EDITORS’ INTRODUCTION

Trans-Atlantic Debate: Is Carotid Artery Disease Responsible for Perioperative Strokes after Coronary Artery Bypass Surgery?*

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The coronary and extracranial carotid vascular beds are often simultaneously affected by significant atherosclerotic disease, and stroke is one of the potential major complications of coronary artery surgery. As a result, there is no shortage of reports in the vascular surgery literature describing simultaneous coronary and carotid artery revascularizations. Generally these reports have found this combination of operations safe, but have stopped short of proving that it is necessary. Intuitively, simultaneous carotid endarterectomy and coronary artery bypass surgery could be justified if the majority of perioperative strokes were the result of a significant carotid stenosis, either directly or indirectly. At first glance this appears to be a fairly straightforward issue, however much of the evidence on both sides of the argument is circumstantial. One significant problem in analyzing outcome by choice of treatment in patients presenting with both coronary and carotid disease is the multiple potential causes of stroke in coronary bypass patients which include hemorrhage, and atheroemboli from aortic atheromas during clamping. But this controversial subject is now open to discussion and our debaters have been given the challenge to clarify the evidence to justify their claims.

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Part One: For the Motion
Carotid Disease is Rarely Responsible for Stroke after Coronary Bypass Surgery

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Significant carotid stenoses (SCS, ≥ 50% stenosis in diameter) are associated with an increased risk of postoperative stroke following coronary artery bypass grafting (CABG) surgery.1–3 Evidence in support of this statement is robust and compelling. The data implicating SCS as the primary cause of the increased stroke risk are neither, even though there seems to be a trend of higher incidence of stroke with more severe carotid stenosis.1,3–5 In our opinion, the impression of a causal relationship between stroke risk and asymptomatic SCS in cardiac surgery has been largely based on a few false assumptions. To bring these to light, we frame our discussion around these areas to test their validity.

Assumption one: The incidence of SCS is high and most perioperative stroke during CABG occurs in the subgroup of patients with SCS.

Data gleaned from preoperative carotid ultrasonography would suggest the contrary. The incidence of SCS is fairly low, ranging from 2% to 22% with an average of 8 to 9% in patients undergoing CABG.3,6 Therefore, in the overwhelming majority of operative patients SCS is not implicated in the mechanism of perioperative stroke. Analysis of the status of the carotid arteries in patients with perioperative stroke also bears this out. For example, Wijdicks et al reported that among the 13 patients with post-

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operative stroke who also had carotid evaluation, only one patient had an ipsilateral SCS.\textsuperscript{7} In one prospective study, 34 of the 38 perioperative strokes (89\%) occurred in patients with less than 80\% carotid stenosis.\textsuperscript{8} Our recent retrospective analysis indicated that 58 of the 76 perioperative strokes (76\%) occurred in patients without SCS.\textsuperscript{8} The low incidence of SCS in patients undergoing CABG suggests it is unlikely to be a major contributor to the perioperative stroke risk.

**Assumption two:** The perioperative stroke in patients undergoing CABG occurs primarily in the territory of carotid artery.

To the contrary, analysis of the laterality and regional distribution of perioperative strokes on brain imaging indicates that the majority of such strokes occur in the territory of multiple vessels, the hemisphere contralateral to existing carotid stenosis or the distribution of vertebrobasilar arteries. For example, Hise et al reported that 8 of 15 patients (53\%) with an evidence of acute infarction on CT scan demonstrated a stroke in the posterior cerebral artery distribution or the cerebellum.\textsuperscript{10} Barbut et al examined 19 patients with infarction on CT scan. Fifteen patients (79\%) and 14 patients (74\%) had stroke in the cerebellum and posterior cerebral artery territories, respectively.\textsuperscript{11} Wityk et al used MRI to examine a group of 14 patients. Nine of 10 patients (90\%) with acute lesions on diffusion weighted imaging (DWI) showed multiple strokes in bilateral hemispheres.\textsuperscript{12} In one of the most comprehensive reviews to date, Naylor and colleagues concluded that primary carotid thrombo-embolic disease alone is not responsible for up to nearly 60\% of strokes based on CT scan or autopsy studies.\textsuperscript{3} Such a distribution pattern of perioperative stroke also holds true for patients with SCS.\textsuperscript{9,13,14} Therefore the majority of perioperative strokes occur outside a single carotid territory. Since less than 3\% of patients undergoing CABG have bilateral SCS,\textsuperscript{3} neither unilateral nor bilateral carotid stenosis is likely responsible for the majority of perioperative stroke based on the infarction territory.

