data reported by Persoon et al33 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. Continuing COSS for an additional 3 years with a 1% to 3% per year rate of stroke in the nonsurgical 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 OEF ratio 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 postoperative period. This perioperative stroke rate of 15% was not significantly different from the international EC-IC Bypass Trial.11 Twelve of these postoperative strokes occurred <2 days of surgery. Eliminating these 12 strokes, the subsequent stroke rate in the remainder of the surgical group was 0.09, significantly less than the nonsurgical group (P = 0.02; 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 perioperative 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 perioperative stroke.35

COSS demonstrated that EC-IC bypass provides no benefit compared with 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 nonsurgical group of COSS.37

Of 98 nonsurgical participants, 91 were included in the analysis: 3 had no postrandomization blood pressures recorded, and 4 had ipsilateral ischemic strokes before the first

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**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 (COSS). EC-IC indicates extracranial–intracranial. Reprinted from Powers et al28 with permission of the publisher. B, Kaplan–Meier cumulative occurrence curves for the on-treatment analysis of the primary end point from the COSS with the 12 strokes that occurred within the first 2 days postoperatively removed from the surgical group.

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**Figure 4.** Kaplan–Meier cumulative occurrence curves for ipsilateral ischemic stroke for 91 patients from the nonsurgical group of the Carotid Occlusion Surgery Study (COSS) comparing the 41 subjects with mean blood pressures (BPs) during follow-up who met the COSS target ≤130/85 mm Hg to the remaining 50 patients with higher BPs. Reprinted from Powers et al37 with permission of the publisher. Copyright ©2014, Wolters Kluwer Health.
blood pressure recording at the 30- to 35-day follow-up visit. We compared the occurrence of ipsilateral ischemic stroke in the 41 subjects with mean blood pressures during follow-up who met the COSS target ≤130/85 mm Hg to the remaining 50 subjects with higher blood pressures. We used only the blood pressures recorded before the stroke occurred for those who experienced an end point 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=0.32).

Of 16 ipsilateral ischemic strokes <2 years of randomization, 3 occurred in the 41 subjects with mean follow-up blood pressure of ≤130/85 mm Hg compared with 13 in the remaining 50 subjects with mean follow-up blood pressures >130/85 mm Hg (hazard ratio, 3.74; 95% CI, 1.07–13.15; P=0.027; Figure 4) The 2-year Kaplan–Meier estimated rates were 0.082 and 0.304, respectively. In the subgroup of 52 subjects who were always taking at least 1 antihypertensive drug at every follow-up visit, there were 2 strokes in 23 patients in the ≤130/85 mm Hg group and 10 strokes in 32 subjects in the >130/85 mm Hg group (hazard ratio, 3.78; 95% CI, 0.83–17.30; 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.

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). 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 because of the lower blood pressure group not being hypertensive to begin with because the hazard ratio was the same for the subgroup always treated with antihypertensive drugs as for the entire cohort.

This series of studies has 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% to 25%. Surgical improvement of hemodynamics by EC-IC bypass does reduce stroke risk, but the perioperative 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 empirical 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 empirical data in choosing individual patient therapy.

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Disclosures
None.

