

◆ This Month in

## ANESTHESIOLOGY

### ■ Does Lumbosacral CSF Volume Contribute to Variability of Spread in Spinal Anesthesia? Carpenter *et al.* (page 24)

Multiple factors have been proposed to influence the spread of spinal anesthesia, including baricity and dose of local anesthesia, injection site, position of patient when injecting nonisobaric solutions, patient's age, anatomic configuration of the spinal column, and pregnancy. To evaluate the possible correlation between lumbosacral cerebrospinal fluid (CSF) volume and extent and duration of spinal anesthesia, Carpenter *et al.* performed lumbar puncture at the L2-L3 interspace on 10 healthy volunteers. They measured dermatomal levels of analgesia to pinprick 1, 2, and 5 min after intrathecal injection of 5% lidocaine (50 mg in dextrose, 7.5%) and at 5-min intervals until 40 min after injection and then every 10 min until recovery of sensation to pinprick at the S2 dermatomal level.

Using 5 s of transcutaneous electrical stimulation (TES) (50 Hz tetanus at 50 mA) to approximate the noxious stimulation of surgical incision, the team estimated onset and duration of surgical anesthesia. Motor strength in the right quadriceps and gastrocnemius muscles was measured using an isometric force dynamometer 0 and 10 min after injection of lidocaine and every 10 min thereafter until return to 90% of baseline strength measurement.

In 9 of the 10 volunteers, low thoracic, lumbar, and sacral axial magnetic resonance images (MRIs) at 8-mm increments were obtained after spinal anesthesia to calculate lumbosacral CSF volume, which in this series included the volume of the nerve root. (The other volunteer had previously had measurement of CSF volume *via* MRI and subsequently consented to receive spinal anesthesia.)

Time to achieve peak sensory block (the height of which ranged from T12 to T2) ranged from 10 to 30 min. The duration of surgical anesthesia assessed by TES at T10 ranged from 0 to 70 min ( $42 \pm 21$  min), from 0 to 110 min ( $68 \pm 29$  min) at T12, from 10 to 130 min ( $80 \pm 32$  min) at L2-L3, and from 10 to 130 min ( $73 \pm 39$  min) at L5-S1. CSF volumes ranged from 42.7 to 81.1 ml and were correlated significantly with peak sensory block level to pinprick and duration of toleration to TES in the L5-S1 dermatomes. However, CSF volume did not correlate with duration of motor blockade, possibly because of the team's use of hyper-

baric local anesthetic solutions and the patients' supine positions. Because CSF volume is not customarily measured before spinal anesthesia and because of the great degree of patient variability, these results probably will not be applicable to clinical practice.

### ■ Respiratory Effects of Sevoflurane and Halothane Compared in Anesthetized Infants and Young Children. Brown *et al.* (page 86)

In a study comparing the respiratory effects of sevoflurane and halothane, Brown *et al.* included 30 infants and young children, ranging in age from 6 to 24 months, who were scheduled for elective peripheral limb surgery or hypospadias repair. All patients were premedicated with oral atropine (20  $\mu$ g/kg) and randomized to receive either 1 MAC halothane or sevoflurane in 66% nitrous oxide in oxygen (6 l/min) for induction and maintenance of anesthesia. Laryngeal masks were used for airway management. Patients breathed the maintenance concentration of the selected agent for 15 min, and the end-tidal concentration of each vapor was then recorded. Flow, airway pressure, and  $PET_{CO_2}$  were measured during spontaneous ventilation and airway occlusions. Chest wall motion was assessed using respiratory inductive plethysmography. After induction of anesthesia, bupivacaine (0.25%) was administered for regional anesthesia. Caudal blocks were given for hypospadias repairs, and brachial plexus blocks were given for upper limb surgery.

All respiratory measurements were completed before surgery. Both groups showed evidence of respiratory depression. At 1 MAC, sevoflurane induced more respiratory depression with less paradoxical depression than did halothane at the same concentration. Minute ventilation and respiratory frequency were significantly lower during sevoflurane anesthesia. The study revealed no differences in respiratory drive between the two agents, although the shape of the flow waveform differed according to anesthetic agent, with peak inspiratory flow arriving later, and peak expiratory flow earlier, in the sevoflurane group. Less thoracoabdominal asynchrony was exhibited during sevoflurane anesthesia. Although their clinical relevance is not clear, the results indicate that sevoflurane and halothane have different effects on the recruitment pattern of the inspiratory motor neurons.



