Barbiturate Protection and Cardiac Surgery: A Different Result

This issue of ANESTHESIOLOGY contains a report by Zaidan and co-workers concerning thiopental and the incidence of major stroke after cardiac surgery.\(^1\) Three hundred patients undergoing coronary artery bypass grafting (CABG) were assigned to receive placebo or thiopental; thiopental was given to an end-point of EEG burst-suppression prior to aortic cannulation and was continued throughout the bypass period. Perioperative care and postoperative assessment was provided by individuals blinded as to treatment group. As expected, patients in the thiopental group more commonly required inotropic support and recovered consciousness more slowly, and their tracheas were extubated later than were those of control patients. However, there was no difference in the incidence of major stroke, which occurred in 2 of 151 (1.3%) control patients, as compared with 5 of 149 (3.3%) patients given thiopental. These group sizes are small for an outcome study of this nature, and the authors did not use pre- and postoperative neuropsychologic testing that might have revealed more subtle deficits. Nevertheless, the conclusion of “no barbiturate benefit” is statistically firm. Moreover, there is little chance that the barbiturate group actually had significantly worse clinical outcome than did patients receiving placebo, and hence it is reasonable to conclude that there was no barbiturate effect.

Most readers immediately will compare the results of this report to those from a paper by Nussmeier et al.\(^2\) In that now classic study, patients given thiopental had a lower incidence of frank stroke (0 of 89) compared to controls (6 of 93 = 6.5%). What can explain this difference? The characteristics of the patient populations reported in the two papers (e.g., age and sex) are similar, although the anesthetics were modestly different. Both studies started and stopped the thiopental infusion at equivalent points in the operation and used the same EEG end-points. Their neurologic evaluations were similar and were performed at similar times. However, as outlined in table 1, there are several important differences. Nussmeier et al. studied patients undergoing open-chamber procedures and used a nonfiltered bypass circuit with a bubble oxygenator. In contrast, Zaidan et al. studied only patients undergoing CABG and used a filtered bypass circuit and a membrane oxygenator. In addition, the patients in the study by Nussmeier et al. underwent normothermic bypass (34 °C), whereas Zaidan and co-workers’ patients were hypothermic (28 °C).

Can these differences explain the apparently inconsistent conclusions regarding the value of barbiturate therapy? The literature is divided on the neurologic risk of open versus closed cardiac procedures.\(^3\)–\(^5\) In the presence of atherosclerosis, both aortic cannulation and cross-clamping can release comparatively large (>150-μm) particles into the cerebral circulation.\(^7\)–\(^8\) Since aortic manipulation is necessary in both open and closed procedures, the risk of a particulate embolus in these two types of procedures should not be very different, except for the added risk of embolized valve fragments. A more important difference between the two studies may relate to the risk of arterial (cerebral) gas emboli. Intracardiac air, as detected by echocardiography, clearly is more common and occurs in greater volumes during open procedures.\(^9\)–\(^10\) Oxygenator type (membrane vs. bubble) and the use of arterial filters also influence the occurrence of arterial air emboli. Padayachee and co-workers, using a transcranial Doppler, found that patients managed with membrane oxygenators and arterial filters had no evidence of emboli in the cerebral circulation, whereas patients managed with bubble oxygenators without arterial filters received increasing numbers of cerebral emboli over the 1st h of bypass.\(^11\) Therefore, it is reasonable to assume that Nussmeier and co-workers’ patients received a greater number of gas emboli during CPB than did Zaidan et al.’s patients.

Unfortunately, the relationship between bubbles and neurologic deficit is unclear. In both studies, the major neurologic events were focal, whereas embolized bubbles should be more diffusely distributed throughout the cerebral circulation. Nevertheless, most human studies and virtually all animal work indicate that less neurologic injury occurs when arterial filters are used in CPB circuits, particularly when bubble oxygenators are used.\(^12\)–\(^14\) Given these considerations, one would expect to see a greater number of deficits in the Nussmeier et al. control group than in the patients studied by Zaidan et al. Although statistical comparisons across studies are to be made only very carefully, this appears to be the case.