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William J. Powers

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경동맥 영역의 일과성 허혈발작 또는 뇌경색을 가진 환자의 5~15%는 내경동맥완전폐색을 가지고 있다.1-3 내과적 치료에도 불구하고 증상 발생 후 2년 동안 뇌졸중의 재발 위험은 모든 뇌졸중에 대해 연간 5~9%, 동측의 허혈뇌졸중에 대해 2~8% 정도이다.4-6 뇌졸중의 재발 방지를 위한 최선의 방법이 무엇인지에 대한 논란은 주로 색전 기전 또는 혈류역학적 기전이 중요하다고 해석되며 집중되어 왔다. 1970년대 후반에서 1980년대 초반에는 폐색된 내경동맥의 근위부에 남아있는 죽상혈전 물질이 외경동맥의 측부순환을 통하여 색전뇌경색을 일으키는 것이 재발성 뇌흉혈의 가장 중요한 요인으로 제시되었다.7,8 이와 비슷한 시기에 폐색된 혈관 원위부 뇌순환의 혈류역학적 상태를 개선하여 뇌졸중 재발을 예방하기 위한 방법으로 두개내외우회로조성술(extracranial–intracranial bypass, EC–IC bypass)의 시행이 점차 증가하였다.9,10 1977년부터 1985년까지 재발성 뇌졸중 예방에 있어 EC–IC bypass가 효과적이었고, 다른 다국적, 다기관 무작위배정 연구가 수행되었다. 무작위배정된 808명의 증상성 경동맥폐색을 가진 환자들에서 수술 치료의 효과는 입증되지 못하였다.11 일부 사람들은 효과가 없는 이유가 뇌졸중의 대부분이 색전 때문인 것으로 결론 지었고, 다른 사람들은 이 연구가 축부순환이 불량하여 수술적 혈관재형성을 도움이 되어서 제시되었기 때문이라고 비판하였다.12,13 그러나 동맥조영상 측부순환의 패턴을 분석해 보았을 때에도 수술이 이득이 되었을 환자들을 확인하는데 실패하였다.14 EC–IC Bypass Study에서는 경동맥폐색에 의한 뇌졸중의 혈류역학적 효과를 평가할 수 있는 신뢰할 만한 검사가 없었다. 비록 동맥–경맥 사이의 산소전도성이 아론 지적한 정신 저 혈압에 의한 전체 혈류(cerebral blood flow, CBF)의 감소와 산소추출율(oxygen extraction fraction, OEF)이 증가한다는 것을 입증하였지만, 경맥 샘플 채취는 일측 경동맥폐색의 혈류역학적 효과를 평가하는 데에는 유용하지 않았다.15,16

OEF는 다음과 같다:

OEF=CMRO2/(CBFxCaO_2)

CMRO2=뇌산소대사율(cerebral metabolic rate of oxygen)

CBF=뇌혈류(cerebral blood flow)

CaO_2=동맥 내 산소의 양(arterial oxygen content)

OEF는 산소의 사용(CMRO2)과 산소의 전달(CBFxCaO_2) 사이의 균형을 반영한다. 정상 OEF는 30~40% 정도이다. 전체 뇌의 CBF가 감소하면, OEF는 최대 2배까지 증가한다. 1980년대 초 양전자방출단층촬영(positron emission tomography; PET)의 개발로 생체 내 국소 대뇌 OEF 측정이 가능해졌다. 안정기 뇌에서 국소혈류의 대사 사이에는 밀접한 관련성이 있기 때문에 OEF는 정상적으로 균일하다(Figure 1).17-19 1981년에 Baron 등20은 경동맥폐색 환자에서 동측의 대뇌 반구의 OEF가 증가한 것으로 보고하였고, 이와 같은 혈류 부족상태를 표현하기 위해 부족관류(misery perfusion)라는 단어를 제안하였다.

1980년대 초에 Washington University에서 본 저자들은 경동맥폐색 환자들에서 PET을 이용한 OEF 측정을 통하여 동측의 대뇌동맥 영역의 뇌순환의 혈류역학적 상태를 평가하기 위한 연구를 시작하였다. 일부 환자에서 폐색 원위부의 대뇌동맥영역의 OEF가 정상이고 측부순환을 통해 산소의 운반과 대사 사이의 정상적 균형이 유지된 것으로 시사하였다. 다른 환자들에게는 국소적인 OEF가 증가하여, 측부순환에 불량하여 CMRO2에 비해 만성적으로 CBF가 감소되어 있음을 시사하였다(Figure 1).21-23 1992년부터 1997년까지 본 저자들은 St Louis Carotid Occlusion Study를 수행하여 증상성 경동맥폐색 원위부의 대뇌반구에서 OEF가 증가된 소견이 내과적 치료를 받는 환자들에서 차
Eighty-one subjects were enrolled and followed through the study. Mean follow-up was 31.5 months. Ipsilateral stroke in 13% of the cases was arterial time–activity curve 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) extracranial–intracranial (EC-IC) bypass surgery.

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<td>1 y</td>
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<td>0.106</td>
<td>0.024</td>
</tr>
<tr>
<td>2 y</td>
<td>0.158</td>
<td>0.265</td>
<td>0.053</td>
</tr>
</tbody>
</table>

OEF indicates oxygen extraction fraction. Reprinted from Grubb et al with permission of the publisher. Copyright ©1998, the American Medical Association.
혈중을 보고하였다(그림 1). 30,31,32,33 그러나 심증적인 임상시험
이 없이 EC-IC 우순환이 이 환자군에서는 추후의 뇌졸중의 발병 위
험을 감소시킬 수 있다고 추정한 수 있다. 수술으로 인한 이환물과
사망률 및 수술 환자의 장기적인 뇌졸중의 위험에 대해서는 알
려진 바가 없다.

