Improving Neurologic Outcome after Cardiac Surgery

IN this issue of Anesthesiology, Roach et al. report that the induction of electroencephalographic burst suppression with propofol during open cardiac surgery (valve replacement) did not lead to better neurologic or neuropsychologic outcome than did an otherwise similar opioid-based anesthetic. At 2 months after surgery, 50% of patients had at least some impairment of neuropsychologic status, 10% had marked impairment, and 6% still had substantial neurologic deficits. This large (225 patient) prospective randomized study used sensitive quantitative measures of neurologic outcome obtained by trained personnel blinded to group assignment. The findings of Roach et al. provide important insight into “brain protection” in general and brain protection in the setting of cardiac surgery in particular.

Burst Suppression

The first important lesson of this study is that pharmacologically induced burst suppression should not be “automatically” assumed to lead to better neurologic outcome. Although this has been discussed before, it deserves reemphasis. In 1974, Michenfelder showed that barbiturates reduce cerebral metabolic rate (CMR) by decreasing spontaneous synaptic activity. Maximal reduction of CMR was coincident with a nearly flat electroencephalographic recording. At the time, it was widely postulated that barbiturate brain protection was mediated via reduction of CMR. Therefore, logically, barbiturate-induced protection should be maximal after CMR was maximally reduced (i.e., at the point of electroencephalographic isoelectricity or burst suppression). Likewise, any anesthetic that could eliminate synaptic activity, induce burst suppression, and reduce CMR might also have cerebral protective properties. However, the idea that pharmacologically induced burst suppression is necessarily protective has crumbled. In transient focal ischemia models, burst suppression with either isoflurane or etomidate does not confer the same degree of brain protection as burst suppression with a barbiturate. In addition, in rats undergoing transient focal ischemia, cerebral protection is equivalent between groups receiving high-dose (burst suppression) or low-dose (active electroencephalographic barbiturate). Therefore, reduction of CMR or burst suppression, or both, are probably not the essential elements of barbiturate brain protection. Thus, pharmacologically induced burst suppression per se would seem to have little to do with clinically relevant brain protection.

Mechanisms of Neurologic Injury during Cardiac Surgery

In any study of cerebral protection, one must understand the underlying cause of injury. In cardiac surgery patients, cerebral emboli constitute a major cause of perioperative neurologic injury. Transcranial Doppler studies show that these patients receive hundreds, sometimes thousands, of cerebral microemboli during the course of surgery. In addition, in open cardiac procedures (e.g., valve replacement), a large embolic shower frequently occurs with resumption of left ventricular ejection. Greater numbers of cerebral microemboli are associated with a greater incidence of postoperative neurologic or neuropsychological abnormalities, or both. During bypass, propofol-induced burst suppression decreases cerebral blood flow and metabolism 35–45%, as compared to an opioid-based anesthetic. Therefore, even if propofol were to have no intrinsic neuroprotective properties (an issue that is still unresolved), marked reduction of cerebral blood flow should result in a reduction in the number of cerebral emboli received during surgery. Presumably, fewer emboli should translate into better neuropsychologic outcome. Because Roach et al. did not measure numbers of cerebral microemboli, it is uncertain whether propofol patients received fewer emboli. Nevertheless, it is quite clear that propofol did not improve


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neurologic outcome. Was it because propofol has no intrinsic neuroprotective properties? Was it because propofol did not decrease the number of emboli? Or was it because neurologic and neuropsychologic abnormalities associated with cardiac surgery can occur by mechanisms unrelated to cerebral blood flow, metabolism, or emboli? The findings of Roach et al.\textsuperscript{1} certainly suggest the latter.