**Assumption three:** Although SCS could be a small contributor to perioperative stroke risk, preoperative carotid revascularization would eliminate stroke in some of these patients and hence should be offered.

Data from the NASCET trial suggested that in patients with SCS, stroke could still be due to small vessel lacunae, thrombotic infarction due to intracranial diseases or even cardioembolic infarction but carotid endarterectomy should not help to prevent such strokes.\textsuperscript{15} The incidence of lacunar infarction and intracranial atherosclerosis may not be trivial in patients undergoing cardiac surgery. For example, Libman et al reported that 16\% of the postoperative stroke following cardiac surgery can be lacunar syndromes secondary to small vessel disease.\textsuperscript{16} Yoon et al reported that 30\% of patients undergoing CABG had stenosis in the intracranial arteries. In multivariate analysis, the presence of intracranial disease was also found to have an independent association with the development of perioperative strokes.\textsuperscript{17}

Furthermore, existing data strongly suggest that most of the perioperative strokes are cardioembolic mainly due to the presence of aortic atherosclerosis and/or atrial fibrillation. Using intra-operative echocardiography, Katz et al identified protruding atheroma in the aortic arch in 23 of 130 patients undergoing cardiac surgery. Five of the 23 patients (22\%) developed a perioperative stroke while the stroke risk was only 2\% in patients without such atheroma.\textsuperscript{18} Gardner and colleagues reported that in patients with intra-operative evidence of severe aortic atherosclerosis, the perioperative stroke risk jumped approximately four fold higher to 14\%.\textsuperscript{19} A multivariable logistic regression analysis on a multicenter database of 19,224 CABG patients suggested that calcified aorta was the single most significant variable associated with perioperative stroke with an odds ratio (OR) of 3.01, whereas the presence of carotid disease was also associated with an OR of 1.59.\textsuperscript{20} In another multivariate analysis, calcified aorta was an independent predictor of perioperative stroke but SCS was not.\textsuperscript{6} Microembolism from the aorta or heart to the brain has been well documented by multiple studies using Transcranial Doppler, correlating with the onset and releasing of aorta clamping.\textsuperscript{21-23} Furthermore, D’Agostino and colleagues reported that atrial fibrillation occurred in approximately 30\% of post-operative patients, and perioperative stroke occurred in 4.6\% of patients with atrial fibrillation compared with 1.5\% patients without.\textsuperscript{13} Lahtinen et al discussed that recurrent atrial fibrillation preceded symptoms of cerebral ischemia in 36.5\% of patients with perioperative stroke by a mean of 21.3 h.\textsuperscript{24} In the subgroup of high-risk patients with new post-operative DWI lesions, 75\% also had post-operative atrial fibrillation.\textsuperscript{25} Therefore, in patients undergoing CABG, cardioembolism and probably intracranial arterial stenosis or small vessel disease are the primary mechanisms of stroke. Preoperative cervical carotid revascularization would not prevent these events.

**Assumption four:** SCS reduces distal internal carotid blood flow and hence puts the ipsilateral cerebral hemisphere at risk of ischemia during cardiopulmonary bypass. The carotid plaque at the bifurcation may either cause a regional hypoperfusion or act as an embolic source in causing a stroke. So far there are no data to suggest that carotid plaque becomes a more active source of embolism during CABG. Although often asserted as facts, there is very little evidence to suggest that unilateral asymptomatic SCS reduces ipsilateral hemisphere blood flow significantly.

Perioperative strokes include both border zone (watershed) and territorial infarctions on brain imaging. Watershed infarctions are now more readily identified on MRI studies.\textsuperscript{26,27} While the development of watershed infarction is frequently attributed to low cerebral flow, this has been challenged repeatedly by autopsy studies. Such watershed infarction may occur without SCS or documented intra-operative hypotension.\textsuperscript{28} Embolic calcified material or cholesterol crystals were detected in vessels adjacent to watershed infarction in patients after cardiac surgery.\textsuperscript{29,30} Watershed infarctions can be caused by microemboli consisting of atheromatous material or tumor masses lodged preferentially in the brain border zone.\textsuperscript{31} Angiography in three patients with watershed infarction did not show SCS in two patients and revealed an embolic occlusion of the arterial branch corresponding to the site of the infarct in another patient.\textsuperscript{28} These brain border zones appear to be favored destinations for microemboli.

