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Scuds, Scads, and Other Air-borne Hazards

By the turn of the millennium, more than 1,000,000 predominantly aged patients will require cardiac surgery annually throughout the world. The cost of this health care likely will exceed 25 billion dollars, with a substantial portion of the overall expense attributable to management of the perioperative morbidity associated with cardiac procedures. For example, serious adverse central nervous system (CNS) events occur in approximately 6% of patients undergoing coronary artery bypass graft surgery; in addition, less apparent cognitive dysfunction occurs in 20–79%, persisting for 2 or more months in 15–57%.[1] A recent study reports that adverse CNS events after coronary revascularization greatly increase the duration of hospitalization and therefore health care costs.[2] Type I (focal injury, stupor, coma) and type II (deterioration in intellectual function, memory deficit, seizure) adverse events not only double the the average length of hospital stay, but also the amount of time spent in intensive care. This report confirms a previous finding that suggests patients with either type I or type II adverse CNS events require a longer hospitalization than those who suffer a postoperative myocardial infarction, left ventricular failure, or renal dysfunction after coronary revascularization.[3] Thus, postoperative CNS morbidity arguably represents the most economically and emotionally costly consequence of cardiac surgery.

The pathophysiology of perioperative adverse CNS events is complex and incompletely understood, but probably includes phenomena that can precipitate focal or global cerebral injury.[4] Focal injury is likely the end-result of marked and persistent hypoperfusion or flow obstruction produced by macroemboli (> 200 micron) consisting of atheromatous material, large air bubbles, or intracardiac thrombi. Subtle nonfocal neurologic symptoms may be the result of microembolism of air, fat, or blood element aggregate. During cardiopulmonary bypass (CPB), air entrained during manipulation of the heart and great vessels, gaseous emboli produced in the extracorporeal circuit, and air bubbles produced by cavitation phenomena in either the patient or bypass circuit circulate to the brain. Cerebral micrographs obtained from animal and human autopsy specimens demonstrate the diffuse presence of small capillary and arteriolar dilations (SCADS) after CPB, probably representing lodgement of gas bubbles or fat particles (fig. 1).[5] Several studies suggest that the magnitude of postoperative cognitive dysfunction may be predicted by the volume of the embolic load, as detected by isonation of

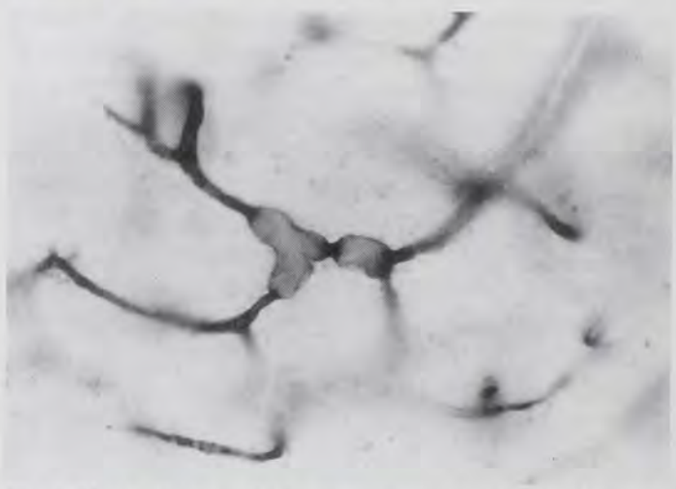

Fig. 1. Photomicrograph demonstrating putative embolic material lodged at the bisection of a cerebral capillary of a patient after cardiopulmonary bypass (CPB). This type of lesion is only present in patients or animals undergoing CPB or proximal aortic instrumentation and is thought to represent the site of air or lipid microemboli. (Courtesy of Dr. Dixon Moody).

Accepted for publication June 2, 1997.

Key words: air embolism, doxycycline, leukocytes, rabbits, somatosensory-evoked potentials.

the middle cerebral artery (MCA).[6,7] Similar phenomena occur in patients undergoing cerebral angiography wherein the presence of Doppler signals suggestive of air emboli in the MCA appears to be associated with nonfocal neurologic symptoms, such as confusion and memory loss.[8]

Do air emboli cause brain injury by occluding arterioles and capillaries—thus creating a web of "mini" cerebral infarctions? Probably not. Most air emboli are cleared or absorbed in a relatively brief period of time (< 5 min) and are unlikely to cause acute energy failure and cell death. Instead, cerebral damage precipitated by air embolism is probably a result of: (1) mechanical trauma to the endothelium causing basement membrane disruption, thrombin production, with release of P-selectin from intracellular vesicles, and synthesis of platelet-activating factor (PAF); and (2) a reperfusion-type injury with the attendant cascading perturbations in inflammation and thrombotic processes. Both endothelial phenomena—abrasion and ischemia—likely impair nitric oxide (NO) production, thereby limiting the important palliative effect of NO on leukocyte-endothelium interaction, allowing leukocytes to adhere and release additional oxygen-free radicals, thus amplifying the postischemic inflammatory response.[9]

In the current issue of ANESTHESIOLOGY, Reasoner *et al.* report that doxycycline, an inexpensive generic antibiotic administered at clinically relevant dosage, attenuates the neurologic dysfunction that occurs after cerebral embolism.[10] Although the potential mechanisms responsible for the apparent neuroprotection—decreased leukocyte infiltration or activation, attenuated endothelial injury, or modulation of other inflammatory mediators—are not assessed, the authors speculate that doxycycline-induced inhibition of leukocytes confers cerebral protection in the presence of air embolism. Their evidence for a neuroprotective effect is compelling: Rabbits treated with intravenous doxycycline (10 μg/kg) before the cerebral arterial infusion of 100 μg/kg of air had less neurologic impairment than untreated animals as measured by a coma scale (modified Baker's) and somatosensory-evoked potentials (SSEP). Significantly greater pathologic changes in SSEP amplitudes were evident in the placebo group within 60 min of the cerebral insult. Because early electrophysiologic (SSEPs) abnormalities mirrored neurologic impairment scores at 4 h, the authors suggest that doxycycline affects a process occurring early (< 1 h) in the pathogenesis of neuronal injury by air embolization.

The authors acknowledge the need for further study. In addition to a small sample size and the lack of data to identify the phenomena responsible for doxycycline-neuroprotection, the current study omits long-term neurologic outcome results. Because the ultimate morbid sequelae after a cerebral insult may evolve over the course of days rather than hours, it is difficult to extend these results to longer-term outcomes. Histologic data corroborating the behavioral and electrophysiologic evidence of cerebral injury would facilitate interpretation of the study results.

The long-term economic consequences of perioperative adverse CNS events—gross and subtle—are unknown; the social and emotional costs of permanent CNS disability have not been examined, but likely range from disturbing to devastating in their impact on the patient and their family. But, optimism is appropriate. Recent advances in molecular neuroscience and insights into etiologies for brain insults have pried open the door to our understanding perioperative cerebral injury. The development of new approaches to CPB, such as epiaortic ultrasonography to identify atheromatous disease, and the use of endovascular clamps, may greatly decrease the cerebral embolic load associated with cardiac surgery. In addition, the development of multiple compounds that may effectively interrupt the pathologic cellular processes associated with cerebral ischemia (glutamate antagonists, adenosine-like moieties, oxygen free radical scavengers, directed monoclonal antibodies, PAF receptor antagonists, and other modulators of inflammation) may attenuate the adverse sequelae associated with cerebral ischemia. Perhaps "the decade of the brain" will end with the availability of definitive treatments to prevent the frequently devastating consequences of cerebral ischemia.

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