Perioperative Cerebral and Myocardial Ischemia and Injury in Surgical Patients Having Known Carotid Artery Stenosis

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IN this issue of ANESTHESIOLOGY, Sonny *et al.*[1] report a retrospective database study that evaluated the relationship between unilateral perioperative carotid artery stenosis and both neurologic and cardiac outcome after general anesthesia for noncardiac, noncarotid surgeries. In 2,110 patients who had surgery over a 5-yr period, there was no correlation between either the presence or extent of perioperative carotid artery stenosis *versus* new-onset neurologic deficit or myocardial injury. The research's conclusion that there was no difference in outcome dictated by carotid stenosis, if reproducible and generalizable, has potential implications for other patients with known or occult carotid artery stenosis and who undergo other surgical procedures, before the carotid artery stenosis can be more extensively evaluated and specific treatment initiated. For now, however, we must interpret the research's findings in the context of the study population, applied methodologies, and high overall rates of neurologic deficits and myocardial injury.

"Is it possible that the differing perceptions of downstream neurologic effects in surgical* versus *nonsurgical patients relate to differences in cerebral insults modulated by tissue disruption far from the brain?"

There are several appealing features of the research by Sonny *et al.*[1] Severe carotid disease was well represented in the study population: 13% of patients had high-grade carotid stenosis and 4.3% had complete or nearly complete carotid occlusion. Further, the carotid stenosis was assessed in all patients in close proximity to their surgery, that is, between 6 months before to 1 month after surgery. The research was conducted in a single, tertiary care medical center, and data were retrieved from electronic medical records and other electronic databases.

The research by Sonny *et al.*[1] also contains several important limitations, including (1) the retrospective nature of the study, (2) selection bias in the patients who had undergone Doppler sonography (*i.e.,* bias in favor of sicker or higher-risk patients), (3) the use of a screening and potentially less quantitative method to assess the extent of carotid artery stenosis (*i.e.,* carotid blood flow velocity, in contrast to the gold standard of carotid artery angiography), and (4) a lack of uniform, standardized assessment of neurologic and cardiac function by trained observers using the most sophisticated techniques. Such study limitations could be particularly consequential for assessing neurologic insults because the research failed to assess neurocognitive and behavioral function of the patients, particularly after the immediate effects of surgery, anesthetics, and sedative/hypnotic drugs had dissipated.

The primary outcome of the research by Sonny *et al.*[1] was deficits of gross neurologic function assessed by the surgeons or others caring for the patients in the immediate postoperative period. (Thirty-day mortality was also a co-primary endpoint, but will not be discussed further.) Neurologic outcome after the patients had been discharged from the hospital was not assessed. Although a new-onset deficit of gross neurologic function is a classic, life-altering endpoint after ischemic brain injury, and this metric alone has been used to assess perioperative neurologic risk in many well-accepted

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studies, new-onset alterations of behavior and neurocognitive function are far more common in clinical practice and—in many instances—equally life-altering. Mills[2] reported that after cardiac surgery, 1% to 6% of patients experience aberrations in or deficits of gross neurologic function, whereas 60% to 80% have short-term deficits in neurocognitive function 1 week after surgery and 20% to 40% at 8 weeks after surgery. In addition, neurocognitive function scores were critical in determining that there was *no beneficial effect* of induced hypothermia in the Intraoperative Hypothermia for Aneurysm Surgery Trial parent study,[3] and in *post hoc* analysis provided more sensitivity than gross neurologic function alone in identifying glucose-associated neurologic deficits.[4] This increased sensitivity of neurocognitive testing has more recently been exploited to assess neurologic function in nonoperative patients having asymptomatic carotid artery stenosis: that is, those with carotid artery stenosis greater than or equal to 50% performed worse on overall neurocognitive function compared with those with normal blood flow, but none had experienced a classic stroke.* These and related reports suggest that many new-onset neurologic deficits in the study by Sonny *et al.*[1] were likely missed, leading to an underestimation in the number and extent of neurologic deficits and reduced sensitivity to test their hypothesis.

