◇ This Month in

ANESTHESIOLOGY

■ Mechanisms of Myocardial β-adrenergic Function Explored in Humans. Booth *et al.* (page 602)

Booth *et al.* enrolled 52 patients undergoing aortocoronary surgery in a study to assess whether myocardial β-adrenergic (βAR) function is reduced after cardiopulmonary bypass (CPB), as the team had previously demonstrated in a canine model. Preoperative cardiac medications were continued until the time of surgery. Of the 52 patients, 31 were taking chronic beta-blockers and received their usual dose the morning of surgery. After oral premedication of methadone, 5–10 mg, and diazepam, 5–10 mg, 1.5 h before surgery, anesthesia was induced with fentanyl, 5–15 mg/kg, and midazolam, 1–5 mg. At the time of atrial cannulation, and just before CPB, the surgical team obtained a small piece of right atrial appendage (30–100 mg wet weight). A second atrial biopsy (10–30 mg wet weight) was obtained proximal to the atrial cannulation suture line when the patient's core body temperature had returned to 36°C, just before terminating CPB (20–30 min after release of the aortic cross-clamp). Immediately placed in liquid nitrogen and stored at −70°C, the samples were later analyzed for myocardial βAR density and functional responsiveness.

The researchers found that CPB decreased isoproterenol-stimulated and basal (unstimulated) adenylyl cyclase activity. The team used βAR density, sodium fluoride-stimulated adenylyl cyclase (representing G protein activity), and manganese-stimulated adenylyl cyclase activity (representing direct stimulation of the adenylyl cyclase moiety) to investigate at which point myocardial BAR dysfunction occurs: at the receptor or in the BAR signal transduction cascade. NaF-stimulated adenylyl cyclase activity decreased 14%, whereas Mn-stimulated adenylyl cyclase activity decreased 21%. Plasma catecholamine levels, determined from blood samples obtained during surgery, increased significantly during CPB.

Receiving chronic βAR antagonists did not protect against the acute decrease of myocardial adenylyl cyclase response to βAR agonists in the adults undergoing CPB in this study. The mechanism underlying acute βAR dysfunction may be a result of direct impairment of the adenylyl cyclase moiety.

■ Risk Factors for Transient Neurologic Symptoms after Spinal Anesthesia: An Epidemiologic Study. Freedman *et al.* (page 633)

To evaluate potential risk factors for transient neurologic symptoms (TNS) after spinal anesthesia, Freedman *et al.* conducted a 14-month prospective, multicenter epidemiologic study of patients receiving spinal anesthesia at 15 Kaiser-Permanente Northern California regional hospitals. On a voluntary basis, anesthetists were asked to submit detailed data sheets on patients undergoing spinal anesthesia. From the 6,092 patients submitted for the study, 2,555 were randomly selected for follow-up evaluation. Of these patients, 1,883 were successfully interviewed. Twenty of the final group were excluded for various reasons. A research nurse blinded to all information except for patient name, medical record number, surgical procedure, and date of surgery then contacted patients sometime within a 6-day postoperative period. She used a structured questionnaire to obtain information regarding postoperative recovery, including neurologic symptoms. Patients who reported unresolved neurologic symptoms at the first call were recontacted within 7–10 days. Further follow-up evaluation proceeded on a case-by-case basis until the problem resolved or until the patient or primary physician declined further contact.

Transient neurologic symptoms were defined as pain or dysesthesia in the legs or buttocks, and the pain was rated on a scale of 0–10 (0 = no pain; 10 = worst pain imaginable). Other neurologic symptoms such as weakness, numbness, or paresthesias of the lower extremities or urinary retention requiring catheterization were also examined.

Among the final 1,863 study participants, 47% had received lidocaine, 40% bupivacaine, and 13% tetracaine. Patients receiving lidocaine were more likely to be men, to have had outpatient surgery, to have had surgery in the lithotomy position, and to have undergone inguinal, rectal, or urologic surgery. Patients given lidocaine were at higher risk for TNS than those receiving bupivacaine or tetracaine. In addition, the lithotomy position and outpatient status were important risk factors in patients receiving lidocaine. Obesity was borderline statistically significant as another risk factor. Age, gender, history of back pain, needle type, and lidocaine dose and concentration did not affect risk of TNS.

