

ANESTHESIOLOGY

■ Three Studies Assess Changes in EEG Activity during Sevoflurane Anesthesia. Yli-Hankala *et al.* (page 1596), Constant *et al.* (page 1604), Kaisti *et al.* (page 1952)

Sevoflurane has been shown in animal models to have proconvulsant properties. Nevertheless, with the exception of case reports of the volatile anesthetic triggering seizures in epileptic children, sevoflurane is not generally considered epileptogenic in otherwise healthy patients. Three studies in this issue address changes in electroencephalographic (EEG) activity during sevoflurane anesthesia. In the first article, Kaisti *et al.* report two EEG-verified cases of epileptiform activity during a study of the effects of sevoflurane anesthesia on regional cerebral blood flow (rCBF). Eight young healthy volunteers were included in the study. There was no premedication given, and anesthesia was induced *via* mask with 7% sevoflurane and 100% oxygen. In addition to positron emission tomography obtained at intervals after increases in end-tidal concentration of anesthetic, there was continuous EEG monitoring.

In the first case, slight clonic movement was noticed 1 h 40 min into anesthesia, when the subject was receiving 2 MAC sevoflurane. End-tidal sevoflurane concentration at the time of positron emission tomography during the seizure was 3.1%. The EEG recording showed a rhythmic epileptiform discharge, a pattern compatible with the clinical seizure type (partial motor seizure). Despite the episode, the subject (who had no history of seizure) awoke from anesthesia and recovered normally. The second patient was the eighth volunteer in the study, who, after 1 h 25 min of sevoflurane anesthesia, had two partial, secondarily generalized EEG discharges, which lasted for 2 and 3 min, respectively. That subject also awoke and recovered normally, and results of magnetic resonance imaging of the brain and clinical neurologic examination were also normal. Although the implications from their findings are unclear, the authors conclude that sevoflurane appears to have epileptogenic potential in healthy patients during burst-suppression anesthesia.

Having noted in a previous study that hyperventilation during sevoflurane nitrous oxide-oxygen mask induction is associated with cardiovascular hyperdynamic response, Yli-Hankala *et al.* designed a randomized controlled study to determine whether hyperdynamic response can be explained by EEG findings during sevoflurane mask induction. The team enrolled 30 pa-

tients, American Society of Anesthesiologists status I or II, scheduled to undergo gynecologic procedures. All participants were premedicated with oral 5 mg diazepam 1 h before anesthesia. Patients were randomly allocated to one of two groups: spontaneous breathing (SB) and controlled hyperventilation (CH). Baseline heart rate, mean arterial pressure, and oxygen saturation by pulse oximetry (Sp_{O_2}) were measured; EEG data were collected before and during the study period, then digitized and stored for later analysis by a neurophysiologist blinded to the patients' ventilation mode.

All patients breathed oxygen *via* a clear face mask for 2 min before induction. Anesthesia was induced using the single-breath method with a semiclosed system primed with a fresh gas flow of 10 l/min and a sevoflurane vaporizer. Observers started a stop watch when patients took the first breath from the face mask. The induction period lasted 6 min, at the end of which arterial blood samples were collected for blood gas analysis. Patients were then intubated and the surgery proceeded.

In most of the patients in the SB group, mixed EEG activity, consisting of monophasic slow delta waves with or without spikes, continued to the end of the study. The EEG of seven of the SB group patients and all patients in the CH group showed epileptiform EEG activity—periods of polyspikes or rhythmic polyspikes. Heart rate increased 54% more than baseline values in the CH group 4 min after induction. The epileptiform EEG patterns elicited by sevoflurane mask induction may be explained by the speed of the anesthetic induction or the ventilation mode itself.

Constant *et al.* also used continuous EEG, in addition to heart rate and finger blood pressure, to evaluate EEG tracings and autonomic cardiovascular activity after induction with either sevoflurane or halothane in children aged 2–12 yr of age scheduled for elective tonsillectomy. After premedication with midazolam, patients were randomly assigned to one of three induction techniques: rapid induction with 7% sevoflurane in 100% O_2 ; incremental induction with 2, 4, 6, and 7% sevoflurane every five breaths in 100% O_2 ; or incremental induction with 1, 2, 3, and 3.5% halothane every five breaths in a 50:50 mixture of oxygen and nitrous oxide.

An additional group of 10 patients was later enrolled after completion of the first study in an open-label, non-randomized arm. Patients received 7% sevoflurane in a 50:50 mixture of oxygen and nitrous oxide. This was

deemed necessary because nitrous oxide was used in the original study's halothane group but was omitted in the sevoflurane groups. The same monitoring of EEG and hemodynamic data was performed.

