Published in final edited form as:
Stroke. 2012 July ; 43(7): 1988–1991. doi:10.1161/STROKEAHA.112.650119.

Revascularization of Collaterals for Hemodynamic Stroke: Insight on pathophysiology from the Carotid Occlusion Surgery Study

Jose G. Romano, MD[1] and **David S. Liebeskind, MD**[2]

[1]University of Miami, Miller School of Medicine, Division of Cerebrovascular Diseases

[2]University of California–Los Angeles Stroke Center, Los Angeles, CA

Keywords

brain ischemia; carotid artery; cerebral hemodynamics; EC-IC bypass; PET

Carotid atherosclerosis accounts for up to 15% of all strokes[1] and approximately 15–20,000 have a symptomatic carotid occlusions in the United States each year.[2] Furthermore, recurrent ipsilateral stroke in unselected patients with carotid occlusion affects 2.1–3.8% on an annual basis.[3,4,5] 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;[6,7] 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.[8] 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.[4,9] 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 (OEF) will maintain tissue metabolism (stage 2 hemodynamic impairment). Thereafter, insufficient flow and oxygen delivery may result in energetic failure and infarction.[10]

The Carotid Occlusion Surgery Study (COSS)[11] provides important data on the role of collaterals in ischemic stroke. COSS directly studied the role of collaterals in stroke. While

Correspondence to: Jose G. Romano.

Contact information: Jose G. Romano, 1120 NW 14th Street, Suite 1357, Miami FL 33136, Tel 305-243-2336, Fax 305-243-7081, jromano@med.miami.edu

collateral flow is a beneficial compensatory mechanism against ischemia, the ischemic insult itself can lead to collateral recruitment.[12] 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;[13] 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.[14] 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.[15] Indeed, systematic analysis confirmed these findings; amongst 21 trials and 2591 patients, no benefit in stroke, death and death and dependency was noted for the procedure.[16] However, a number of smaller studies and series reported a high risk of stroke in patients with observed impaired hemodynamics tested with various techniques,[17] with an overall estimated annual risk of ipsilateral stroke of 9.5%.[3] Moreover, small non-randomized studies suggested a benefit of EC-IC bypass surgery in those with impaired hemodynamic distal to the occlusion.[18] The Japanese EC-IC Trial (JET) randomized patients with hemodynamic impairment diagnosed by single photon emission computed tomography (SPECT) CBF with an acetazolamide challenge to EC-IC bypass or medical therapy; an interim analysis reported more ischemic events in the medical arm.[19,20]

As a consequence of the finding of higher risk in the presence of impaired hemodynamics, the Carotid Occlusion Surgery Study (COSS) was designed to test the specific hypothesis that hemodynamic impairment with increased OEF on positron emission tomography (PET) 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 TIA.[11] 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) vs. 40% in the medical arm.[21,22] However, after 195 patients had been enrolled in COSS, the study was terminated for futility. Although the OEF improved at a follow-up PET 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% vs. 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 below 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 to an estimated 40% based on previous studies.[21,22] This is in line with recent trials where 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, where the observed rate of 5.8% for stroke and death at 30 days in recently symptomatic intracranial atherosclerotic disease[23] was lower than the estimated 10.7% from a subanalysis of similar patients enrolled in the Warfarin Aspirin Symptomatic Intracranial Disease (WASID) trial.[24] 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 LDL 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[25] and more robust collateral flow.[26] In addition, statins may prevent progression of the contralateral carotid stenosis;[27] 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 in order to avoid distal hypoperfusion. Subanalysis of the WASID study of patients with intracranial 50–99% stenosis revealed that elevated blood pressure above 160 mm Hg during the conduct of the trial was associated with a greater risk of ipsilateral risk, while levels below 120 mm Hg did not increase risk.[28] 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 while 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 greater than 1.13 to select patients. The original study design called for a higher ratio of more than 1.16, but this was lowered to improve enrollment. This ratio comes from prior studies showing that the upper confidence interval 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 11/39 patients with impaired OEF vs. 2/42 with normal OEF.[21] Hemispheric ratios were deemed equivalent to quantitative methods by some investigators.[29] This premise was recently reviewed by Carlson and colleagues;[30] they argue that the OEF ratio method, and the threshold employed, does not adequately identify a cohort with hemodynamic compromise. In general, the imaging selection employed 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 as it does not consider regional variations of hypoperfusion that may determine stroke recurrence and severity.[31] 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 PET study found improvement in OEF and cerebral blood flow that was proportional to longer time of follow-up.[32] Therefore, the methodology to identify a high-risk group and the fluctuating nature of the hemodynamic compromise are challenges to any study employing 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.[33] 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.[34] 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.[35,36] 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.[37,38] Deep white matter perfusion can be difficult to quantitate;[39] similar values have been described for the white matter in the territory of an occluded carotid compared to the contralateral patent territory.[40] 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.[41] 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 to healthy controls.[42] 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 14/93 (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.[15] 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.[23] 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[43] or the less invasive encephaloduroarteriosynangiosis[44] 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 PET-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 dataset 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 employed in a multicenter setting. As 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.

