

## ON THE COVER:

Anesthesiologists likely provide mechanical ventilation for more patients than any other care providers. The 2014 Journal Symposium focused on improving anesthesiologists' understanding of mechanical ventilation, with the aim of making improvements in morbidity and for those receiving respiratory care during the course of surgery. The articles in the current issue of ANESTHESIOLOGY discuss and clarify many aspects of the perioperative use of mechanical ventilation.

- Wiener-Kronish and Vidal Melo: New Investigations of Core Competencies: Perioperative Mechanical Ventilation and Assessment of Lung Function, p. 723
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#### **New Investigations of Core Competencies: Perioperative Mechanical Ventilation and Assessment of Lung Function**

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*J. P. Wiener-Kronish and M. F. Vidal Melo*



#### **Targeting Neutrophil Extracellular Traps in Acute Lung Injury: A Novel Therapeutic Approach in Acute Respiratory Distress Syndrome?**

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#### **Norepinephrine for Spinal Hypotension during Cesarean Delivery: Another Paradigm Shift?**

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This is a Mechanical Ventilation article

🌐 See Supplemental Digital Content

CME CME Article

## ■ PERIOPERATIVE MEDICINE

## CLINICAL SCIENCE

- ◆◆ **Randomized Double-blinded Comparison of Norepinephrine and Phenylephrine for Maintenance of Blood Pressure during Spinal Anesthesia for Cesarean Delivery** 736

*W. D. Ngan Kee, S. W. Y. Lee, F. F. Ng, P. E. Tan, and K. S. Khaw*

In a randomized study of 104 healthy patients undergoing cesarean delivery under spinal anesthesia, maternal blood pressure and Apgar scores of neonates were similar whether norepinephrine or phenylephrine was administered. Maternal cardiac output and heart rate were greater in women treated with norepinephrine compared with that in women treated with phenylephrine, but further work is needed to assess safety and efficacy of norepinephrine in this setting.

- Pharmacokinetics of Tranexamic Acid in Neonates, Infants, and Children Undergoing Cardiac Surgery with Cardiopulmonary Bypass** 746

*M. C. Wesley, L. M. Pereira, L. A. Scharp, S. M. Emani, F. X. McGowan, Jr., and J. A. DiNardo*

Tranexamic acid pharmacokinetics were determined during cardiac surgery in 55 children categorized into three age groups: less than 2 months old; 2 months to 1 yr old; and more than 1 yr old and weighing up to 20 kg. Dosing recommendations were modeled for each age group for plasma concentrations of 20, 60, and 150 µg/ml. The safe and effective tranexamic acid concentration range needs to be better defined.

- Feasibility of Closed-loop Titration of Propofol and Remifentanyl Guided by the Bispectral Monitor in Pediatric and Adolescent Patients: A Prospective Randomized Study** 759

*G. A. Orliaguet, F. Benabbes Lambert, T. Chazot, P. Glasman, M. Fischler, and N. Liu*

Bispectral index–guided automated control of propofol hypnosis and remifentanyl analgesia is feasible and maintains bispectral index in the range of 40 to 60 in 6- to 16-yr-old old patients better than skilled manual control. Propofol consumption during maintenance of anesthesia was similar in the two groups, but remifentanyl consumption was higher in the automated control group.

## BASIC SCIENCE

-  **Transient Receptor Potential A1 Activation Prolongs Isoflurane Induction Latency and Impairs Respiratory Function in Mice** 768

*F. Li, C. J. Guo, C.-C. Huang, G. Yu, S. M. Brown, S. Xu, and Q. Liu*

Mice not expressing Transient Receptor Potential A1 (TRPA1) had faster onset of isoflurane anesthesia than wild-type or TRPV1-deficient mice, whereas sevoflurane onset was independent of genotype. Onset of the pungent anesthetic isoflurane is delayed due to activation of TRPA1 receptor–mediated nocifensive reflexes that reduce ventilation, pulmonary compliance, and anesthetic uptake.