Although cerebral embolism is well-established as a mechanism of injury, it is unknown whether all neurologic changes that occur in association with cardiac surgery can be ascribed to this mechanism. For more than 20 yr, the duration of bypass has been consistently identified as a risk factor for postoperative neurologic injury.\textsuperscript{22} Bypass duration remains a risk factor\textsuperscript{23–25} even though membrane oxygenation and arterial filtration have greatly reduced the number of microemboli produced by bypass circuits.\textsuperscript{11,14,26} Is there some other aspect of bypass that either directly injures the brain or worsens brain injury when it occurs? Frankly, no one knows. By and large, the problem does not appear to be primarily related to a global impairment of cerebral perfusion or oxygenation. With well-conducted bypass, global impairment of cerebral perfusion and oxygenation does not occur.\textsuperscript{27–30} and various measures of cerebral oxygen delivery (e.g., jugular venous hemoglobin saturation) do not correspond with neurologic and neuropsychologic disorders.\textsuperscript{30–32} If not oxygen, then what? Advancing age,\textsuperscript{17,23–25,31} previous neurologic injury,\textsuperscript{25,25.35} and specific genetic markers\textsuperscript{53} appear to place cardiac surgery patients at increased risk. Does the brain’s response to bypass differ with these conditions, or does the brain’s response to injury differ with these conditions? Again, nobody knows. Recent work indicates the systemic inflammatory response triggered by bypass adversely affects overall perioperative outcome.\textsuperscript{34,35} The degree to which bypass-induced systemic inflammatory responses affect the brain is virtually unexplored.

Neuroprotection Trials during Cardiac Surgery

Although we still lack fundamental knowledge about how the brain is injured during cardiac surgery, we want to improve outcomes now instead of later. Therefore, in the hope of helping, we are tempted to give cardiac surgery patients agents that appear to be effective in animal ischemia models or clinical stroke trials. We think to ourselves, “if drug x works against one type of neurologic injury, maybe it will work during heart surgery.” We have to be very careful when we think this. Drugs that are protective against one type of brain insult are not always protective against another. For example, although nimodipine improves neurologic outcome after subarachnoid hemorrhage,\textsuperscript{37–38} it is much less effective in the setting of cerebral infarction.\textsuperscript{39} Also, perhaps even more important, drugs that are safe in a nonsurgical setting may not be safe when used during cardiac surgery. For example, a trial of nimodipine in cardiac surgery patients was discontinued because of excessive mortality in the nimodipine group, largely because of bleeding.\textsuperscript{40} Moreover, there was no suggestion of improved neurologic outcome, even in nimodipine survivors. In the study by Roach et al.\textsuperscript{1} there was also no suggestion of improved neurologic outcome in the study (propofol) group.\textsuperscript{1} There was, however, a much greater incidence of hypotension in patients receiving propofol, and the data suggest tendencies toward a greater need for intraaortic balloon pumping (6% vs. 2%, \(P = 0.11\)), and a greater incidence of early neurologic deficits (18% vs. 8%, \(P = 0.07\)). Thus, in both the nimodipine and the propofol trials, not only were neurologic outcomes not improved by treatment, overall outcomes were worse.

These results highlight the special difficulty of prophylactic neuroprotection trials during cardiac surgery—these patients are sick. Given the nature of their disease and their surgery, they are likely to be very sensitive to any adverse side effect. Severe neurologic and neuropsychologic abnormalities do not occur in every cardiac surgery patient and, even when they occur, most are not fatal. Therefore, a drug that decreases the risk of stroke or neuropsychologic deterioration but results in a greater risk of perioperative morbidity or mortality will probably not be acceptable to patients or their doctors. For example, it was recently reported that patients randomized to receive a 9-day course of a glutamate (NMDA) antagonist (before and after cardiac surgery) had slightly better cognitive outcomes (in 3 of 10 tests) 2 months after surgery than control patients.\textsuperscript{2} However, patients receiving the glutamate antagonist were more frequently dizzy (46% vs. 5%), ataxic (8% vs. 1%), and drowsy (9% vs. 2%) than controls. Was the small long-term benefit worth the short-term cost and morbidity?