Acknowledgments

Disclosures:

1. Jose G. Romano: Site PI, SAMMPRIS study (NIH/NINDS); site PI SPS3 Study (NIH/NINDS); Scientific Advisory Board, NovaVision
2. David S. Liebeskind: Consultant to Concentric Medical and CoAxia; supported by NIH/NINDS K23NS054084, P50NS044378, K24NS072272

References

1. Schulz UG, Rothwell PM. Differences in vascular risk factors between etiological subtypes of ischemic stroke: importance of population-based studies. Stroke. 2003; 34:2050–2059. [PubMed: 12829866]
2. Flaherty ML, Flemming KD, McClelland R, Jorgensen NW, Brown RD Jr. Population-based study of symptomatic internal carotid artery occlusion: incidence and long-term follow-up. Stroke. 2004; 35:e349–e352. [PubMed: 15232124]
3. Klijn CJ, Kappelle LJ, Tulleken CA, van Gijn J. Symptomatic carotid artery occlusion. A reappraisal of hemodynamic factors. Stroke. 1997; 28:2084–2093. [PubMed: 9341723]
4. Klijn CJ, van Buren PA, Kappelle LJ, Tulleken CA, Eikelboom BC, Algra A, et al. Outcome in patients with symptomatic occlusion of the internal carotid artery. Eur J Vasc Endovasc Surg. 2000; 19:579–586. [PubMed: 10873724]
5. Persoon S, Luitse MJ, de Borst GJ, van der Zwan A, Algra A, Kappelle LJ, et al. Symptomatic internal carotid artery occlusion: a long-term follow-up study. J Neurol Neurosurg Psychiatry. 2011; 82:521–526. [PubMed: 20884678]
6. Barnett HJ. Delayed cerebral ischemic episodes distal to occlusion of major cerebral arteries. Neurology. 1978; 28:769–774. [PubMed: 567293]
7. Klijn CJ, Kappelle LJ. Haemodynamic stroke: clinical features, prognosis, and management. Lancet Neurol. 2010; 9:1008–1017. [PubMed: 20864053]
8. Caplan LR, Hennerici M. Impaired clearance of emboli (washout) is an important link between hypoperfusion, embolism, and ischemic stroke. Arch Neurol. 1998; 55:1475–1482. [PubMed: 9823834]
9. Bogousslavsky J, Regli F. Borderzone infarctions distal to internal carotid artery occlusion: prognostic implications. Ann Neurol. 1986; 20:346–350. [PubMed: 3767318]
10. Powers WJ. Cerebral hemodynamics in ischemic cerebrovascular disease. Ann Neurol. 1991; 29:231–240. [PubMed: 2042939]
11. Powers WJ, Clarke WR, Grubb RL Jr, Videen TO, Adams HP Jr, Derdeyn CP, et al. Extracranial-intracranial bypass surgery for stroke prevention in hemodynamic cerebral ischemia: the Carotid Occlusion Surgery Study randomized trial. JAMA. 2011; 306:1983–1992. [PubMed: 22068990]
12. Liebeskind DS. Collateral circulation. Stroke. 2003; 34:2279–2284. [PubMed: 12881609]
13. Liebeskind DS, Cotsonis GA, Saver JL, Lynn MJ, Cloft HJ, Chimowitz MI, et al. Collateral circulation in symptomatic intracranial atherosclerosis. J Cereb Blood Flow Metab. 2011; 31:1293–1301. [PubMed: 21157476]
14. Yasargil MG, Yonekawa Y. Results of microsurgical extraintracranial arterial bypass in the treatment of cerebral ischemia. Neurosurgery. 1977; 1:22–24. [PubMed: 615948]