On the other hand, there is no compelling evidence that cerebral blood flow is significantly reduced distal to SCS in
association with cardiopulmonary bypass. Lundar and colleagues described that blood flow in the middle cerebral and internal carotid arteries actually increased rather than decrease during cardiopulmonary bypass as a result of hemodilution.\textsuperscript{32,33} In a study using positron emission tomography in patients with asymptomatic unilateral SCS, most patients had normal cerebral flow.\textsuperscript{34} Hupperts et al reported 10 of 37 patients with perioperative strokes had infarction in the vascular border zones. Registered periods of hypotension, lowest mean arterial pressure and lowest hematocrit were similar among the subgroups of patients with border zone, territorial infarction or no infarction.\textsuperscript{35}

Therefore in patients with unilateral asymptomatic SCS undergoing CABG, the ipsilateral hemispheric blood flow is unlikely to be significantly altered in most patients if significant and prolonged hypotension can be avoided perioperatively. Furthermore, it is arguable whether carotid revascularization would significantly improve cerebral blood flow. Waaijer et al studied cerebral perfusion in a group of 36 patients with SCS and a mean degree of stenosis of 86%. On an average there was merely a 10% increase in cerebral blood flow following carotid stenting or endarterectomy.\textsuperscript{36}

**Assumption five:** Preoperative carotid endarterectomy is necessary to avoid carotid territory stroke in patients undergoing CABG.

To the contrary, studies suggest that a conservative management of SCS can be safe for patients undergoing cardiac surgery. Gerraty and colleagues reported 53 patients with SCS or occlusion (28 patients with 80% greater stenosis or occlusion) underwent vascular or cardiac surgeries. None suffered an ipsilateral perioperative stroke despite 22 patients experiencing a period of hypotension.\textsuperscript{37} Safa et al reported that in a group of 94 patients with SCS undergoing cardiac surgery 71 patients had unilateral (80–99%), 17 patients had bilateral (80–99%), and six patients had unilateral SCS together with a contralateral carotid occlusion. Only one patient developed a perioperative stroke in the hemisphere contralateral to the carotid stenosis.\textsuperscript{38} Ghosh et al reported 50 patients with asymptomatic SCS (20 patients with bilateral 80–99% disease, and five patients with unilateral occlusion and 70–79% contralateral stenosis) underwent CABG with optimal medical prevention. No stroke occurred within 30 days of surgery.\textsuperscript{39} Baiou et al reported a total of 61 cardiac procedures in patients with unilateral asymptomatic 70–99% stenosis (56% patients also had a contralateral 50–69% stenosis). No strokes occurred in the 30-day post-operative period.\textsuperscript{40} Although larger confirmation studies are still needed, it appears safe and effective in most cases to conservatively manage CABG patients with SCS without the need for preoperative corrective carotid revascularization.

In summary, there is compelling evidence to conclude that SCS is not the primary cause of most strokes following CABG surgery. This is consistent with the analysis by Stamou and colleagues who reported that only 6% of the perioperative 333 strokes were secondary to carotid disease.\textsuperscript{41} This was also borne out in our own single center retrospective analysis of 4335 patients undergoing cardiac surgeries. Of the 76 patients with perioperative strokes, 72 (95%) were not related to SCS at the bifurcation.\textsuperscript{9}

**Does SCS play a significant role in causing stroke following CABG under any circumstance? Exceptions might exist in patients with symptomatic SCS, patients with bilateral critically severe carotid disease (> 80% diameter reduction), and patients with recent carotid occlusion. Overall 95% of the carotid stenosis in patients undergoing CABG is asymptomatic and less than 1.5% patients have such bilateral critically severe carotid disease.\textsuperscript{3} Only a small fraction of patients would fit in this category.**