The Need for a Disease Model

So, what therapy should be tested next? Ideally, before any neuroprotective therapy is tested in humans, it will
have been shown to be effective and well-tolerated in an appropriate animal model. But here is yet another problem. Currently, there is no appropriate neurologic injury/bypass model in which to test experimental compounds. As a starting point, microembolic models would seem to be more likely to represent the type of insults experienced by cardiac surgery patients than standard forebrain ischemia or temporary focal ischemia models. (Notably, glutamate antagonists are moderately protective in microembolic stroke models\textsuperscript{11,12}; see above.) However, not all emboli are alike. Cerebral microemboli occurring during cardiac surgery consist of atheromatous debris,\textsuperscript{13} microbubbles,\textsuperscript{14} and fat\textsuperscript{14} and/or small fibrin-platelet complexes.\textsuperscript{15} Currently, little is known about how microemboli of these differing compositions affect the brain.\textsuperscript{16} Some types of microemboli may be more damaging than others, and how they injure the brain may involve far more than classic ischemia/infarction pathophysiology. For example, with microscopic gas emboli, inflammatory mechanisms probably play a greater role in injury than ischemia per se.\textsuperscript{17,18} As if that were not enough, how bypass modifies the physiology of brain injury is also largely unknown. Therapies that are effective against insults in the absence of bypass may not necessarily result in better outcome in the presence of bypass.\textsuperscript{19} Therefore, it will be necessary to incorporate bypass into any model of brain injury and protective therapy to increase the chances of clinical effectiveness and safety in a subsequent human trial.

**Past Progress and Current Challenges**

To be sure, substantial progress has been made toward reducing neurologic injury during cardiac surgery. For example, incorporation of an arterial filter in bypass circuits using a bubble oxygenator leads to better neuropsychologic outcome.\textsuperscript{14} Choice of hypothermic acid-base management (\(a\) stat vs. \(pH\) stat) also affects neurologic outcome.\textsuperscript{24,50} Although less rigorously documented, methods to reduce disruption of atheromatous plaque from the ascending aorta may also result in better outcome.\textsuperscript{16,17} For the most part, these measures focus on primary prevention, by either reducing embolic load or improving ischemic tolerance. Do patients really need anything more? The findings of Roach \textit{et al.}\textsuperscript{1} show that current practice is still associated with a high incidence of neurologic abnormalities.\textsuperscript{1} Clearly, there is a need for new approaches directed toward reducing neurologic and neuropsychologic injury \textit{after} the insult has occurred, because prevention is not always effective.

As the “decade of the brain” comes to a close, there is a difficult choice to make. We can continue to test neuroprotective drugs \(x\), \(y\), and \(z\) in cardiac surgery patients, recognizing that we are not totally sure of what we are treating or the risk/benefit ratio to the patient. Alternatively, we can make an investment in basic science and develop specific therapies. With the later approach, we must also recognize that history shows that what is effective in the lab is not always effective in real life.\textsuperscript{51,52} For all the reasons discussed herein, improving neurologic outcome after cardiac surgery is probably going to remain a tough problem for some years to come. The “good” news is, the goal is worthy of the effort.

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Hyperchloremic Metabolic Acidosis Is a Predictable Consequence of Intraoperative Infusion of 0.9% Saline

IN this issue of ANESTHESIOLOGY, Scheinigraber et al.1 quantify two phenomena that are important to anesthesiologists and other clinicians caring for perioperative patients: (1) intravenous infusion of 0.9% saline in patients undergoing gynecologic surgery results in hyperchloremic metabolic acidosis and (2) intravenous infusion of either 0.9% saline or lactated Ringer’s solution results in hypoproteinemia and a decreased anion gap. Although neither of these observations is surprising, no other data define so clearly the expected effects of conventional intraoperative therapy in a population of patients undergoing common procedures of intermediate magnitude. Clarification of these effects is important in interpreting perioperative acid–base changes and in assessing the need for treatment to modify those changes.

A brief review of the key observations of this study is necessary to appreciate its importance. Scheinigraber et al.1 randomized 24 women to receive either 0.9% saline or lactated Ringer’s solution while undergoing elective gynecologic lower abdominal surgery. During surgical procedures averaging slightly more than 2 h in duration, subjects lost a mean volume of approximately 850 ml blood, received a mean volume of either of the two crystalloids of almost 70 ml/kg, and excreted a mean volume of almost 900 ml urine. During the first 2 h of saline infusion, the serum bicarbonate concentration (HCO₃⁻), calculated from the Henderson–Hasselbalch equation) decreased from 23.5 ± 2.2 mm to 18.4 ± 2.0 mm. The anion gap concentration decreased from 16.2 ± 1.2 mm to 11.2 mm, and the mean serum chloride concentration (Cl⁻) increased from 104 to 115. During the same interval, HCO₃⁻ in the group receiving lactated Ringer’s solution remained similar (23.8 ± 2.0 mm and

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