15. The EC/IC Bypass Study Group. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke. Results of an international randomized trial. N Engl J Med. 1985; 313:1191–1200. [PubMed: 2865674]
16. Fluri F, Engelter S, Lyrer P. Extracranial-intracranial arterial bypass surgery for occlusive carotid artery disease. Cochrane Database Syst Rev. 2010:CD005953. [PubMed: 20166076]
17. Garrett MC, Komotar RJ, Starke RM, Merkow MB, Otten ML, Sciacca RR, et al. The efficacy of direct extracranial-intracranial bypass in the treatment of symptomatic hemodynamic failure secondary to athero-occlusive disease: a systematic review. Clin Neurol Neurosurg. 2009; 111:319–326. [PubMed: 19201526]
18. Ishikawa T, Yasui N, Suzuki A, Hadeishi H, Shishido F, Uemura K. STA-MCA bypass surgery for internal carotid artery occlusion--comparative follow-up study. Neurol Med Chir (Tokyo). 1992; 32:5–9. [PubMed: 1375987]
19. Ogasawara K, Ogawa A. JET study (Japanese EC-IC Bypass Trial). Nihon Rinsho. 2006; 64:524–527. [PubMed: 17461199]
20. Ogasawara K, Kikuchi H, Yamadori S, Hayashida K, Mori E, Kirino, et al. Japanese EC–IC Bypass Trial (JET Study): the second interim analysis. Surg Cereb Stroke. 2002; 30:434–437.
21. Grubb RL Jr, Derdeyn CP, Fritsch SM, Carpenter DA, Yundt KD, Videen TO, et al. Importance of hemodynamic factors in the prognosis of symptomatic carotid occlusion. JAMA. 1998; 280:1055–1060. [PubMed: 9757852]
22. Derdeyn CP, Gage BF, Grubb RL Jr, Powers WJ. Cost-effectiveness analysis of therapy for symptomatic carotid occlusion: PET screening before selective extracranial-to-intracranial bypass versus medical treatment. J Nucl Med. 2000; 41:800–807. [PubMed: 10809195]
23. Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med. 2011; 365:993–1003. [PubMed: 21899409]
24. Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. N Engl J Med. 2005; 352:1305–1316. [PubMed: 15800226]
25. Forteza A, Romano JG, Campo-Bustillo I, Campo N, Haussen DC, Gutierrez J, et al. High-Dose Atorvastatin Enhances Impaired CerebralVasomotor Reactivity. J Stroke Cerebrovasc Dis. 2011 Feb 18. [Epub ahead of print] PubMed PMID: 21334223.
26. Ovbiagele B, Saver JL, Starkman S, Kim D, Ali LK, Jahan R, et al. Statin enhancement of collateralization in acute stroke. Neurology. 2007; 68:2129–2131. [PubMed: 17562834]
27. Hegland O, Kurz MW, Munk PS, Larsen JP. The effect of statin therapy on the progression of carotid artery stenosis in relation to stenosis severity. Acta Neurol Scand. 2010; 121:11–15. [PubMed: 19919642]
28. Turan TN, Cotsonis G, Lynn MJ, Chaturvedi S, Chimowitz M. Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Trial Investigators. Relationship between blood pressure and stroke recurrence in patients with intracranial arterial stenosis. Circulation. 2007; 115:2969–2975. [PubMed: 17515467]
29. Derdeyn CP, Videen TO, Yundt KD, Fritsch SM, Carpenter DA, Grubb RL, et al. Variability of cerebral blood volume and oxygen extraction: stages of cerebral haemodynamic impairment revisited. Brain. 2002; 125:595–607. [PubMed: 11872616]
30. Carlson AP, Yonas H, Chang YF, Nemoto EM. Failure of cerebral hemodynamic selection in general or of specific positron emission tomography methodology?: Carotid Occlusion Surgery Study (COSS). Stroke. 2011; 42:3637–3639. [PubMed: 21960571]
31. Bang OY, Saver JL, Alger JR, Starkman S, Ovbiagele B, Liebeskind DS, et al. Determinants of the distribution and severity ofhypoperfusion in patients with ischemic stroke. Neurology. 2008; 71:1804–1811. [PubMed: 19029520]
32. Derdeyn CP, Videen TO, Fritsch SM, Carpenter DA, Grubb RL Jr, Powers WJ. Compensatory mechanisms for chronic cerebral hypoperfusion in patients with carotid occlusion. Stroke. 1999; 30:1019–1024. [PubMed: 10229738]

