◇ This Month in

ANESTHESIOLOGY

■ Does High-dose Fentanyl Contribute to Postoperative Cognitive Dysfunction after Bypass Surgery? Silbert *et al.* (page 1137)

In an effort to elucidate the etiology of postoperative cognitive dysfunction (POCD) after coronary artery bypass graft surgery, Silbert *et al.* conducted a randomized controlled trial of high- *versus* low-dose fentanyl in patients undergoing the procedure. The authors recruited 350 patients aged 55 yr or older and randomized them to receive either high-dose fentanyl of 50 μg/kg or low-dose fentanyl of 10 μg/kg as induction anesthesia. Both groups of patients received premedication consisting of oral temazepam and ranitidine.

Patients were further stratified into on-pump and off-pump surgery groups. In all patients, postoperative pain relief consisted of morphine infusion for the first 24 h, acetaminophen (with or without codeine) orally, and indomethacin orally or rectally. Patients were treated for perioperative hypotension, hypertension, and tachycardia based on preset parameters. A battery of eight neuropsychological tests was administered prior to surgery; on postoperative day 6 or before discharge, whichever came first; 3 months after surgery; and 12 months after surgery. Visual analog scales were used to assess anxiety and depression at the time of testing, so as not to confound results of cognitive function assessments. The authors used both the 20% rule and the one SD rule to analyze results from the four testing intervals. A total of 326 patients (168 in the high-dose group and 158 in the low-dose group) was included in the final analysis. The one SD rule detected significantly more patients with POCD in the low-dose fentanyl group than the high-dose group at 1 week, but not at the other testing times. Patients with POCD spent an average of 1.2 days longer in the hospital than those without POCD. High-dose fentanyl was not associated with a difference in the incidence of POCD at 3 or 12 months after surgery.

■ Authors Measure Propensity of Sedative Drugs to Cause Upper Airway Obstruction. Norton *et al.* (page 1155)

Norton *et al.* used the application of negative airway pressure to determine the pressure that causes upper airway obstruction in normal subjects sedated with midazolam or propofol. Twelve male and eight female subjects were recruited for the study, and asked to refrain from ingesting alcohol and caffeine for 24 h prior to the experiment. Baseline pulse, blood pressure, and electrocardiogram measurements were taken as the participants lay supine on stretchers. Respiratory inductance plethysmography bands were placed on subjects' chests and abdomens, and Bispectral Index leads applied to their foreheads.

On different study days, subjects received either midazolam or propofol in random order, given by intravenous computer-controlled infusion. After they reached an equivalent depth of sedation (defined by a Bispectral Index value of 75 and an Observer's Assessment of Alertness/Sedation score of 2 or 3), participants' ventilation, end-tidal gases, respiratory inductance plethysmographic signals, and Bispectral Index values were monitored for 5 min. Then, in steps of 3 cm H_2O, from −3 to −18 cm H_2O, negative airway pressure was applied *via* facemask. Upper airway obstruction was assessed by cessation of inspiratory air flow and asynchrony between abdomen and chest respiratory inductance plethysmographic signals.

The authors found no significant difference between the drugs' effects on the negative pressure resulting in upper airway obstruction. Five female participants and one male participant receiving midazolam and four female participants and one male participant receiving propofol did not show any evidence of upper airway obstruction, even at −18 cm H_2O. Overall, females required higher negative pressures to cause upper airway obstruction with midazolam but not with propofol. The authors recommend that patient and pharmacokinetic factors, beyond those explored in this study, be investigated so that these drugs can be used safely during moderate levels of sedation.

■ Can Erythromycin Ameliorate Effects of Transient Global Cerebral Ischemia? Brambrink *et al.* (page 1208)

Although numerous preconditioning stimuli (*e.g.*, hypoxia, hyperthermia) have been shown to be effective in decreasing cell death after global cerebral ischemia, the serious side effects associated with these preconditioning stimuli render them unsuitable for clinical use. Brambrink *et al.* decided to investigate whether erythromycin pretreatment might exert long-term protective effects in an *in vivo* model of global cerebral ischemia.

Male Wistar rats received pretreatment with either erythromycin (25 mg/kg intramuscularly) or vehicle and were then subjected to 15 min of transient global cerebral ischemia 6, 12, or 24 h later. Animals were allowed to recover for 7 days after the ischemic insult, and their neurologic status was assessed at specific intervals. On day 7, the animals were killed and neuronal survival was assessed *via*

microscopic examination of hematoxylin and eosin–stained coronal brain slides. In a parallel series of experiments, 18 rats were used to assess the effects of erythromycin on cerebral bcl-2 messenger RNA and protein expression.

Neurologic evaluations, performed at baseline and then once daily after induction of transient ischemia, were conducted by an investigator blinded to the animals' group assignments. Consciousness, breathing, smell, vision and hearing, reflexes, orientation, and other factors were scored according to a neurologic deficit score. Results demonstrated that erythromycin improved postischemic neuronal survival in hippocampal CA1 and CA3 sectors and reduced functional deficits, especially at 12 h posttreatment with the antibiotic. In addition, pretreatment with erythromycin transiently up-regulated bcl-2 messenger RNA in the neocortex 6 h later. Because the changes erythromycin induced in bcl-2 expression were small and transient, the induction of that pathway may be less relevant for the neuroprotective effects of pharmacologic preconditioning. The authors' sample size is a potential limitation of the study. But the fact that the antibiotic induced tolerance in this study suggests there may be a potential role for its use in preemptive neuroprotection.

■ Strategies to Guide Fluid Management and Improve Ventricular Function after Ischemia. Jacob *et al.* (page 1223)

In this issue, Jacob *et al.* report on experiments using an isolated perfused guinea pig heart model to compare the impact of different resuscitation fluids (human albumin, hydroxyethyl starch, and saline) on vascular integrity after ischemia reperfusion.

The team first measured aortic pressure and transudate formation in the isolated hearts during perfusion with Krebs-Henseleit buffer at four flow rates (3, 4, 6, and 8 ml/min). In the next step of the experiment, 0.9% saline, 5% albumin, 2.5% albumin, and 6% hydroxyethyl starch were added to the Krebs-Henseleit buffer. Samples of transudate and effluent were collected after perfusion with the additive solutions, and aortic pressure was measured 5 min later at different perfusion rates. The team then induced 20 min of global, stopped-flow ischemia by clamping the aortic feed line, and then reperfused the hearts at minute 60. A second series of experiments entailed applying the four respective perfusates after enzymatic digestion of the endothelial glycocalyx. The authors found that albumin prevented fluid extravasation in the heart more effectively than did the solutions containing hydroxyethyl starch or saline. The power of albumin to prevent tissue edema is dependent, they say, on an undamaged endothelial glycocalyx. Based on their data in this *ex vivo* model, the authors recommend maintaining an albumin blood concentration from the onset of a surgical procedure, especially in the ischemia–reperfusion setting and in critically ill patients. The optimal serum level in critically ill patients, however, remains controversial, and more clinical trials are urgently needed to establish a standard of care.

Gretchen Henkel