Failure of Cerebral Hemodynamic Selection in General or of Specific Positron Emission Tomography Methodology? Carotid Occlusion Surgery Study (COSS)

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Background and Purpose—The Carotid Occlusion Surgery Study (COSS) was an improvement over the Extracranial–Intracranial Bypass Study, which did not utilize physiological selection. To assess possible reasons for early closure of the COSS trial, we reviewed COSS methods used to identify high-risk patients and compared results with separate quantitative data.

Methods—Increased oxygen extraction fraction (OEF) by positron emission tomography is a gold standard for ischemia, but the specific thresholds and equivalency of the semiquantitative OEF ratio utilized in COSS and quantitative OEF are at issue.

Results—The semiquantitative hemispheric OEF ratio used in COSS did not identify the same group of patients as did quantitative OEF using a threshold of 50%.

Conclusions—The failure of COSS is likely caused by a failure of the semiquantitative, hemispheric OEF ratio method rather than by the selection for bypass based on hemodynamic compromise. (Stroke. 2011;42:00-00.)

Key Words: cerebrovascular reserve • carotid occlusion • oxygen extraction fraction • positron emission tomography

The Carotid Occlusion Surgery Study (COSS)1,2 represented a methodological advance over the failed Extracranial–Intracranial (EC–IC) Bypass Study,3 where patients were not screened for hemodynamic compromise. The COSS trial1 screened patients with hemodynamic compromise by semiquantitative oxygen extraction fraction (OEF) hemispheric ratio by positron emission tomography, an independent predictor of increased stroke risk in patients with occlusive vascular disease.4 COSS appeared to have addressed the major criticisms of the failed EC–IC Bypass trial, but the latter was prematurely terminated. There were 98 patients randomized to medical treatment and 97 patients randomized to EC–IC bypass, of which 93 patients had surgery. The 2-year stroke rate in the medical group was 23% and 21% in the surgical group.2 These stroke rates are similar to the 18% medical and 20% surgical in the original bypass trial.3 We review the methods used in COSS to assess possible reasons for its failure.

Thresholds and Ratio-Based Techniques
Quantitative OEF to define ischemic thresholds based on 95% CI shows that increased OEF is an independent predictor of increased stroke risk.5,6 In 40 symptomatic patients with occlusive vascular disease and 10 normal controls studied by quantitative OEF, Yamauchi et al6 reported OEF of 42.6±5.1% (mean±SD) in 20 normal hemispheres and a 95% CI OEF threshold of 53.3%. In 5 years, there were 5/7 strokes in high-OEF patients (71%) and 6/33 strokes in normal-OEF patients (18%). Hokari5 measured quantitative OEF in 9 volunteers with OEF of 40.0±5% (mean±SD) and threshold of 50% (mean±2SD). At 3.1 years, strokes occurred in 3/9 of high-OEF patients (33%) and 0/11 of normal-OEF patients. These studies support the threshold of around 50% that we have used.7,8 COSS was based on the 1998 study by Grubb et al,4 where stroke risk was assessed in unilateral carotid occlusion using hemispheric, semiquantitative OEF ratio by a count rate method.9 The range of ratios in 18 normal volunteers was 0.914 to 1.082 and the upper limit of 1.082 used as the threshold for increased OEF; this is roughly equivalent to an absolute threshold of 43%, well below the 50% threshold of quantitative OEF. Using this threshold, strokes occurred in 12/39 of patients (31%) with elevated OEF ratio compared with 3/42 patients (7%) with normal OEF ratio. Yamauchi6 evaluated the OEF ratio method and reported 6/14 strokes in patients with OEF asymmetry outside of the 95% CI (43%), compared with 5/26 of patients without OEF asymmetry (19%); the latter was not significant, compared with significant quantitative data in the same group. Derdeyn

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et al. compared absolute OEF values in the patients from Grubb’s study with 2 ratio-based methods; the quantitative OEF hemispheric ratio method used by Yamauchi and a semiquantitative, count-based hemispheric OEF ratio. Mean OEF in the 18 volunteers was $41 \pm 9\%$ (mean$\pm$SD). The authors quote a 95% CI threshold in normals of 44%, which predicted 8/9 strokes. The actual 95% CI based on their data should have been 58.6% (mean$\pm$1.96*SD), and would have identified only 3/9 strokes.

The Quantitative Occlusive Vascular Disease Study (QUOVADIS) compared the COSS semiquantitative hemispheric ratio method with quantitative OEF with their respective thresholds (Figure 1 shows comparison of the regions of interest used) in 14 patients with unilateral carotid occlusion; they found that these methods do not identify the same patients (Figure 2; unpublished results) which may also be partly due to differences in VOI used. These preliminary data suggest that the count rate ratio method does not identify adequately patients with hemodynamic compromise.

Powers and colleagues had good reason to conduct COSS using a semiquantitative ratio method. First, of the 70+ positron emission tomography facilities in the United States, only a few sites are able to perform quantitative OEF. Second, quantitative OEF requires arterial catheterization, which is problematic in patients receiving anticoagulants. Compromises were made in COSS to increase enrollment. First, the threshold was lowered from 1.16 to 1.12. Second, up to 12% of patients with contralateral stenosis $\geq 60\%$ or occlusion was allowed.

Powers suggested that the lower-than-expected stroke risk in this group may be because of improvements in medical treatment, such as statins. Without stroke data from the patients deemed low-risk in their study, this explanation cannot be evaluated, and it seems equally likely that a
high-risk group was not identified by the positron emission tomography methodology, especially given the similar stroke rates to those in the initial bypass trial.

Conclusions
The failure in COSS was likely caused by failure to select patients at high risk for stroke. It seems that we have not yet answered the question as to whether EC–IC bypass has a role in the care of advanced occlusive vascular disease patients.

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Disclosures
None.

References
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