Propofol Brain and Lung Distribution Kinetics in Rats. Dutta *et al.* (page 678)

To understand the formulation-induced changes in pharmacokinetics and time course of electroencephalographic effect (EEG), Dutta *et al.* investigated propofol brain and lung distribution kinetics in rats infused with equieffective (EEG burst suppression) doses of propofol in emulsion or lipid-free formulations.

Intravenous and intra-arterial catheters were implanted in 42 male Wistar rats during isoflurane anesthesia 24 h before the study began. In 21 rats, propofol in emulsion was infused at 5 $mg \cdot min^{-1} \cdot kg^{-1}$ for 2 min. In another 21 rats, propofol in lipid-free formulation was administered using two syringe pumps that simultaneously infused propofol in ethanol and carrier solution into a mixing tube that was connected to the rat's jugular cannula. Arterial blood samples were obtained at 1, 2, 3, 5, 7, 10, or 15 min from the start of the infusion. Three animals from each infusion group were decapitated at each of the same time intervals, and their brains and lungs immediately harvested, frozen, and stored at −20°C for later assays for propofol.

The researchers used deconvolution and moment analysis to calculate the half-life for propofol brain turnover (BT) and brain:plasma partition coefficient (Kp). Lung concentration–time profiles were also compared for the two formulations. The peak propofol plasma concentrations for the lipid-free formulation was 50% of that observed for the emulsion formulation. The peak lung concentrations for the lipid-free formulation were 300-fold higher than for the emulsion formulation, indicating extensive pulmonary sequestration of propofol. Propofol's brain:plasma coefficient was high and in agreement with its high lipophilicity, showing a trend toward a higher brain:plasma partition coefficient with the lipid-free formulation.

Comparing the two formulations, the researchers concluded that emulsion reduces pulmonary sequestration or uptake, produces higher peak plasma concentrations of propofol at lower doses, and allows rapid redistribution of propofol from the brain to systemic circulation. Pulmonary sequestration observed with the lipid-free formulation leads to lower plasma concentrations and a delay in time to peak concentrations in the brain. This explains the higher dose potency of emulsion formulations and the higher steady state potency (and delay in time to maximal effect and sluggish offset of sedative effect) of lipid-free formulations. The half-times for turnover of propofol in the brain were similar to effect-site equilibration half-times and independent of formulation.

Does Inhibition of Enzymic Degradation of Muscle Relaxants Affect Onset Time of Neuromuscular Block? Beaufort *et al.* (page 707)

Using 20 male pigs, Beaufort *et al.* designed a study to assess whether the rate of decrease in the concentration of a muscle relaxant in plasma would influence the onset times for neuromuscular block. After anesthesia with intramuscular midazolam and ketamine, the pigs' femoral arteries were cannulated for collection of blood samples. Femoral veins were cannulated for administration of either suxamethonium (10 pigs) or mivacurium (10 pigs). Electrodes were attached to the left common peroneal nerve in each pig, and response of the tibialis anterior muscle was registered mechanomyographically. Five pigs from each muscle relaxant group were then randomly assigned to receive a plasma cholinesterase inhibitor, tetraisopropyl pyrophosphoramide (iso-OMPA), and the other five pigs in each group served as controls. Each pig then received six sequential doses of muscle relaxant, aimed at producing between 50% and 90% depression of initial twitch height, with doses #4–6 serving as intraindividual and interindividual comparisons. The time interval between doses was 90 min, to allow for recovery of twitch height to 100%. For pigs randomized to receive the plasma cholinesterase inhibitor, iso-OMPA was administered between the fourth and fifth doses, and a longer interval of 120 min allowed to compensate for reduced clearance time and to prevent accumulation of the muscle relaxant in the presence of iso-OMPA.

Plasma cholinesterase activity was measured in all pigs using ultraviolet spectrophotometry at 405 nm with butrylthiocholine as substrate. In the control groups (those pigs in both the suxamethonium and mivacurium groups not receiving iso-OMPA), the activity was measured in blood samples taken before and at the end of each experiment. Results showed that when equipotent doses of drug were given, inhibiting plasma cholinesterase activity by 93% increased the onset time of suxamethonium from 40 s to 131 s. Similarly cholinesterase inhibition increased onset time of mivacurium from 52 s to 105 s. Inhibition of degradation decreased the ED_{70} of suxamethonium from 900 μg/kg to 150 μg/kg and of mivacurium from 100 μg/kg to 35 μg/kg. The investigators believe that obtaining onset times of 1 min or less may require development of muscle relaxants that have a low affinity for the receptor and a rapid clearance from plasma.

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