



## ON THE COVER:

$\gamma$ -Aminobutyric acid type A (GABA<sub>A</sub>) receptors mediate important effects of intravenous general anesthetics. Prior studies have defined the detailed molecular structure of this voltage-gated ion channel and how general anesthetics like propofol and etomidate bind to these channels. In this issue of ANESTHESIOLOGY, Nourmahnad *et al.* use mutation-based strategies combined with voltage-clamp electrophysiology to identify distinct binding sites for four intravenous anesthetics.

- Nourmahnad *et al.*: Tryptophan and Cysteine Mutations in M1 Helices of  $\alpha 1\beta 3\gamma 2L$   $\gamma$ -Aminobutyric Acid Type A Receptors Indicate Distinct Intersubunit Sites for Four Intravenous Anesthetics and One Orphan Site, p. 1144
- Jenkins and Jenkins: Anesthetic–Receptor Relationship Status: It’s Complicated, p. 1088

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<p>◆ <b>Quality of Quality Measurement: Impact of Risk Adjustment, Hospital Volume, and Hospital Performance</b> <i>L. G. Glance, Y. Li, and A. W. Dick</i></p>	1092

Using Monte Carlo simulation, nonhierarchical modeling frequently misclassified average-quality hospitals as low quality, whereas hierarchical modeling commonly misclassified low-quality hospitals as average.

<p>◆ Refers to This Month in Anesthesiology</p> <p>◆ Refers to Editorial Views</p> <p> This article has an Audio Podcast</p>	<p> See Supplemental Digital Content</p> <p> CME Article</p> <p> This article has a Video Abstract</p>
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- ◆◆ **Role of Cytochrome P4502B6 Polymorphisms in Ketamine Metabolism and Clearance** 1103  
*L. K. Rao, A. M. Flaker, C. C. Friedel, and E. D. Kharasch*  
 Healthy volunteers with *CYP2B6*\*1/\*1, \*1/\*6, or \*6/\*6 genotypes received a single oral ketamine dose. There was no significant difference between *CYP2B6* genotypes in ketamine or norketamine plasma concentrations or ketamine metabolism.
- ◆ **Effectiveness of an Electronic Alert for Hypotension and Low Bispectral Index on 90-day Postoperative Mortality: A Prospective, Randomized Trial** 1113  
 *P. J. McCormick, M. A. Levin, H.-M. Lin, D. I. Sessler, and D. L. Reich*  
 In a randomized trial of over 19,000 patients, the duration of double low was slightly reduced when alarms occurred during this condition, but 90-day mortality was not affected.
- ◆ **Perioperative Aspirin for Prevention of Venous Thromboembolism: The PeriOperative ISchema Evaluation-2 Trial and a Pooled Analysis of the Randomized Trials** 1121  
 *J. W. Eikelboom, C. Kearon, G. Guyatt, D. I. Sessler, S. Yusuf, D. Cook, J. Douketis, A. Patel, A. Kurz, R. Allard, P. M. Jones, R. J. Dennis, T. W. Painter, S. D. Bergese, K. Leslie, D. N. Wijeyesundera, K. Balasubramanian, E. Duceppe, S. Miller, J. Diedericks, and P. J. Devereaux*  
 From a large database of 10,010 patients undergoing noncardiac surgery who received 200 mg aspirin or placebo 2 to 4 h before surgery and then 100 mg aspirin daily or placebo for up to 30 days postoperatively, it was found that aspirin did not reduce venous thromboembolism. However, two thirds of the patients also received anticoagulant prophylaxis, and there were few venous thromboembolism events overall.
- Median Effective Dose of Intranasal Dexmedetomidine for Rescue Sedation in Pediatric Patients Undergoing Magnetic Resonance Imaging** 1130  
*W. Zhang, Y. Fan, T. Zhao, J. Chen, G. Zhang, and X. Song*  
 The median effective dose of intranasal dexmedetomidine for rescue sedation after failed chloral hydrate was determined and found to increase with age during the initial 3 yr of life.
- ◆ **Dose–response and Cardiopulmonary Side Effects of the Novel Neuromuscular-blocking Drug CW002 in Man** 1136  
*P. M. Heerd, H. Sunaga, J. S. Owen, M. T. Murrell, J. K. Malhotra, D. Godfrey, M. Steinkamp, P. Savard, J. J. Savarese, and C. A. Lien*  
 CW002 is a relatively potent nondepolarizing neuromuscular-blocking agent with a duration of action less than 40 min at  $-1.8\times$  the  $ED_{95}$ . During the dose range studied, CW002 elicited no histamine release and had minimal cardiopulmonary effects.
- BASIC SCIENCE**
- ◆◆ **Tryptophan and Cysteine Mutations in M1 Helices of  $\alpha 1\beta 3\gamma 2L$   $\gamma$ -Aminobutyric Acid Type A Receptors Indicate Distinct Intersubunit Sites for Four Intravenous Anesthetics and One Orphan Site** 1144  
 *A. Nourmahnad, A. T. Stern, M. Hotta, D. S. Stewart, A. M. Ziemba, A. Szabo, and S. A. Forman*  
 Complementary structure–function studies involving site-directed mutagenesis of amino acid residues lining the five predicted intersubunit binding pockets in a typical  $\gamma$ -aminobutyric acid type A receptor show that four intravenous anesthetics have distinct but overlapping patterns of interaction with the receptor. These findings validate previous anesthetic photolabeling findings and further define the properties of the distinct sites that mediate the potentiating effects of various intravenous anesthetics with  $\gamma$ -aminobutyric acid type A receptors.
- ◆◆ **Long-term Fate Mapping to Assess the Impact of Postnatal Isoflurane Exposure on Hippocampal Progenitor Cell Productivity** 1159  
*Y. Jiang, D. Tong, R. D. Hofacer, A. W. Loepke, Q. Lian, and S. C. Danzer*  
 As expected, isoflurane increased apoptosis of granule cells of the dentate gyrus. Changes in neurogenesis were not detected. There were no differences in the density of labeled granule cells in adult animals. The data are consistent with the premise that the neuron number in the dentate gyrus can be restored after anesthetic-induced cell loss. The mechanism remains to be found.

