



## ON THE COVER:

New techniques in functional brain imaging are adding to our understanding of the mechanisms by which general anesthetics produce loss of consciousness. In this issue of ANESTHESIOLOGY, three original research articles suggest common themes across a variety of states (sleep, anesthesia), anesthetics (sevoflurane, propofol, ketamine), and species (rats and humans): a loss of the functional connectivity among specific regions of the brain. Three accompanying Editorial Views place these new findings in the broader context of our evolving understanding of the mechanisms of general anesthetics.

- Pal *et al.*: Neural Correlates of Wakefulness, Sleep, and General Anesthesia: An Experimental Study in Rat, p. 929
- Bonhomme *et al.*: Resting-state Network-specific Breakdown of Functional Connectivity during Ketamine Alteration of Consciousness in Volunteers, p. 873
- Ranft *et al.*: Neural Correlates of Sevoflurane-induced Unconsciousness Identified by Simultaneous Functional Magnetic Resonance Imaging and Electroencephalography, p. 861
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◆ Refers to This Month in Anesthesiology

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### ■ SPECIAL ARTICLES

#### ◇ Preclinical Pain Research: Can We Do Better? 846

J. D. Clark

Preclinical pain research has a poor record of translation into patient populations. The possible reasons and potential solutions are discussed.

#### Sites Related to Crawford Williamson Long in Georgia 850

K. J. Roddy, V. Starnes, and S. P. Desai

Crawford Williamson Long remains an unsung pioneer. Detailed descriptions are provided of a museum that bears his name, Oconee Hill Cemetery where he and members of his family are buried, and other sites and artifacts associated with him.

### ■ PERIOPERATIVE MEDICINE

#### CLINICAL SCIENCE

#### ◇◆🌐 Neural Correlates of Sevoflurane-induced Unconsciousness Identified by Simultaneous Functional Magnetic Resonance Imaging and Electroencephalography 861

A. Ranft, D. Golkowski, T. Kiel, V. Riedl, P. Kohl, G. Rohrer, J. Pientka, S. Berger, A. Thul, M. Maurer, C. Preibisch, C. Zimmer, G. A. Mashour, E. F. Kochs, D. Jordan, and R. Ilg

Anesthetic concentrations of sevoflurane disrupted connectivity in higher order frontal and thalamic networks, but not in primary sensory networks, and reduced cortical information processing, similar to the effects observed for propofol. Intraoperative measurements of frontal electroencephalography might provide real-time intraoperative assessment of neurophysiologic correlates of anesthetic-induced unconsciousness. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

#### ◇◆🌐 Resting-state Network-specific Breakdown of Functional Connectivity during Ketamine Alteration of Consciousness in Volunteers 873

V. Bonhomme, A. Vanhaudenhuyse, A. Demertzi, M.-A. Bruno, O. Jaquet, M. Ali Bahri, A. Plenevaux, M. Boly, P. Boveroux, A. Soddu, J. F. Brichant, P. Maquet, and S. Laureys

In human volunteers, ketamine alters connectivity within and between resting-state consciousness networks, notably by disrupting frontoparietal connectivity while sensory and sensorimotor networks are preserved. While ketamine has certain distinct effects on connectivity within and between resting-state consciousness networks, its functional disruption of frontoparietal cortical communication is shared by several other general anesthetics with distinct pharmacologic profiles. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

#### ◇🌐 Distinct Cortical Signatures Associated with Sedation and Respiratory Rate Depression by Morphine in a Pediatric Population 889

G. Montandon, S. L. Cushing, F. Campbell, E. J. Propst, R. L. Horner, and I. Narang

Morphine reduced frontal high-frequency ( $\beta$ ) electroencephalography power and reduced frontal-occipital  $\beta$  coherence. Analgesic doses of morphine are associated with reduction in respiratory rate when accompanied by reduction in  $\beta$  power. These results indicate an effect of cortical arousal state per se in respiratory rate depression by morphine. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

#### 🌐 Reference Values for Noninvasive Blood Pressure in Children during Anesthesia: A Multicentered Retrospective Observational Cohort Study 904


