



**Perioperative Gabapentinoids: Choice of Agent, Dose, Timing, and Effects on Chronic Postsurgical Pain (Clinical Concepts and Commentary)** 1215

The gabapentinoids, gabapentin and pregabalin, reduce early postoperative pain and opioid use. Their mechanism of action, pharmacokinetics, adverse effects, preoperative dose timing, optimal perioperative dose, and use to prevent chronic postoperative pain are reviewed as is drug choice. Work to be done before they can be recommended as the standard of care is identified.

**Epigenetic Regulation of Spinal CXCR2 Signaling in Incisional Hypersensitivity in Mice** 1198

Increased histone acetylation causes chromatin relaxation and elevated transcriptional activity, while decreased acetylation results in tighter DNA coiling and gene silencing. Histone deacetylase inhibition enhanced incisional pain in male mice by epigenetic regulation of spinal expression of chemokine receptor 2 (CXCR2) and its ligand, keratinocyte-derived chemokine. Regulation of histone acetylation can control nociceptive sensitization after incision.

**Positive End-expiratory Pressure Influences Echocardiographic Measures of Diastolic Function: A Randomized, Crossover Study in Cardiac Surgery Patients** 1078

Echocardiographic measures of diastolic function were made postoperatively in 30 anesthetized cardiac surgery patients in six randomly assigned combinations of positive end-expiratory pressure (PEEP) and positions. PEEP decreased lateral and septal  $e'$ , the early peak diastolic velocity of the septal and mitral valve annuli, in both horizontal and Trendelenburg positions. Measurements of  $e'$  should be made at the same PEEP.

**Using Exome Data to Identify Malignant Hyperthermia Susceptibility Mutations** 1043

Malignant hyperthermia susceptibility (MHS) gene and variant studies have generally been performed on families with multiple generations affected with typical MHS. Exome sequencing on 870 volunteers identified RYR1 variants predicted to be pathogenic for MHS in 3 subjects without medical or family history of MHS. Variants previously described as pathogenic were reclassified to be of unknown pathogenicity. See the accompanying Editorial View on page 1006

**Realizing Improved Patient Care through Human-centered Operating Room Design: A Human Factors Methodology for Observing Flow Disruptions in the Cardiothoracic Operating Room** 1066

Flow disruptions in the operating room introduce distractions. Two human factors engineers observed 10 cardiac procedures and, with the aid of detailed architectural diagrams, developed a framework for identifying and classifying flow disruptions. More than 1,000 flow disruptions were identified and organized into six categories. Most common disruptions were related to operating room layout and design.

**Intrathecal Substance P-Saporin in the Dog: Efficacy in Bone Cancer Pain** 1178

Substance P-saporin (SAP) is a chemical conjugate of substance P, a tachykinin neuropeptide, and saporin, a recombinant version of a ribosomal-inactivating protein, that selectively destroys superficial neurokinin-1 receptor bearing cells in the spinal dorsal horn when it is administered intrathecally. Bone cancer is commonly associated with severe pain that evolves over time and is refractory to conventional pain therapies in both dogs and humans. Seventy companion dogs with bone cancer pain were randomly assigned to receive standard analgesic therapy alone or with intrathecally administered SAP. Intrathecally administered SAP produced a time-dependent antinociceptive effect; owners requested unblinding and additional intervention by 6 weeks in 74% of control dogs and 24% of SAP-treated dogs. There was no evidence of deafferentiation in the SAP-treated dogs, but hind limb weakness and ataxia were observed in some dogs receiving cisternal injections of SAP before doses for animals with front limb tumors were decreased. See the accompanying Editorial View on page 999



**Simultaneous Electroencephalographic and Functional Magnetic Resonance Imaging Indicate Impaired Cortical Top-down Processing in Association with Anesthetic-induced Unconsciousness** 1031

Functional connectivity (FC) analysis of the resting brain, measured as spatiotemporal coherence of spontaneous blood oxygen level-dependent fluctuations in functional magnetic resonance imaging (fMRI), has found alterations of FC during unconsciousness, which is consistent with reports of anesthesia impaired top-down processing (directional connectivity [DC]), the information exchange between corresponding electroencephalographic (EEG) channels measured by symbolic transfer entropy. To further understand the underlying mechanism of anesthesia-induced unconsciousness, the relationship between FC and DC was determined in 10 male subjects for whom there were complete simultaneous EEG-fMRI data sets in the awake and propofol-induced loss of consciousness states. The correlation of changes in FC in fMRI in the unconscious state with simultaneous changes in DC in the EEG indicate the breakdown of directional feedback connectivity is an underlying mechanism of functional decoupling of higher-order frontal and lower-order parietal processes during unconsciousness. These results suggest entropy-based measures could be used to monitor changes in frontal to posterior information processing as a measure of unconsciousness during general anesthesia. See the accompanying Editorial View on page 1003

**Nocturnal Intermittent Hypoxia Is Independently Associated with Pain in Subjects Suffering from Sleep-disordered Breathing** 1149

The two basic phenotypic components of obstructive sleep apnea (OSA), recurrent nocturnal hypoxemia and sleep fragmentation, may have different effects on pain sensitivity and experience. Data for the present study included sleep phenotype data and spontaneous pain reports collected from 634 adult participants in the last examination cycle of the Cleveland Family Study, a longitudinal cohort designed to evaluate familial aggregation of OSA. Nocturnal hypoxemia, measured as minimum arterial oxygen saturation during sleep, increased the odds for three of four types of pain assessed and the pain composite, independent of the presence of sleep fragmentation, assessed by polysomnography, and systemic inflammation, assessed by serum cytokine concentrations. Because sleep-related pain may be a direct consequence of hypoxia, these results could have important implications for chronic pain patients, who may develop sleep apnea and associated hypoxemia due to opioid effects on ventilatory control. See the accompanying Editorial View on page 1011