-  **Inhalational Anesthetics Disrupt Postsynaptic Density Protein-95, Drosophila Disc Large Tumor Suppressor, and Zonula Occludens-1 Domain Protein Interactions Critical to Action of Several Excitatory Receptor Channels Related to Anesthesia** 776


*F. Tao, Q. Chen, Y. Sato, J. Skinner, P. Tang, and R. A. Johns*

Halothane and isoflurane disrupted PDZ domain–mediated interactions between potassium channel Kv1.4 and GluA2 subunit of AMPA receptor with their respective binding partners. Neither agent affected binding of  $\gamma$ -aminobutyric acid type B receptors with their binding partners. Anesthetics affected binding to PDZ1 and PDZ2 but not PDZ3 domains. Anesthetics interfere with PDZ domain–mediated protein–protein interactions of several receptors that are important to neuronal function. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

- Structural Comparisons of Ligand-gated Ion Channels in Open, Closed, and Desensitized States Identify a Novel Propofol-binding Site on Mammalian  $\gamma$ -Aminobutyric Acid Type A Receptors** 787

*N. P. Franks*

Molecular docking calculations of propofol binding to a  $\gamma$ -aminobutyric acid type A receptor identified putative binding sites in a region with maximal predicted movement during channel opening. These calculations support a model of state-dependent binding of propofol resulting in enhanced  $\gamma$ -aminobutyric acid type A receptor opening.

-  **Up-regulation of MicroRNA-21 Mediates Isoflurane-induced Protection of Cardiomyocytes** 795  
*J. M. Olson, Y. Yan, X. Bai, Z.-D. Ge, M. Liang, A. J. Kriegel, D. M. Twaroski, and Z. J. Bosnjak*

Isoflurane directly affects microRNA expression profiles in cardiomyocytes and that miR-21 is acting to protect cardiomyocytes after isoflurane exposure, most likely through its actions on programmed cell death protein 4. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

- Enhanced Effects of Isoflurane on the Long QT Syndrome 1-associated A341V Mutant** 806  
*I. Mikuni, C. G. Torres, T. Bakshi, A. Tampo, B. E. Carlson, M. W. Bienengraeber, and W.-M. Kwok*


The long QT syndrome-associated A341V mutation rendered the slowly activating delayed rectifier potassium (IKs) channel more sensitive to the inhibitory effects of isoflurane compared to wild-type IKs in transfected cell lines.

- Repeated Exposure to Ketamine–Xylazine during Early Development Impairs Motor Learning–dependent Dendritic Spine Plasticity in Adulthood** 821  
*L. Huang and G. Yang*


Early multiple exposures to ketamine/xylazine, a veterinary anesthetic combination, resulted in impaired motor learning and learning-dependent spine plasticity in motor cortex, both of which could be prevented by an enriched environment. Further studies are necessary to determine whether early exposure to more clinically relevant anesthetics has similar effects on learning and synaptic plasticity.

■ CRITICAL CARE MEDICINE


CLINICAL SCIENCE

-  **A Randomized Controlled Trial of Adaptive Support Ventilation Mode to Wean Patients after Fast-track Cardiac Valvular Surgery** 832  
*F. Zhu, C. D. Gomersall, S. Keung Ng, M. J. Underwood, and A. Lee*

Use of closed-loop weaning with adaptive support ventilation results in more rapid weaning of patients after cardiac valvular surgery than physician-directed weaning, without an increase in morbidity.


-  **High-frequency Ventilation Does Not Provide Mortality Benefit in Comparison with Conventional Lung-protective Ventilation in Acute Respiratory Distress Syndrome: A Meta-analysis of the Randomized Controlled Trials** 841  
*S. Maitra, S. Bhattacharjee, P. Khanna, and D. K. Baidya*

A meta-analysis of 1,759 patients from seven randomized controlled trials documents that the use of HFOV does not offer a mortality benefit and appears to prolong the duration of mechanical ventilation.