Given the higher rate of stroke among control patients in the Nussmeier et al. study, their observed effects of thiopental were striking. It has been argued, however,
that their findings should not be extrapolated to other surgical situations, particularly when hypothermia is used.\(^\text{15}\) Is the difference between the studies of Nussmeier et al. and Zaidan et al. related to the use of hypothermia? It has been established that hypothermia confers a degree of neurologic protection from temporary cerebral ischemia and may "buy time" for the brain while gas emboli are cleared. Thus, it is possible that the lower stroke rate among Zaidan et al.'s patients is related not to their procedure or choice of oxygenator, but to their use of hypothermia. In such conditions, any further beneficial effects of thiopental may be relatively minor. By contrast, the use of normothermic bypass by Nussmeier et al. resulted in conditions wherein the protective effect of thiopental had a better chance to be seen relative to a "high-risk" control group.

An alternative explanation may relate to the duration of barbiturate therapy in the two studies. Evidence for barbiturate protection in the face of permanent focal cerebral ischemia is weak unless the duration of barbiturate coma is prolonged (e.g., 96 h).\(^\text{16}\) If the cause of stroke during cardiac surgery is embolization of atheromatous plaque (perhaps a form of "permanent" focal occlusion), one can argue that Zaidan et al. simply did not maintain the barbiturate coma long enough into the postoperative interval to provide such protection. (Note, however, that such prolonged treatment can hardly be viewed as reasonable in the 98% of patients who did not suffer a stroke.) The track record of barbiturate protection is much better when the occlusion is temporary.\(^\text{17}\) If the embolic events in the patients of Nussmeier et al. were due to air (which should be a more transient insult), then a brief period of barbiturate therapy might have been adequate.

If there is a rational explanation for the differences between the results of Nussmeier et al. and Zaidan et al., then we can conclude that both groups are "right." Where does this leave us with respect to the use of barbiturates in cardiac surgery? We believe that the answer is clear. The work of Zaidan et al. suggests that currently, routine thiopental therapy has no place in the management of patients undergoing CABG. This is supported by the study by Slogoff et al., who observed no beneficial effects of thiopental in patients undergoing CABG.\(^\text{7}\) We cannot argue with the landmark work of Nussmeier, but we do believe that the demonstration of barbiturate protection in normothermic, nonfiltered, bubble-oxygenator bypass is not a reasonable argument for barbiturate use during alternative bypass circumstances unless the appropriate trials are performed.

**Future Directions**

Where do we go from here? First, an effort should be made to examine the contention that the major cause of neurologic injury in patients undergoing cardiac surgery is related to air or to particulate emboli or to both. The technology is available. Transcranial Doppler techniques allow detection of emboli entering the cerebral circulation. Spectral analysis of the signal might allow us to discriminate between air and solid particles (as well as to distinguish between large and small particles). A prospective observational trial comparing the amount, nature, and timing of emboli with neurologic outcome could be performed in any of a number of cardiac surgical centers. The study needs to be large enough to permit reliable multivariate analysis since it is probable that the etiology of stroke is multifactorial, e.g., a combination of low blood pressure and a certain embolic load. This type of monitoring might also allow us better to define the patients at risk (e.g., those with a certain volume of embolized material) who can be specifically treated. It should be noted that future outcome studies must use measures of neurologic function that are more sophisticated than those used by either Nussmeier et al. or Zaidan et al. Frank stroke is only "the tip of the iceberg": neuropsychiatric dysfunction is much more common (estimated at 30–60%) and probably explains the typical complaints of "Uncle Joe just isn't the same since his surgery." Furthermore, these "minor changes" are more compatible with a multifocal, embolic phenomenon (perhaps air), and hence may be easier to prevent or treat.

Next, we need to expand our knowledge of the central nervous system (CNS) effects of cardiopulmonary bypass. This requires more than simple cerebral blood flow (CBF) and cerebral metabolic rate (CMR) measurements. For example, we measure CBF, but we still do not know the relationship between CBF and ischemic injury. What is the ischemic CBF threshold during alpha-stat CO\(_2\) management at 28°C when the hematocrit is 22%? We also need to understand the influence of factors such as pump flow, pulsatility, and hematocrit on outcome when an embolic event has already occurred. Regional perfusion after focal cerebrovascular occlusion is critically dependent on collaterals. We need to understand the combinations of pressure, flow, hematocrit, and other factors that are necessary to convert a subcritical embolic event (where collateral flow is sufficient to maintain viability) into an infarction.

