◇ This Month in

ANESTHESIOLOGY

■ Predicting Level of Consciousness during Administration of Low-dose Isoflurane in Volunteers. Plourde *et al.* (page 844)

After a pilot study conducted to assess end-tidal concentrations for loss of consciousness during slow induction with isoflurane, Plourde *et al.* recruited 12 ASA physical status I volunteers for examination of the effects of isoflurane, 0.26–0.50%, on auditory steady-state response (ASSR) and level of consciousness. The team obtained baseline ASSR recordings and began administration of isoflurane, manually titrating inspired concentrations to reach target end-tidal concentrations of 0.50%, 0.38%, and 0.26%. Subjects breathed spontaneously through airtight face masks, and concentrations were kept constant for 15 min before recording ASSRs to allow for equilibration of partial pressures between the brain and lungs.

In addition to baseline ASSR recordings, which included one recording with earphones disconnected to estimate residual electroencephalographic noise, the team obtained recordings at each end-tidal concentration and at recovery (15 min after end of isoflurane administration). The stimuli consisted of 500-Hz tonebursts (10 ms, 82 dB PeSPL) delivered to the right ear at the rate of 35, 40, or 45 per second. (Inserts were placed in volunteers' left ears to partially block ambient noise.) Because of restlessness and nausea, recovery recordings could not be obtained in three volunteers. Consciousness was defined as responsiveness to either or both of the following verbal commands: "open your eyes" and "squeeze my fingers." During recording periods, commands were given at 1-min intervals, but separately from the auditory stimuli to assess ASSR.

The ASSR amplitude during baseline and recovery was larger than during isoflurane, 0.38% and 0.50%, whereas the amplitude at 0.26% was the largest of all concentrations. An ASSR amplitude of less than 0.07 μV was always associated with unconsciousness. The investigators found that suppression of consciousness and maximal attenuation of ASSR occurred in the same isoflurane concentration ranges and that profound attenuation of ASSR appears to reflect unconsciousness (defined as unresponsive to verbal commands).

■ Protecting Patients with Bronchial Hyperreactivity against Bronchospasm during Inhalational Challenge with Histamine. Groeben *et al.* (page 862)

Searching for prophylaxis without the risk of cardiac side effects in patients with bronchial hyperreactivity who undergo airway instrumentation, Groeben *et al.* enrolled 15 volunteers in a randomized, double-blind, placebo-controlled study using histamine challenge as a "stand-in" for the stimulation evoked by endotracheal intubation. The participants all had moderate bronchial hyperreactivity, confirmed by inhalational provocation with histamine, with histories of either active asthma, childhood asthma, severe hay fever, or chronic obstructive respiratory disease. Patients with more severe bronchial hyperreactivity were excluded because the planned histamine challenge would have caused a greater risk of bronchospasm.

Researchers inserted a cannula into each participant's right antecubital vein for infusion of either lidocaine or placebo and into the left vein for measurement of lidocaine plasma concentrations. Baseline lung function was assessed before any other measurements took place. All lung function measurements were made by a single investigator blinded as to type of drug administered. On four different days, participants were subjected to histamine challenges, with concentrations of histamine diphosphate ranging from 0.074 to 18 mg/ml after pretreatment with, in random order: inhaled salbutamol aerosol, intravenous lidocaine, inhaled salbutamol followed by intravenous lidocaine, or placebo (inhaled and intravenous saline). When participants were pretreated with intravenous lidocaine, the histamine threshold increased to 14.2 ± 9.5 mg/ml (over a baseline PC_{20} of 6.4 ± 4.3), whereas inhaled salbutamol increased the threshold to 16.8 ± 10.0 mg/ml. Combining lidocaine and salbutamol increased PC_{20} significantly, compared with either drug given alone, to 30.7 ± 15.7 mg/ml. Heart rate and arterial blood pressure were not affected by lidocaine infusion, and only one volunteer had a reproducible increase in heart rate after each salbutamol inhalation. Given the ability of combined lidocaine–salbutamol to attenuate participants' responses to inhalational histamine challenge in this study, the authors recommend pretreatment of patients with bronchial hyperreactivity with a β-mimetic aerosol and intravenous lidocaine before endotracheal intubation or bronchoscopy.