■ Effects of Acute and Chronic Administration of 7-Nitroindazole on Sevoflurane MAC and Cyclic GMP Concentrations. Ichinose *et al.* (page 143)

Ichinose *et al.* studied the relationship between the minimum alveolar concentration (MAC) for sevoflurane and levels of cyclic guanosine monophosphate (cGMP) in brain cells after administration of 7-nitroindazole (7-NI), a nitric oxide synthase (NOS) inhibitor. Ninety-six mice were used in acute administration experiments, and 64 animals were used in chronic administration studies. In acute administration experiments, 96 mice were administered 7-NI intraperitoneally (in doses of 20, 60, 80, 120, 500, or 1000 mg/kg) and then separated into two groups. The first 48 mice were used for cGMP determinations, and the second group of 48 underwent MAC determinations. In groups of eight, mice were placed in individual acrylic cylinders fitted with a rubber stopper, through which the mouse's tail and a rectal temperature probe protruded. Anesthetic concentrations were measured with an infrared analyzer. Mice initially breathed 4.0% sevoflurane in oxygen (4 l/min total gas flow) for 30 min. Responses to tail-clamp stimulation were observed and recorded. After 15-min equilibration periods at each change of concentration, anesthetic concentrations were increased or decreased in steps of 0.3–0.4% until the positive response disappeared (or vice versa).

The other unanesthetized group of 48 mice were killed approximately 60 min after intraperitoneal administration of 7-NI; their cerebella were dissected, weighed, and frozen; and the tissue was assayed for cGMP concentrations.

The chronic administration studies entailed administration of 500 mg/kg of 7-NI in a volume of 2 ml/kg of the same volume of arachis oil to 64 mice by oral gavage feeding every 8 h for 4 consecutive days. The mice then were assigned to one of two groups of 32 each, and sevoflurane MAC determinations started after the last daily gavage feeding. Eight mice also were killed after each daily gavage feeding, on days 1–4, for a total of 32 mice.

Acute administration of 7-NI (from 20 to 1,000 mg/kg) yielded a modest decrease in sevoflurane MAC, which was completely reversed by intraperitoneal administration of L-arginine, 600 mg/kg. In the chronic administration group, sevoflurane MAC was reduced for only the first 2 days and returned to baseline after the third day of 7-NI feeding. Values ranged from  $3.22 \pm$

0.38% on day 1 to  $2.88 \pm 0.52\%$  on day 4. The cGMP concentrations were time-dependently depressed for 4 days. The results also showed a dissociation between sevoflurane MAC and cerebellar cGMP during chronic NOS inhibition, suggesting that MAC-reducing effects of 7-NI may not be mediated *via* GC-cGMP system, or that there may be cGMP-independent compensatory mechanisms that mediate nociception when NOS is inhibited in a chronic manner.

■ Anesthetic Additivity and Response to Lipophilic Compounds Studied in Yeast. Wolfe *et al.* (page 174)

Because of the ease of isolating recessive or dominant mutations, short generation time, and relatively small size of the genome, the yeast *Saccharomyces cerevisiae* was chosen by Wolfe *et al.* for investigations of anesthetic additivity and growth inhibition effects of lipophilic compounds involved in the anesthetic response. Yeast strains derived from haploid  $Zzz^+$  wild-type yeast were first grown to saturation in liquid media, diluted, spotted on various media, incubated, and scored for growth. For additivity studies, the concentration of methoxyflurane was held constant at 0.25, 0.50, or 0.75 times the yeast minimum inhibitory concentration (MIC), the minimum concentration of an agent that prevents visible growth on solid medium after 3 days at 30°C. The isoflurane concentration was varied at 0.05 MIC increments to determine the smallest concentration that prevents visible growth for 3 days. Volumes of liquid agents necessary to produce the desired partial MIC concentrations were sequentially injected into the partially evacuated, sealed chambers containing the yeast. Similar studies were conducted using combinations of methoxyflurane plus halothane and isoflurane plus halothane.

Effectiveness of volatile nonanesthetics as yeast growth inhibitors was tested in a similar manner. Strains were exposed to a combination of saturated nonanesthetic plus 0.75 MIC conventional anesthetic, yielding additive MICs of 1.71 for 1,2-dichlorohexafluorocyclobutane and 1.40 for 2,3-dichlorooctafluorobutane. Plates containing cycloheximide, cadmium, chloramphenicol, or sulfometuran methyl were incubated at 30°C for 2–3 days and scored for growth. Another series of experiments tested whether yeast pleiotropic drug resistance (PDR) mutants, which confer resistance to a variety of lipophilic compounds, are involved in anesthetic response.

Results showed that combinations of volatile anes-



tics inhibit growth of wild-type  $Zzz^+$  strains when concentrations equal 1.0 MIC. This was not the case for anesthetic-resistant  $Zzz^-$  strains, which continued to grow in the presence of the anesthetics. The  $Zzz^+$  strains grown in an atmosphere saturated with lipophilic nonanesthetic polyhalogenated compounds showed no inhibitory effects from the compounds alone. When combined with 1.0 MIC of methoxyflurane or isoflurane, the nonanesthetics did not antagonize the activity of the anesthetics, and growth was again inhibited. The  $Zzz$ -mutant strains grew in environments containing mixtures of anesthetics and nonanesthetics.

Obviously these results cannot easily be extrapolated to mammalian systems. The MIC required to completely inhibit growth is ninefold higher than MAC, the concentration required to induce anesthesia. However, our understanding of yeast genetics and our ability to manipulate the yeast genome makes this species a potentially powerful tool for studying the cellular actions of many drugs. Only time — and more studies such as this — will tell us whether yeast genetics can be exploited to help us better understand the actions of anesthetics.

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