How then is the observed increased risk of post-operative stroke in patients with SCS explained? One likely explanation is that carotid stenosis is an epiphenomena serving as a marker of severe underlying systemic atherosclerotic disease. Patients with concomitant cerebrovascular and coronary artery disease represent a subset of patients with advanced arteriosclerosis, not only in the coronary and cerebrovascular vessels, but also other areas of arterial system. In patients with SCS, the incidence of other vascular complications such as coronary ischemic events is much higher than the stroke risk.\textsuperscript{42} Similar to SCS, there appears to be a positive correlation between the incidence of perioperative stroke and the severity of aortic atherosclerosis.\textsuperscript{43}

Over the last twenty years, many prospective randomized trials were undertaken in carefully selected patients with symptomatic and asymptomatic SCS.\textsuperscript{44–48} All trials showed clear benefits of carotid revascularization in reducing subsequent stroke risk in patients with SCS but most excluded patients with symptomatic and severe coronary artery diseases. The results of these trials have undoubtedly had major influence on medical decision making but caution should be taken in extending their results to populations of patients with concomitant carotid and coronary artery diseases. More recently published data suggested that under intense medical therapy, the stroke risk for asymptomatic stenosis is exceedingly low, as low as less than 0.5% annually.\textsuperscript{49,50} In the population of patients undergoing CABG, more effort should be geared towards reducing the overall risk of vascular complications with intense medical therapy, and preventing cardioembolism which remains to be the major source of stroke following cardiac surgery.

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Part Two: Against the Motion

Carotid Disease is Responsible for the Increased Risk of Stroke after Coronary Bypass Surgery

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Stroke remains the major noncardiac complication of coronary bypass surgery (CABG), with an absolute incidence of 2%. Severe carotid artery disease has been associated with a fourfold increased risk of perioperative stroke after CABG. It is well recognized that there are a number of potential etiologies for perioperative stroke in the cardiac surgical patient, including embolization of atherosclerotic debris or thrombus from the aortic cannulation site, air embolus, dislodgement of a left ventricular thrombus, aortic dissection, low cardiac output, and intracerebral disease, in addition to significant extracranial carotid artery disease. While clinically significant carotid disease may be responsible for only a part of perioperative strokes in this patient population, it remains the one etiology that can be identified preoperatively and noninvasively and can be prevented by timely intervention.

In a recently published systematic review by Naylor et al., favourable clinical outcome without any stroke in patients with carotid and coronary artery disease undergoing isolated CABG have been described. However, this data represents a fraction of data compared to the vast amount of previous information demonstrating a high stroke incidence (9.2–11.5%) in isolated CABG, and also describe different patient populations (OFF and ON pump bypass surgery).

Nevertheless, this information provides indirect proof and does not clarify the true etiology of stroke caused by significant carotid stenosis during cardiac surgery.

Cerebral Hemodynamics and Measurements

Normally, vasodilation of cerebral arteries allows the brain to tolerate a mild to moderate reduction of cerebral perfusion pressure. In patients with significant cerebrovascular disease, maximal autoregulatory vasodilation is already compensating for chronic circulatory insufficiency. In addition, “poor” cerebral collateral flow, defined by an impaired Circle of Willis, (visualized through absent cross-filling on selective carotid angiogram or dampened, low velocity middle cerebral artery velocity spectra on transcranial Doppler) contributes to the reduced hemodynamic response during cardiopulmonary bypass causing cerebral hypoperfusion. Atheroembolization also plays a role in the origin of perioperative stroke in patients undergoing cardiac surgery. However, it seems likely that the effects of atheroembolic particles are influenced by the presence of perfusion deficits. These essential findings implicate carotid stenosis as having a pivotal role in the multifactorial etiology of stroke after coronary bypass.

In one of the few randomized trials, Gold et al. assigned 124 patients to a low mean arterial pressure group (50–60 mm Hg) and 124 patients to a high mean arterial pressure group (80–100 mm Hg) during cardiopulmonary bypass. Those in the high pressure group had fewer combined cardiac and neurological complications (4.8% versus 13%) and fewer strokes (2.4% versus 7.2%). Caplan and Hennenrici have suggested that decreased flow may result in reduced washout of microembolic materials from the brain, and that the watershed areas are particularly susceptible to this combination. This latter hypothesis thus brings together two of the putative underlying mechanisms for vascular damage during CABG, suggesting that microembolism in the context of hypoperfusion may be associated with greater risk of ischemic injury.