■ Anesthesia Requirements Quantified during Three Types of Surgical Stimuli. Kazama *et al.* (page 894)

Kazama *et al.* designed a randomized study to characterize the pharmacodynamic interaction between propofol

and fentanyl and the resulting suppression of somatic and hemodynamic responses during skin incision (SI), peritoneum incision (PI), or abdominal wall retraction (RET). In 99 ASA physical status I or II patients set for elective surgery involving gastric resection, a central venous catheter was inserted *via* the right jugular vein during regional anesthesia 1 day before surgery, to be used for propofol and fentanyl administration on the following day. Propofol and fentanyl were administered *via* computer-assisted continuous infusion to provide equilibration between plasma–blood concentration and biophase concentration.

After induction of anesthesia with propofol, patients were randomly assigned to one of nine groups: those receiving no fentanyl, or predetermined target plasma concentrations of 0.5, 1.0, 2.0, 3.0, 5.0, 7.0, 8.0, or 9.0 fentanyl. Skin incision was performed no sooner than 30 min after the start of fentanyl infusion. If the somatic response to skin incision was negative without persistent hypertension, the target concentration of propofol was not changed before proceeding to PI. Positive somatic responses warranted immediate increases of propofol, in descending concentrations depending on the beginning concentration (an increase of 10.0 in the group receiving 0.5; an increase of 7.0 in the group receiving 1.0, and so on). Propofol concentrations were adjusted for PI and abdominal wall retraction in the same manner. Vecuronium was used only when absolutely necessary and in the smallest doses needed to facilitate surgery and incision.

The researchers found that patients' somatic and hemodynamic responses varied depending on the type of surgical stimulus. The respective fentanyl and propofol concentrations that suppressed 50% probability of somatic response and 50% probability of moderate hemodynamic change (defined as a 15% increase in systolic blood pressure over prestimulation values) were 3.6 ng/ml and 2.5 μg/ml for SI, 8.4 ng/ml and 1.6 μg/ml for PI, and 5.9 ng/ml and 5.1 μg/ml for RET. Both drugs had a synergistic interaction on systolic blood pressure increase after various surgical stimulations. Additional evidence of synergism was seen when increasing fentanyl concentration reduced propofol Cp50si, Cp50pi, and Cp50ret for somatic responses.

■ Induction Profiles of Immediate-early Genes in Ovine Brain after CPB and HCA. Bokesch *et al.* (page 961)

Cardiopulmonary bypass (CPB) and hypothermic circulatory arrest (HCA) induce transcription and translation of immediate-early gene c-fos, the protein products (c-Fos and c-Jun) of which form hetero- and homodimers that function as transcriptional regulators at the AP-1 binding site on DNA. The levels of these proteins may have positive and negative transcriptional functions, resulting in either cell survival or cell death. Bokesch *et al.* studied neonatal lambs anesthetized with isoflurane and cannulated for CPB to assess the effects of aptiganel, a noncompetitive NMDA antagonist, on immediate- early gene expression, neuronal necrosis, and functional outcome. One group of 22 animals received intravenous aptiganel, 1.25 mg/kg, 5–10 min before the right atrium was cannulated, whereas the second group of 25 received saline vehicle. After initiation of CPB, animals were cooled to 14–16°C, and their heads were packed in ice. The CPB pump was turned off, and HCA was maintained for 90 min in 22 animals (14 saline- and 8 aptiganel-treated) and 120 min in another 23 animals (11 saline- and 12 aptiganel-treated).

After HCA, animals were rewarmed on CPB to 38°C and weaned off bypass. In the aptiganel-treated animals, a second dose of 1.25 mg/kg was administered during rewarming. One hour after rewarming, 23 animals were killed, and the remaining animals were allowed to recover for 48–72 h before they were killed. During brain tissue analysis, the number of dead neurons in the hippocampal formation were counted by a blinded observer. Additional immunohistochemical analysis was performed to locate and quantify neurons with intranuclear c-Jun and c-Fos–like immunoreactivity within specific regions of the hippocampal formation. These samples were compared with brain tissue from a control group (six animals) that had received general anesthesia for 3 h without CPB. The animals in the survivor group were assessed using a modified ovine behavioral scale (10 = normal function and 0 = brain death).

Cardiopulmonary bypass and HCA differentially induced c-Jun and Fos proteins in the hippocampal formation. The team found that c-Jun expression, apparent in all neurons except the dentate gyrus (DG), increased with the duration of HCA. Fos protein expression, found in all neurons including the DG, was greatest after 90 min of HCA. Necrosis was observed in CA1 and CA3 neurons but not in the DG after 120 min of HCA. Aptiganel completely inhibited c-Jun (but not Fos) expression, improved functional outcome, and attenuated neuronal necrosis. c-Jun expression is associated with neuronal necrosis, whereas Fos protein expression is associated with cell survival.

Gretchen Henkel