J. C. de Graaff, W. Pasma, S. van Buuren, J. J. Duijghuisen, O. O. Nafiu, S. Kheterpal, and W. A. van Klei

The authors evaluated more than 116,000 children from 10 centers to determine blood pressure averages and ranges. The analysis was restricted to two periods: (1) after anesthetic induction but before incision and (2) a brief initial stable portion of surgery. Mean arterial pressure increased from about 40 mmHg at 1 month to 65 mmHg at 18 yr, with little difference in boys and girls. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

- CME** **Unplanned, Postoperative Intubation in Pediatric Surgical Patients: Development and Validation of a Multivariable Prediction Model** 914  
*E. C. Cheon, H. L. Palac, K. H. Paik, J. Hajduk, G. S. De Oliveira, N. Jagannathan, and S. Suresh*

Of 87,920 patients of a quality improvement database, 540 children experienced unplanned postoperative intubation (UPI) within the first 30 postoperative days, and 178 events (0.2%) occurred within the first 72 h after surgery. Independent predictors of UPI within 72 h after surgery were operation time, severe cardiac risk factors, American Society of Anesthesiologists physical status classification more than 2, central nervous system tumor, developmental delay/impaired cognitive function, past or current malignancy, and neonate status. When children experienced a UPI, unadjusted 30-day mortality increased by over 11-fold.

## BASIC SCIENCE

- ◆◆🌐 **Neural Correlates of Wakefulness, Sleep, and General Anesthesia: An Experimental Study in Rat** 929  
 *D. Pal, B. H. Silverstein, H. Lee, and G. A. Mashour*

Disruption of cortical connectivity in the high  $\gamma$  band correlated with anesthetic- and sleep-induced unconsciousness, while  $\theta$  connectivity correlated with cholinergic tone and an activated cortex. Functional fragmentation of high-frequency activity in the cortex may be a common network-level mechanism of unconsciousness during general anesthesia and sleep. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

- Sedative-hypnotic Binding to 11 $\beta$ -hydroxylase** 943  
*E. Pejo, X. Zhou, S. S. Husain, and D. E. Raines*

The *in vitro* dissociation constant of etomidate for 11 $\beta$ -hydroxylase is approximately 30 nM, which is nearly two orders of magnitude lower than its hypnotic concentration. Cyclopropyl methoxycarbonyl metomidate produces less adrenocortical suppression than etomidate because it is metabolized faster and binds to 11 $\beta$ -hydroxylase with lower affinity. The carboxylic acid metabolites of etomidate and cyclopropyl methoxycarbonyl metomidate bind to 11 $\beta$ -hydroxylase with affinities that are at most 1% that of their parent hypnotics. Carboetomidate, dexmedetomidine, ketamine, and propofol do not suppress adrenocortical function at hypnotic concentrations because they bind to 11 $\beta$ -hydroxylase with very low affinities.

- ◆🌐 **Exposure of Stored Packed Erythrocytes to Nitric Oxide Prevents Transfusion-associated Pulmonary Hypertension** 952  
*S. Muenster, A. Beloiartsev, B. Yu, E Du, S. Abidi, M. Dao, G. Fabry, J. A. Graw, M. Wepler, R. Malhotra, B. O. Fernandez, M. Feelisch, K. D. Bloch, D. B. Bloch, and W. M. Zapol*

In an ovine model, pretreatment of stored packed erythrocytes with nitric oxide before transfusion increases their survival after transfusion, prevents increases in pulmonary vascular resistance, and may provide a potential approach to mitigate adverse effects of stored erythrocyte transfusions. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

- Enhanced Thalamic Spillover Inhibition during Non-rapid-eye-movement Sleep Triggers an Electro cortical Signature of Anesthetic Hypnosis** 964  
*L. Mesbah-Oskui and R. L. Horner*

Microperfusion of etomidate increased non-rapid-eye-movement  $\alpha$ - $\beta$  electrocortical activity and decreased wakefulness. The thalamus is implicated in triggering this increase in  $\alpha$ - $\beta$  frequency activity in the cortex during anesthetic hypnosis. The means by which thalamic activity coordinates cortical  $\alpha$ - $\beta$  activity in the cortex are not clear. The data suggest that the sedative properties of etomidate first lead to a non-rapid-eye-movement sleep state, followed by a spillover extrasynaptic  $\gamma$ -aminobutyric acid receptor type A-mediated inhibition in the thalamus, which then leads to thalamocortical oscillation in the  $\alpha$ - $\beta$  range.