Carotid Occlusion Surgery Study (COSS)는 전향적인 무작위
대조군 랜덤 총점 임상연구로 내경동맥폐색과 PET 검사에서 동측
OEF 증가로 확인된 혈류역학적 뇌혈류로 인해 최근(120일 이내)
발생한 반응 증상을 가진 환자들을 대상으로 EC-IC 우순환이 2년
이내 동측 혈류저출증의 발생을 감소시킬 수 있는지를 평가하는
연구였다. 30 이 연구는 2002년부터 2010년까지 미국과 캐나다에서
49개의 임상센터 및 48개의 PET 센터에서 수행되었다. PET 검사
의 선정기준은 반복적 대비 동측의 count-based OEF ratio가
1.130보다 큰 경우로 정의하였다. 동맥내 카테터혈관조영술로 1)
중상성 내경동맥폐색 및 2) 문화와 적합한 두 개 내/외의 혈관이 있
음을 확인하는 것도 요구되었다. 수술군에서 수술 전후의 혈관학
치료는 COSS 선정의회의사들에 의하여 결정이 되었다. 다른 경우
에서는 모든 환자들이 의사가 원하는 혈관학 치료가 유지되었
다. 위험인자 조절을 위한 목표로 혈압은 130/85 mmHg, 저밀도
콜레스테롤은 100 mg/dL, 증상지의 경우 150 mg/dL, 당화혈
당은 126 mg/dL, 고혈압은 130/85 mmHg, 당뇨병은 200 mg/dL, 고밀도
콜레스테롤은 40 mg/dL로 정의하였다. 31 이 연구는 2년 추적관찰
후에 복용관찰 후에 PET 검사가 이루어졌다. 무작
위배정 후 제3의 간격으로 24개월까지 혹은 연구 종료까지 추
적관찰을 하였다.

수술군이 배정되어 수술을 시행 받은 모든 환자들의 일차
종점을 (1) 수술 후 30일까지의 모든 뇌졸중 및 사망 및 (2) 무
작위배정 후 2년 이내 동측에 발생한 혈류저출증으로 정의하였
다. 수술군 또는 수술군으로 배정되었으나 수술을 받지 않은 환
자들에 대한 일차 종점은 (1) 무작위배정 후 30일이 경과한 시간까
지의 모든 뇌졸중 및 사망 및 (2) 무작위배정 후 2년 이내 동측에 발
생한 혈류저출증으로 정의하였다. 동측의 혈류저출증은 24시간 이
상 지속되는 폐색된 내경동맥 혈관영역의 증상으로 국소화할 수
있는 국소신경학적 증상이 임상적으로 진단된 경우로 정의하였다.
뇌졸중 종점에 대한 최종 종점은 뇌졸중 판정위원회 소속 3명의
연구자들에 의해 이루어졌다.

COSS 연구는 2년 추적관찰을 마친 139명의 환자들을 대상으로
중간 분석 결과 Data, Safety, and Monitoring Board의 결정에
의해 중단되었다. 총 156명의 환자들이 참여하여 97명은 수술군으
로 나머지 98명은 비수술군으로 무작위배정되었다. 24개의 기본
비교 변수들 중 수측기 혈압을 제외하고 P<0.05 수준 이하의 차
이를 보이는 변수들은 없었다. 마지막 추적관찰 방식까지 위험인
자 조절 정도는 두 군에서 모두 유사하였다.

일차 종점에 대한 추적관찰은 99%에서 완료되었다. 모든 일차
종점의 동측의 혈류저출증은 두 군에서 각각 20례의 발생이 있
았다. 일차 종점에 대한 치료병리분석에서 2년 동안의 뇌졸중 발생
률은 수술군에서 0.210, 비수술군에서 0.227 (P=0.78; Figure
3A)이었다. COSS 연구는 90%의 검정력으로 16%의 위험 감소효
과를 확인하기 위해 설계되었다. 최종 종점과 수술의 이득은 95% 초
과의 신뢰도로 배제되었다.