33. Hendrikse J, Petersen ET, Chèze A, Chng SM, Venketasubramanian N, Golay X. Relation between cerebral perfusion territories and location of cerebral infarcts. Stroke. 2009; 40:1617–1622. [PubMed: 19299630]
34. Hendrikse J, van der Grond J, Lu H, van Zijl PC, Golay X. Flow territory mapping of the cerebral arteries with regional perfusion MRI. Stroke. 2004; 35:882–887. [PubMed: 14988567]
35. van Laar PJ, van der Grond J, Bremmer JP, Klijn CJ, Hendrikse J. Assessment of the contribution of the external carotid artery to brain perfusion in patients with internal carotid artery occlusion. Stroke. 2008; 39:3003–3008. [PubMed: 18688004]
36. van Laar PJ, Hendrikse J, Klijn CJ, Kappelle LJ, van Osch MJ, van der Grond J. Symptomatic carotid artery occlusion: flow territories of major brain-feeding arteries. Radiology. 2007; 242:526–534. [PubMed: 17255422]
37. Sanossian N, Ovbiagele B, Saver JL, Alger JR, Starkman S, Kim D, et al. Leukoaraiosis and collaterals in acute ischemic stroke. J Neuroimaging. 2011; 21:232–235. [PubMed: 20977524]
38. Bang OY, Saver JL, Buck BH, Alger JR, Starkman S, Ovbiagele B, et al. Impactof collateral flow on tissue fate in acute ischaemic stroke. J Neurol Neurosurg Psychiatry. 2008; 79:625–629. [PubMed: 18077482]
39. van Gelderen P, de Zwart JA, Duyn JH. Pittfalls of MRI measurement of white matter perfusion based on arterial spin labeling. Magn Reson Med. 2008; 59:788–795. [PubMed: 18383289]
40. Bokkers RP, Bremmer JP, van Berckel BN, Lammertsma AA, Hendrikse J, Pluim JP, et al. Arterial spin labeling perfusion MRI at multiple delay times: a correlative study with H(2)(15)O positron emission tomography in patients with symptomatic carotid artery occlusion. J Cereb Blood Flow Metab. 2010; 30:222–229. [PubMed: 19809464]
41. Conklin J, Fierstra J, Crawley AP, Han JS, Poublanc J, Silver FL, et al. Mapping white matter diffusion and cerebrovascular reactivity in carotid occlusive disease. Neurology. 2011; 77:431–438. [PubMed: 21775744]
42. Bokkers RP, van Osch MJ, Klijn CJ, Kappelle LJ, Hendrikse J. Cerebrovascular reactivity within perfusion territories in patients with an internal carotid artery occlusion. J Neurol Neurosurg Psychiatry. 2011; 82:1011–1016. [PubMed: 21386110]
43. van Doormaal TP, Klijn CJ, van Doormaal PT, Kappelle LJ, Regli L, Tulleken CA, et al. High-flow extracranial-to-intracranial excimer laser-assisted nonocclusive anastomosis bypass for symptomatic carotid artery occlusion. Neurosurgery. 2011; 68:1687–1694. [PubMed: 21389885]
44. Komotar RJ, Starke RM, Otten ML, Merkow MB, Garrett MC, Marshall RS, et al. The role of indirect extracranial-intracranial bypass in the treatment of symptomatic intracranial atheroocclusive disease. J Neurosurg. 2009; 110:896–904. [PubMed: 19199456]