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### 🌐 **Transient Receptor Potential Ankyrin 1 Activation within the Cardiac Myocyte Limits Ischemia–reperfusion Injury in Rodents** 1171

*Y. Lu, H. Piplani, S. L. McAllister, C. M. Hurt, and E. R. Gross*

The authors report that the transient receptor potential ankyrin 1 (TRPA1) receptors exist within the cardiac myocyte, and TRPA1 activation protects the heart from myocardial ischemia–reperfusion injury. The results reported have the potential to impact novel targets for cardiac protection and have significant implications regarding the safety of TRPA1 antagonists being developed as pain medications.

## ■ CRITICAL CARE MEDICINE

### CLINICAL SCIENCE

### **New Setting of Neurally Adjusted Ventilatory Assist during Noninvasive Ventilation through a Helmet** 1181

*G. Cammarota, F. Longhini, R. Perucca, C. Ronco, D. Colombo, A. Messina, R. Vaschetto, and P. Navalesi*

Pressure support (PS) ventilation with a helmet was studied after extubation in 15 patients. Neurally adjusted PS increased comfort and improved patient–ventilator interactions when compared with standard (pneumatic) PS or neurally adjusted ventilatory assist.

### BASIC SCIENCE

### 🌐 **Heme Oxygenase-1/Carbon Monoxide-regulated Mitochondrial Dynamic Equilibrium Contributes to the Attenuation of Endotoxin-induced Acute Lung Injury in Rats and in Lipopolysaccharide-activated Macrophages** 1190

*J. Yu, J. Shi, D. Wang, S. Dong, Y. Zhang, M. Wang, L. Gong, Q. Fu, and D. Liu*

Using isolated cell and *in vivo* models, it was found that heme oxygenase-1 regulates mitochondrial dynamic equilibrium in the setting of lipopolysaccharide injury, and this contributes to a negative feedback loop that dampens endotoxin-induced acute lung injury.

## ■ PAIN MEDICINE

### BASIC SCIENCE

### 🌐 **Neurosteroid Allopregnanolone Suppresses Median Nerve Injury–induced Mechanical Hypersensitivity and Glial Extracellular Signal–regulated Kinase Activation through $\gamma$ -Aminobutyric Acid Type A Receptor Modulation in the Rat Cuneate Nucleus** 1202

*C.-T. Huang, S.-H. Chen, J.-H. Lue, C.-F. Chang, W.-H. Wen, and Y.-J. Tsai*

Median nerve injury in rats leads to the activation of glia and production of pronociceptive cytokines in the cuneate nucleus. The endogenous neurosteroid allopregnanolone moderates glial activation after nerve injury, thus reducing cytokine production and nociceptive sensitization.

## ■ EDUCATION

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*E. E. Naoum, L. S. Oh, and W. C. Levine*

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*A. Van Meter, A. Zavala, U. U. Williams, and P. Owusu-Agyemang*

## ORIGINAL INVESTIGATIONS IN EDUCATION

- ◇ **Appropriateness of Language Used in Patient Educational Materials from 24 National Anesthesiology Associations** 1221

*D. Govender, A. Villafranca, C. Hamlin, B. Hiebert, D. Parveen, and E. Jacobsohn*

Twenty-four national anesthesia society Web sites were explored, and 67% provided online information. All material was above grade 8 level (*i.e.*, too complex for lay comprehension), especially text describing the anesthesiologist's role. Such materials should be simplified and validated.

## CLINICAL CONCEPTS AND COMMENTARY

- ◆ **Intensive Care Unit Delirium: A Review of Diagnosis, Prevention, and Treatment** 1229

*C. J. Hayhurst, P. P. Pandharipande, and C. G. Hughes*

This review examines the most recent evidence for the diagnosis, prevention, and treatment of delirium in the ICU.

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