COSS의 어떠한 이차 종점 분석에서도 수술의 이득이 유의하지
않았다. The Randomized Evaluation of Carotid Occlusion and
Neurocognition (RECON) 연구는 COSS 환자들 중 일부 환자들
을 2년간 추적관찰하여 인지기능의 변화를 보았으나 수술군과 비
수술군의 인지기능의 차이는 보이지 않았다(P=0.9). RECON
연구에 등록된 대상자 수는 두 치료 사이에 종합 인지기능 변화 점

<table>
<thead>
<tr>
<th>Table 2. Two-Year Kaplan–Meier Ipsilateral Stroke Rates From Studies Measuring OEF in Patients With Cerebrovascular Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>High OEF (n)</td>
</tr>
<tr>
<td>Grubb et al3</td>
</tr>
<tr>
<td>Yamauchi et al25</td>
</tr>
<tr>
<td>Hokari et al27</td>
</tr>
<tr>
<td>Powers et al28</td>
</tr>
</tbody>
</table>

OEF indicates oxygen extraction fraction.
수에서 0.8 SD 이상의 차이를 확인하기 위한 에비리연구 결과가 제시된 사례에 있어서 50% 신뢰구간은 0.5로 0.8 SD로 중등도 효과는 보였으며, 더 많은 환자들을 모집하였을 경우 하나의 치료가 다른 치료에 비해 경도 또는 중등도의 유의한 효과를 보였을 가능성도 있지만 0의 값에 가까운 점추정치로 이런 가능성은 매우 낮다.

COSS는 2년간의 종점을 분석하기 위해 계획되었다. 중상성 대혈관성경화 환자들을 대상으로 치료한 연구에서 2년 후 뇌졸중의 발생이 대폭 감소함이 보고되었다. EC-IC Bypass Study의 경우 2년 동안의 뇌졸중의 발생률은 20%였으나 4년째까지 추가적인 뇌졸중 발생률은 6% 증가하는 경향이 있었다. 정동맥내막절제술 연구에서는 70~99%의 혈착을 가진 환자들에게서 2년간 뇌졸중의 발생률은 0%였으나, 4년 동안의 추적관찰 결과 뇌졸중의 추가적인 발생은 4%에 불과하였다. 정동맥내막절제술 환자들 중 정상 혈압을 가진 Person 등은 보고에 의하면 2년간의 재발성 혈활류증의 발생률은 12%였으며, 4년 동안에는 14%로 소폭의 증가를 보였다. COSS 연구는 3년 이상 연구하여 수술군에서 추가적인 뇌졸중의 발생이 2~3%로 가장하고 수술군에서 추가적인 뇌졸중의 발생이 전혀 없다고 가정하여도 수술의 유인한 효과는 보이지 않았을 것이다. St Louis Carotid Occlusion Surgery Study에서 COSS의 선정기준을 만족하는 36명의 환자의 추가 분석에서 선정 조건 결정을 위한 count-based OEF ratio의 유의성을 확인하였다. COSS ratio 기준에 맞는 환자들의 동측 뇌졸중 발생 위험(7/18, 39%)은 정량적 OEF 역지 기준인 50% 이상을 가진 환자들의 위험도(4/10, 40%)에 비해 유의한 차이가 있었다. 그러나 COSS ratio 방법은 절대적 OEF 기준(4/9)보다 뇌졸중 발생위험이 있는 환자들을 더 많이(7/9) 확인할 수 있었다.

COSS 수술군에서 수술혈압의 개통성은 30일째 98%, 마지막 추적관찰에서 96%였다. 평균 OEF ratio는 0,5에서 0,8로 개선되었다. 수술군의 20례 뇌졸중 중에서 14례는 수술 후 30일 이내에 발생하였다. 이러한 수술 전후의 뇌졸중 발생률은 15%로 EC-IC Bypass Trial의 결과와 유의한 차이가 없었다. 수술 후 뇌졸중 중 12례는 수술 후 2주 이내에 발생하였다. 이 12례의 뇌졸중을 봤던 남은 수술군에서의 뇌졸중의 발생률은 0.09로 비수술군에 비해 유의하게 낮았다.(P=0.02; Figure 3B)

COSS 연구는 정동맥내막절제의 치료에 있어 뇌혈류역학의 중요성을 보여주었다. 병태생리학적 가설은 옳았다. EC-IC 우회술에 의한 혈류역학의 개선은 뇌졸중의 위험을 감소시켰다. 그러나 치료
역시 질병만큼이나 나빴다. 수술 전후의 뇌졸중의 발생이 많아 치료 효과를 상쇄하였다. 다각적인 사후분석에서도 수술 전후의 뇌졸중 위험이 증가하였고 치료 효과를 상쇄하였다. 다각적인 사후분석에서도 수술 전후의 뇌졸중 위험 증가를 예측할 수 있는 환자의 특성, 시술관련 및 집도 의사의 특성을 파악하는데 실패하였다.