Additionally, several risk factors for perioperative stroke rate in patients undergoing noncardiac, nonvascular surgery were included in the data analysis model by Sonny *et al.*,[1] although other reported factors—including renal failure (and high blood urea concentrations), cardiac valve disease, past or current congestive heart failure, smoking, and cancer[5]—plus heretofore unknown factors (discussed below) were not included in their data analysis model. Observational studies cannot account for all confounding factors, and it is possible that this limitation could have influenced the lack of association between the extent of carotid artery stenosis and perioperative outcomes in the research by Sonny *et al.*[1]

The secondary outcome in the study by Sonny *et al.*[1] was new-onset myocardial injury after noncardiac surgery. The authors used International Classification of Diseases, Ninth Revision, criteria and serum troponin concentrations for documenting myocardial injury after noncardiac surgery. However, postoperative troponins were measured on a clinical practice basis only, and thus were not measured in all subjects. The criteria for initiating troponin assay were not reported, and it is quite possible that many patients had silent insults (*e.g.,* as is common in diabetic patients [which accounted for 42% of the population studied by Sonny *et al.*[1]]). In addition, the fraction of total study patients who had workup for myocardial ischemia or infarction was not reported.

Studies in nonsurgical patients support the concept that carotid stenosis is a marker of generalized arteriosclerosis and predisposes patients to both cerebral and myocardial ischemic events. For example, in a study of 2,684 consecutive patients with clinical manifestations of arterial disease or type 2 diabetes mellitus but no history of cerebral ischemia, carotid stenosis (estimated using Duplex scanning) was correlated to subsequent vascular events over a mean follow-up of 3.6 yr (SD, 2.3 yr). Those with 50% to 99% stenosis had a two-fold greater risk for the composite of first vascular events (*i.e.,* vascular death, ischemic stroke, or myocardial infarction) (CI, 1.5–2.8) and a two-fold greater risk of myocardial infarction alone (CI, 1.3–3.0), although not for ischemic stroke (hazard ratio, 1.3; CI, 0.6 to 3.1),[6] perhaps due to the smaller number of stroke events (rate of 2.2% over 5 yr *vs.* 8.0% for myocardial infarction). Another study of 1,820 patients with unilateral symptomatic carotid artery stenosis demonstrated that angiographically determined stenosis, whether in the symptomatic or asymptomatic side, was associated with an ipsilateral increased 5-yr stroke incidence, with stroke risk progressively increasing in concert with the degree of stenosis over the range of < 50%, 50–59%, 60–74%, and 75–94% stenosis per artery.[7] Although the remaining literature is sparse and sometimes open to multiple interpretations, the aforementioned examples support the concept that carotid artery stenosis may predict an increase in both cerebral ischemic injury and myocardial infarction in nonoperative, medically managed patients.

The reason that the report by Sonny *et al.*[1] found no relationship between the extent of carotid stenosis *versus* either stroke or myocardial injury after noncardiac surgery is unclear. It is possible that knowledge of carotid artery stenosis, which was available in 83% of patients preoperatively, may have biased the clinical decision-making (*e.g.,* blood pressure control and glucose control) in these patients differently from that in patients with lesser or no carotid artery stenosis in a manner that could not be evaluated in a retrospective electronic medical records evaluation.

In addition, the high 2.6% perioperative stroke rate in the study by Sonny *et al.*[1], and its relationship to the employed study methods (*i.e.,* one that should have underestimated ischemic brain insults and injury), suggests that the authors were studying a high-risk subgroup of patients. One might reasonably conclude from the results of Sonny *et al.*[1] that (1) clinician's suspicions that a patient might be at neurologic risk related to carotid artery stenosis, and (2) scheduling the patient for sonographic assessment of the carotid arteries, in turn, (3) selected a population of study patients who had an increased risk of perioperative stroke that overwhelms any possible effect of the degree of stenosis on this risk.

It is also possible that there is more to the pathophysiology linking ischemia of the brain and myocardium than can be explained by simple vessel stenosis dictating the supply side of supply–demand metabolism. Instead, it is possible that humoral or other factors, triggered by surgical

* Sullivan MG: Asymptomatic stenosis could cause cognitive impairment, Clinical Psychiatry News, April 21, 2014. Available at: http://www.clinicalpsychiatrynews.com/home/article/asymptomatic-stenosis-could-cause-cognitive-impairment/0a50a0f2e27acd5cbd89559ad9fe43c2.html. Accessed June 2, 2014.

