◇ This Month in

ANESTHESIOLOGY

■ Investigating Practicality of Genetic Testing for Malignant Hyperthermia Susceptibility. Sei *et al.* (page 824)

Susceptibility to malignant hyperthermia (MH), a fundamental defect in the ability of muscle to adequately regulate calcium concentration, is primarily diagnosed by the *in vitro* contracture test and the caffeine–halothane contracture test. Furthering the search for less invasive testing, Sei *et al.* conducted a genetic study of 124 unrelated patients who had already been diagnosed as MH susceptible using the caffeine–halothane contracture test.

The team extracted DNA from muscle tissue, peripheral blood, or buccal cells for analysis. To screen for mutations in the N-terminus, central, and C-terminus regions of the *RyR1* gene (the primary gene responsible for susceptibility to MH), they used restriction fragment length polymorphism, single-strand conformation polymorphism, or denaturing high-performance liquid chromatography analysis. They also performed measurements of relative changes of calcium responses in B cells. A total of 14 *RyR1* mutations—12 known and 2 novel—were detected in 29 patients, resulting in an estimated overall incidence of 23%. Twenty of the 29 mutations, or 69%, originated from the MH/CCD2, or central, region. In 8 patients, mutations were identified in the MH/CCD1 region. Screening the MH/CCD3 region yielded a novel mutation Leu4824Pro in a single patient who had previously been diagnosed with central core disease.

Although genetic testing cannot yet replace the caffeine–halothane contracture test as the standard diagnostic test for MH, results from this study suggest that in families in which inheritance of the mutation has been identified, genetic screening of other family members could be beneficial. Based on patterns of mutations these investigators found, initial screening for mutations in the MH/CCD2 region of the *RyR1* gene cluster now may be the most cost-effective strategy for the North American population.

■ Is Apolipoprotein E Genotype Associated with Postoperative Cognitive Dysfunction? Abildstrom *et al.* (page 855)

The E4-allele of apolipoprotein E (APOE) has been shown to be a risk factor for Alzheimer disease, poor postcerebral injury outcome, and accelerated cognitive decline in normal aging. Abildstrom *et al.* designed a multicenter study to explore whether presence of the E4-allele in patients is associated with decline of cognitive function after noncardiac surgery.

The team recruited 976 patients over the age of 40 set to undergo noncardiac surgery. They conducted neuropsychological tests with participants preoperatively and 1 week and 3 months postsurgery to see whether any had experienced postoperative cognitive dysfunction (POCD). They also determined the patients' genotypes using blood sample analysis. The E4-allele was found in 272 patients. One week after surgery, the incidence of POCD was 11.7% in patients with the allele and 9.9% in patients without the allele. Three months later, POCD was 10.3% and 8.4%, respectively. The researchers were unable to demonstrate an association between presence of the apolipoprotein E genotype and POCD after noncardiac surgery. It may be that the study's small sample size was responsible for a lower incidence of POCD than had been expected. However, POCD, a serious complication of surgery, still warrants further research to elucidate the contributing mechanisms.

■ Do Neuroprotective Benefits of Propofol Extend beyond 8 Days Postischemia? Engelhard *et al.* (page 912)

Studies in laboratory animals have shown that anesthetic agents can reduce neuronal damage after cerebral ischemia, but most investigations have assessed outcome less than 8 days after ischemic insult. In an effort to determine whether the neuroprotective benefits of propofol are sustained, Engelhard *et al.* extended the period of postischemic assessment to 28 days.

In 64 anesthetized rats, the investigators inserted catheters for blood withdrawal and drug administration and placed a loose ligature around the right common carotid artery for later clamping. After these preparations and baseline measurements, the animals were randomized to one of two groups: group 1 (n = 32) served as the control group, receiving intravenous fentanyl and nitrous oxide. Group 2 (n = 32) received intravenous propofol and oxygen in air. After a 45-min equilibration period, cerebral ischemia was induced. The occlusion of the carotid artery was concluded after 45 min, and the withdrawn blood was reinfused over a 15-min period. Vecuronium was given as a continuous infusion to maintain neuromuscular blockade. After wound closing, the animals were extubated and assigned to one of four time-control groups and were allowed to survive 1, 3, 7,

or 28 days. At the end of the designated observation period, the animals' brains were removed under deep halothane anesthesia and prepared for tissue analysis.

Investigators blinded to group assignment counted number of eosinophilic neurons from hippocampal areas CA 1–3 from the ischemic hemisphere. The amount of apoptosis-related proteins Bax, p53, Bcl-2, and Mdm-2 and neurons positive for activated caspase-3 were analyzed. Depending on time of survival, between 16–54% of hippocampal neurons from control rats' brains were eosinophilic. There were no eosinophilic neurons detected in the brains of rats given propofol. In control animals, the concentration of Bax was 70–200% higher after cerebral ischemia compared to animals receiving propofol over time. During the first 3 days, Bcl-2 was 50% lower in control animals compared to those anesthetized with propofol. The activated caspase-3–dependent apoptotic pathways did not appear to be affected by propofol. Since isoflurane was given for 1 h during the preparation period, the authors cannot rule out a preconditioning effect from isoflurane. However, they were able to show that propofol inhibits neuronal damage after incomplete cerebral ischemia for at least 28 days after injury.

■ Remifentanil's Protective Effect Investigated in the Rat Heart. Zhang *et al.* (page 918)

Zhang *et al.* studied the effects of remifentanil, the ultrashort-acting phenylpiperidine opioid used in high doses for anesthesia, as anesthetic preconditioning against myocardial ischemia reperfusion injury in the rat heart. Prior to a 30-min period of left coronary artery occlusion, rats received saline vehicle, ischemic preconditioning (5 min of occlusion and 5 min of reperfusion, repeated three times), or remifentanil preconditioning, using five different doses. Then, to test which opioid receptor was involved in mediating the effects of remifentanil and ischemic preconditioning, the experiment was repeated, with rats randomly assigned to receive δ–, κ–, or μ–opioid receptor antagonists before preconditioning.

A total of 107 animals were used in the study. After reperfusion was completed, each rat heart was excised, injected with stain, frozen, and cut into 2 mm slices for analysis. The volumes of infarct size and area at risk for each heart were calculated. Investigators found that both ischemic and remifentanil preconditioning significantly reduced infarct size. The reduction in infarct size by remifentanil preconditioning occurred in a dose-dependent manner. The remifentanil preconditioning effect was prevented or significantly attenuated by coadministration of a μ–, κ–, or δ–opioid receptor antagonist. The infarct-sparing effect of ischemic preconditioning was abolished by blockage of κ– or δ–opioid receptor, but not μ–opioid receptor. Remifentanil produced its maximum effect at a dose of 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with an ED_{50} of 2.7 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Since μ–opioid receptors have not been found in the rat heart, the authors theorize that the effect of remifentanil may have been mediated by μ-agonist activity outside the myocardium.

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