COSS 연구는 증상성 경동맥폐색을 가진 환자들, 심지어는 OEF가 증가되어 있는 환자들에서 EC-IC 우회술이 내과적인 치료와 비교하여 뇌졸중의 예방에 효과가 없음을 보여주었다. 그러나 이러한 환자들에서 적절한 혈압조절이 이루어졌는지 혹은 혈관 사례를 보존하여 뇌졸중 예방을 위해 높은 혈압이 필요하였는지에 대해 이견이 있다. 이러한 문제들을 다루기 위해 저자들은 COSS 연구의 비수술군 자료를 분석하였다.

이러한 문제들을 다루기 위해 저자들은 COSS 연구의 비수술군 자료를 분석하였다. 98명의 비수술군 환자들 중에서 91명이 분석에 포함되었다. 3명은 무작위배정 후 혈압 기록이 없었고, 4명은 30~35일 추적관찰에서의 혈압 측정 이전에 동측의 허혈뇌졸중이 확인되어 분석에서 제외되었다. COSS의 목표혈압인 130/85 이하로 조절된 41명과 혈압이 높았던 50명에서의 동측 허혈뇌졸중 발생을 비교하였다. 연구의 중점은 동측 허혈뇌졸중을 경험한 환자들의 경우에는 뇌졸중 발생에 기여한 혈압만을 사용하였다. 다른 환자들은에서는 측정된 모든 혈압 측정치를 사용하였다. 연구의 시작에서부터 무작위배정까지의 기간을 제외하고 추적관찰 기간 동안 기본적인 특징 및 내과적 치료에 대해 두 군에서 차이가 없었으며, 연구 동록 후 무작위배정까지 시간에 차이가 있었으나 이는 뇌졸중의 발생에 한 유인한 예측인자가 아니었다 (P=0.32).

무작위배정 2년 이내에 발생한 16례 동측 허혈뇌졸중 중, 3례는 평균 추적 혈압이 135/85 mmHg 이하인 41명의 환자들에서 발생하였고, 나머지 13례는 평균 추적 혈압이 135/85 mmHg를 초과한 50명의 환자들 중에서 발생하였다(위험도, 3.74; 95% CI, 1.07~13.15, P=0.027, Figure 4). 2년 간의 Kaplan–Meier 추정 발생률은 각각 0.082 및 0.304였다. 매 추적 방문시에 적어도 1개 이상의 항고혈압제를 항상 복용하고 있었던 52명의 환자들로 분석을 한 경우, 130/85 mmHg 이하 환자군 23명 중 2례의 뇌졸중의 발생이 있었고, 130/85 mmHg 초과 환자군 32명 중 10례의 뇌졸중이 발생하였다(위험도, 3.78; 95% CI, 0.83~17.30, P=0.065, log–rank). 이와 같이 동측 고혈압을 조절하였던 하위 그룹에서의 뇌졸중 발생 위험도 3.78은 일차분석에서 얻은 3.74와 상당히 동일한 수치였다. J 커브 효과에 대한 증거는 없었다.

이러한 연구결과들은 또한 심층적 자료의 필요성을 더 강조하고 있다. 뇌졸중의 발생에 대해 당연한 것과 같이 여겨진 기전에 기초한 치료의 효과가 너무 자주 잘못된 결론에 도달하는 경우가 많다. 뇌졸중의 병태생리학적 및 다양한 치료의 생물학적 효과에 대한 연구들은 임상시험에 대한 다양한 이유를 제공할 수는 있으나 개별적인 환자들의 치료를 선택하는데 있어 실험적인 데이터를 대체할 수는 없다.

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Disclosures
None.

References

Key Words: brain ischemia • carotid artery diseases • extracranial-intracranial arterial bypass • hypertension • positron emission tomography • stroke