procedures remote from the brain and myocardium (as in the population studied by Sonny *et al.*[1]), may in turn augment the frequency and severity of ischemic insults, making injury to the downstream tissues more common and less correlated with isolated vessel stenosis. Ng *et al.*[5] have recently reviewed the possibility of "a synergistic interaction between the inflammatory changes normally associated with stroke and those normally occurring after surgery"; however, the list may also include other unquantified, or perhaps currently unknown, modulators. Such a possibility has support from anesthesiologists' anecdotal experiences in which patients who have immense tissue manipulation during nonneurologic, noncardiac surgery not uncommonly report that "the effects of my anesthetic did not wear off for weeks," well after the known pharmacologic effects of anesthetics and postoperative analgesics and sedatives would have ceased. By contrast, when we (W.L.L., W.J.P.) anesthetize large numbers of patients each year who are at even higher risk for new-onset neurologic insults, yet the anesthetics are for magnetic resonance imaging (*i.e.,* no tissue disruption), we are unaware of any patient who has reported persistence of their "anesthetics" effects, even in those patients who have received multiple anesthetics delivered by our same team of personnel and speak freely to us about previous anesthetic experiences. Is it possible that the differing perceptions of downstream neurologic effects in surgical *versus* nonsurgical patients relate to differences in cerebral insults modulated by tissue disruption far from the brain? And could similar mechanisms have influenced the high rate of brain and myocardial injury in the research by Sonny *et al.*[1]?

Aside from these speculations, we believe that the contribution of the research by Sonny *et al.*[1] lies primarily in hypothesis generation rather than definitive testing. As such, others should attempt to validate this research retrospectively in other populations and, ultimately, attempts should be made to validate the observations prospectively. Any future prospective study evaluating a relationship between baseline carotid artery stenosis and postoperative neurologic and cardiac function should ensure that (1) there is no selection bias or treatment bias in the patients who get preoperative carotid artery assessment, (2) both gross neurologic and neuropsychologic function are assessed in a systematic fashion, and (3) cardiac assessment is uniformly applied in all patients. It may also be useful to screen for common markers of inflammation and store biologic samples in a biobank so that future hypotheses related to mechanisms can be tested against known patients and outcomes. Such research will be far more expensive and difficult than the current hypothesis-generating retrospective study; however, the important results should be well worth the effort.

The greatest contribution of the research by Sonny *et al.*[1] may not be in its ability to provide clear-cut answers concerning perioperative risk to the brains and hearts of patients having preexisting carotid artery disease. Instead, their greatest contribution, in our opinion, is that they may have identified a heretofore unacknowledged high-risk population worthy of future study, and have incrementally improved our understanding of how difficult and expensive it will be to formulate a proper prospective study design and apply appropriate controls and endpoints, so that any new phenomenon may be better understood.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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References

1. Sonny A, Gornik HL, Yang D, Mascha EJ, Sessler DI: Lack of association between carotid artery stenosis and stroke or myocardial injury after noncardiac surgery in high-risk patients. Anesthesiology 2014; 121:922–9
2. Mills SA: Cerebral injury and cardiac operations. Ann Thorac Surg 1993; 56(5 Suppl):S86–91
3. Todd MM, Hindman BJ, Clarke WR, Torner JC; Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) Investigators: Mild intraoperative hypothermia during surgery for intracranial aneurysm. N Engl J Med 2005; 352:135–45
4. Pasternak JJ, McGregor DG, Schroeder DR, Lanier WL, Shi Q, Hindman BJ, Clarke WR, Torner JC, Weeks JB, Todd MM; IHAST Investigators: Hyperglycemia in patients undergoing cerebral aneurysm surgery: Its association with long-term gross neurologic and neuropsychological function. Mayo Clin Proc 2008; 83:406–17
5. Ng JL, Chan MT, Gelb AW: Perioperative stroke in noncardiac, nonneurosurgical surgery. Anesthesiology 2011; 115:879–90
6. Goessens BM, Visseren FL, Kappelle LJ, Algra A, van der Graaf Y: Asymptomatic carotid artery stenosis and the risk of new vascular events in patients with manifest arterial disease: The SMART study. Stroke 2007; 38:1470–5
7. Inzitari D, Eliasziw M, Gates P, Sharpe BL, Chan RK, Meldrum HE, Barnett HJ: The causes and risk of stroke in patients with asymptomatic internal-carotid-artery stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 2000; 342:1693–700