## CRITICAL CARE MEDICINE

### CLINICAL SCIENCE

- ◆ **Low-dose Dexmedetomidine Improves Sleep Quality Pattern in Elderly Patients after Noncardiac Surgery in the Intensive Care Unit: A Pilot Randomized Controlled Trial** 979  
*X.-H. Wu, F. Cui, C. Zhang, Z.-T. Meng, D.-X. Wang, J. Ma, G.-F. Wang, S.-N. Zhu, and D. Ma*

In a pilot trial of 76 adults (age, greater than 65 yr) admitted to intensive care unit after noncardiac surgery, patients were randomized to receive low-dose dexmedetomidine infusion versus placebo for 15 h. Dexmedetomidine increased stage N2 (and decreased N1) sleep, total sleep time, sleep efficiency, and subjective sleep quality but caused hypotension.

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*T. J. Wellman, N. de Prost, M. Tucci, T. Winkler, R. M. Baron, P. Filipczak, B. Raby, J.-h. Chu, R. S. Harris, G. Musch, L. F. dos Reis Falcao, V. Capelozzi, J. G. Venegas, and M. F. Vidal Melo*
- Sheep pretreated with endotoxin were ventilated and studied with computed tomographic and positron emission tomographic scans followed by lung biopsy. Metabolic activation preceded radiographic infiltration and was colocalized with gene activation and histologic injury. This provides rationale for therapies directed at metabolic or gene products in adult respiratory distress syndrome. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*
- 🌐 **Vagus Nerve Attenuates Hepatocyte Apoptosis upon Ischemia–Reperfusion via  $\alpha 7$  Nicotinic Acetylcholine Receptor on Kupffer Cells in Mice** 1005  
*M. Ni, H. Fu, F. Huang, T. Zhao, J.-K. Chen, D.-J. Li, and F.-M. Shen*
- Using experimental models with hepatic vagotomized mice and Kupffer cell–eliminated mice, it was shown that the hepatic vagus nerve could minimize ischemia–reperfusion–induced liver apoptosis through activating  $\alpha 7$  nicotinic acetylcholine receptors on Kupffer cells, possibly by preventing their excessive production of reactive oxygen species. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

### ■ PAIN MEDICINE

### BASIC SCIENCE

- ◆ **STR-324, a Stable Analog of Opiorphin, Causes Analgesia in Postoperative Pain by Activating Endogenous Opioid Receptor–dependent Pathways** 1017  
*P. Sitbon, A. Van Elstraete, L. Hamdi, V. Juarez-Perez, J.-X. Mazoit, D. Benhamou, and C. Rougeot*
- Opiorphin and STR-324 reduced mechanical hypersensitivity without adverse cardiorespiratory effects in a rat incisional pain model through opioid receptor–mediated mechanisms. Inhibitors of enkephalin breakdown represent a promising class of long-acting analgesics with improved side-effect profiles compared to direct opioid receptor agonists.
- AMPAkines Target the Nucleus Accumbens to Relieve Postoperative Pain** 1030  
*C. Su, H. Y. Lin, R. Yang, D. Xu, M. Lee, N. Pawlak, M. Norcini, A. Sideris, E. Recio-Pinto, D. Huang, and J. Wang*
- Systemic administration of an AMPAkin reduced pain and depression behavior. AMPAkin administration directly into the nucleus accumbens similarly reduced acute pain. The data suggest AMPAkines are novel analgesics for postoperative pain whose effect is mediated in part by activity in the nucleus accumbens.

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*H. Sun, Y. Zhou, D. J. Culley, C. A. Lien, A. E. Harman, and D. O. Warner*

More than 600 candidates for the cognitive examination enrolled in the Maintenance of Certification in Anesthesiology Minute Program® in 2014, and those individuals who enrolled and completed the activity scored higher on the cognitive examination, suggesting that the Maintenance of Certification in Anesthesiology Minute enhances learning.

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*K. M. J. M. H. Lombarts, A. Ferguson, M. W. Hollmann, B. Malling, SMART Collaborators, and O. A. Arah*

System for Evaluation of Teaching Qualities *Smart* questionnaires were developed and validated for assessing teaching performance of faculty in residency training programs in different countries through a multicenter survey. System for Evaluation of Teaching Qualities *Smart* scores correlated with global ratings and yielded reliable feedback from three to five resident evaluations, thus providing a validated tool for international resident teaching assessment.

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