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**Table 1.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nussmeier et al.</th>
<th>Zaidan et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedures</td>
<td>Open chamber</td>
<td>CABG</td>
</tr>
<tr>
<td>Oxygenator type</td>
<td>Bubble</td>
<td>Membrane</td>
</tr>
<tr>
<td>Arterial filter</td>
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<td>Yes</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Duration of bypass (min)</td>
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<td>90</td>
</tr>
<tr>
<td>Pump flow rate (/min)</td>
<td>3.0–4.4</td>
<td>2.5</td>
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Finally, we must broaden our horizons. Our mechanistic concepts of brain injury and protection govern the way we search for answers. If our concepts are wrong, we may look in the wrong places for those answers. We believe that our traditional approaches are, at best, incomplete. Most anesthesiologists have long accepted the intuitively attractive “metabolic suppression” explanation for protection. Although it is not possible to present all of the appropriate arguments here, there are many observations that are simply incompatible with this idea. For example, the differing susceptibilities of the various brain regions to ischemic injury does not reflect metabolic activity in those regions. Isoflurane, which has EEG and CMR effects similar to those of the barbiturates, has not been shown provide protection from injury except during relatively modest ischemic conditions. Similarly, high-dose fentanyl anesthesia can profoundly reduce CMR, and yet efforts to demonstrate protection with this drug have not been successful. Most importantly, mild hypothermia (e.g., 34°C) has been found to be dramatically protective, even though CMR at these temperatures is much higher than that obtained with barbiturates.

Brain ischemia and protection are much more complex than just supply and demand. They involve ion channels and gradients (e.g., calcium), the synthesis and release of both excitatory and inhibitory neurotransmitters (e.g., glutamate, norepinephrine, dopamine, and γ-aminobutyric acid [GABA]), protein synthesis, and DNA transcription. Slowing the rate at which energy failure occurs may “buy time” in the event of a mild ischemic event. However, when tissue O2 delivery is profoundly reduced, the time gained may be minimal. More importantly, once energy failure occurs, the cascade of biochemical events that is triggered can lead to far-ranging and persistent alterations in CNS function, despite normalization of whole-brain metabolic activity. If anesthesiologists are to continue making real contributions to this field, we must understand this physiology and biochemistry and move beyond our simplified concept that protection is a matter of decreasing CMR or producing a burst-suppressed EEG with whatever agent is capable of doing so.

The cardiac operating room is the perfect site in which protective therapies can be tested. This may be the primary location in which drugs such as nimodipine, nicardipine, glutamate antagonists, and serotonin antagonists (in addition to other anesthetics, e.g., propofol) should be examined. In fact, it may be the only place where we can truly study “protection” (as opposed to treatment begun after injury). Methods are available to carefully assess the effects of therapy—particularly since baseline information can be obtained from all patients. Major and “minor” deficits are sufficiently common and the number of procedures performed is sufficiently large to allow studies to be performed in single surgical centers within reasonable periods of time. There is no proven protective therapy available, and hence there are no ethical problems associated with having an untreated control group. There are problems concerning the risks of treatment per se, but assuming that the chosen drug is not a major myocardial depressant (and few drugs are likely to be “worse” than high-dose barbiturates!), there seems to be no better place to test them than in a population of patients who are intensively monitored, whose lungs are ventilated, and who will be cared for in sophisticated intensive care units.

These are exciting times. Anesthesiologists are in a position to design and direct the definitive trials needed to make the transition from laboratory brain protection to real-world therapy. We hope that the work of Zaidan et al. (as well as that of Nussmeier et al.) will continue, and that it will prompt other groups to undertake the clinical experiments that will remove one of the remaining obstacles to safer cardiac surgery.

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References

7. McKibbin DW, Bulkley BH, Green WR, Gott VL, Hutchins GM:

EDITORIAL VIEWS

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