In contrast to the observations made in the Kaisti *et al.* and Yli-Hankala *et al.* studies, researchers found no seizure-like activity in the 45 EEG tracings obtained. Induction of anesthesia was associated in all four groups with an increase in TSP and a shift toward the low-frequency bands. Sevoflurane induced greater withdrawal of parasympathetic activity than halothane, and transient relative increases in sympathetic vascular tone at loss of eyelash reflex.

■ Study Examines Interaction of Pain and Dyspnea in Healthy Volunteers. Nishino *et al.* (page 1633)

In clinical situations, such as with terminal cancer and chronic obstructive pulmonary disease, pain and dyspnea frequently coexist. To elucidate a possible association between pain and dyspneic sensations, Nishino *et al.* induced experimental pain and dyspnea during controlled conditions in 15 healthy volunteers (11 men and 4 women, aged 25–32 yr).

Volunteers were seated throughout the experiment and breathed through an apparatus that included a face mask, a pneumotachograph, and a one-way valve system. Dyspneic sensation was induced by a combination of inspiratory resistive loading and hypercapnia induced by extra dead space, while an orthopedic inflatable tourniquet was placed around the calf and inflated to 350 mmHg to induce experimental pain. Subjects were asked to rate their pain or dyspnea according to a visual analogue scale (VAS) from 0 to 100 during each experimental protocol.

In randomized order, volunteers were subjected to added respiratory load without pain for 9 min; pain stimulus for 9 min without additional respiratory load; addition of pain stimulus 4 min after the start of breathing with an added load; and addition of external respiratory load after 4 min of pain stimulation. In addition to recording of the VAS scores on a linear potentiometer, airflow, Pmask, partial pressure of end-tidal carbon dioxide (P_{ETCO_2}), and $P_{O.1}$ were all recorded on a thermal array recorder. Later analysis of the recorded data revealed that, with the start of respiratory loading, \dot{V}_I and P_{ETCO_2} immediately increased, with a simultaneous increase in the dyspneic VAS score. These changes stabilized within 3 min and remained nearly steady for the

duration of the protocol. The pain stimulus also elicited an immediate increase in pain VAS score, which tended to subside after 3 min.

When pain stimulus was added to loaded breathing component, subjects registered higher dyspneic VAS scores. However, adding respiratory loading during pain stimulation did not change the pain VAS score. The researchers point out that pain in these healthy subjects does not duplicate pain experienced in sick and dying patients, nor can tourniquet pain be generalized to other types of pain, such as visceral or neuropathic pain. However, given the results from this study, it is possible that attention to adequate pain management in sick patients may help to relieve their dyspnea.

■ Effects of Cigarette Smoke Exposure on Alveolar Macrophage Functions during Halothane and Isoflurane in Rats. Kotani *et al.* (page 1823)

The antimicrobial and proinflammatory functions of alveolar macrophages are altered during anesthesia and surgery. Kotani *et al.* evaluated how previous long-term exposure to cigarette smoke might further affect these functions during halothane and isoflurane anesthesia in rats. Sixty rats were exposed to filter-tipped cigarettes for 30 min/day during a 60-day period using a Hamburg II smoking machine. Sixty additional rats were sham exposed and served as controls during the experiments.

Thirty control and 30 smoke-exposed rats were mechanically ventilated with 1.5 MAC halothane and isoflurane. Ten smoke-exposed and control animals were assigned to one of three different anesthetic durations. Immediately after induction of anesthesia, 10 smoke-exposed and control rats were killed for whole pulmonary lavage. Another 10 others from each group were killed at 2 and 6 h after onset of anesthesia. The lavage fluid was evaluated for total cell count, viability and cell differentiation, and aggregation. Alveolar macrophages were separated from bronchoalveolar lavage fluid by centrifugation, then resuspended in a saline-dextrose solution to determine phagocytosis. Antimicrobial activity of the macrophages was determined by the number of *Listeria monocytogenes* remaining after a 48-h culturing period. The rate at which the macrophages killed *Listeria* was determined by comparing bacteria surviving in control (cell-free) tubes with those combined with separated macrophages.

Overall, the concentration and total number of alveolar cells in the lavage fluid were five times greater in the smoke-exposed rats than in the control rats during halo-

thane anesthesia. In rats exposed to smoke and in controls, macrophage aggregation and neutrophil influx increased over the 6-h course of halothane anesthesia, but the aggregation in smoke-exposed rats was twice that of non-smoke-exposed rats. Gene expression and production of proinflammatory cytokines (except for IL-6) increased 2- to 20-fold during anesthesia. The increases in IL-1 β , IFN- γ and TNF- α in the control rats were 1.5-8 times greater than those in the smoke-exposed rats.

Extrapolation of the results to humans must be done cautiously, and surgical stress cannot be discounted as a contributor to the augmentation of leukocyte adhesion molecules and activation of neutrophil function. However, even 6 weeks of exposure to cigarette smoke impairs antimicrobial and proinflammatory functions of alveolar macrophages.

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