-  **Up-regulation of Programmed Cell Death 1 Ligand 1 on Neutrophils May Be Involved in Sepsis-induced Immunosuppression: An Animal Study and a Prospective Case-control Study** 852  
*J.-F. Wang, J.-B. Li, Y.-J. Zhao, W.-J. Yi, J.-J. Bian, X.-J. Wan, K.-M. Zhu, and X.-M. Deng*

Programmed cell death 1 ligand 1 is up-regulated on neutrophils during sepsis, which may be associated with sepsis-induced immunosuppression. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

BASIC SCIENCE

-  **Mechanical Ventilation Induces Neutrophil Extracellular Trap Formation** 864  
*C. Yildiz, N. Palaniyar, G. Otulakowski, M. A. Khan, M. Post, W. M. Kuebler, K. Tanswell, R. Belcastro, A. Masood, D. Engelberts, and B. P. Kavanagh*

By creating lung injury in mice using intratracheal lipopolysaccharide and mechanical ventilation, the authors documented that neutrophil extracellular traps were formed when lipopolysaccharide was present during high tidal ventilation and could be treated with deoxyribonuclease I. The treatment cleared the neutrophil extracellular traps and improved lung mechanics, but other measures of lung injury (including increased neutrophil count, increased protein content in lavage fluid, and low oxygenation) persisted, documenting a limited role for the neutrophil extracellular traps in this form of lung injury. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

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### **Effects of Acute Respiratory and Metabolic Acidosis on Diaphragm Muscle Obtained from Rats** 876

*P. Michelet, S. Carreira, A. Demoule, J. Amour, O. Langeron, B. Riou, and C. Coirault*

Diaphragm strips were exposed to a pH of 7.0 using carbon dioxide or strips exposed to low bicarbonate and both compared with strips exposed to a pH of 7.4. The strips exposed to high carbon dioxide had impairment in contraction and even more impairment in relaxation–contraction coupling. In contrast, diaphragmatic strips exposed to lower bicarbonate had no significant differences in diaphragmatic contraction, relaxation, or contraction–relaxation coupling.

## ■ PAIN MEDICINE

### CLINICAL SCIENCE

#### ◆◆ **Analgesic Effect of Perioperative Escitalopram in High Pain Catastrophizing Patients after Total Knee Arthroplasty: A Randomized, Double-blind, Placebo-controlled Trial** 884

*T. H. Lunn, V. G. Frokjaer, T. B. Hansen, P. W. Kristensen, T. Lind, and H. Kehlet*

In 120 patients with high pain catastrophizing scores before total knee arthroplasty, 1 week treatment with the serotonin selective reuptake inhibitor escitalopram did not differ from placebo in pain on ambulation 24 h after surgery.

### BASIC SCIENCE

#### ◆◆ **Individual Differences in Acute Pain-induced Endogenous Analgesia Predict Time to Resolution of Postoperative Pain in the Rat** 895

*C. M. Peters, K.-i. Hayashida, T. Suto, T. T. Houle, C. A. Aschenbrenner, T. J. Martin, and J. C. Eisenach*

In a preclinical model of postoperative nerve injury, weak conditioned pain modulation and spinal noradrenergic depletion predicted persistent pain suggesting possible mechanisms for persistent pain after surgery.

#### **Spinal Peroxynitrite Contributes to Remifentanyl-induced Postoperative Hyperalgesia via Enhancement of Divalent Metal Transporter 1 without Iron-responsive Element-mediated Iron Accumulation in Rats** 908

*R.-C. Shu, L.-L. Zhang, C.-Y. Wang, N. Li, H.-Y. Wang, K.-L. Xie, Y.-H. Yu, and G.-L. Wang*

Spinal cord levels of 3-nitrotyrosine, a biomarker for peroxynitrite production, were elevated after remifentanyl infusion in rats. The administration of hydrogen-rich saline both reduced peroxynitrite production and reduced hyperalgesia after remifentanyl infusion.

## ■ EDUCATION

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*D. W. Barbara*

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*J. A. Sáez*

### CLINICAL CONCEPTS AND COMMENTARY

#### ◆ **Prothrombin Complex Concentrates in Trauma and Perioperative Bleeding** 923

*O. Grottke and J. H. Levy*

There is increasing interest in prothrombin complex concentrates as therapy for perioperative and trauma-related bleeding. A suitable point-of-care test is needed to guide such therapy, and randomized controlled trials are needed for robust, evidence-based recommendations.

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-  **Hypoxic Pulmonary Vasoconstriction: Physiology and Anesthetic Implications** 932  
*A. B. Lumb and P. Slinger*

Hypoxic pulmonary vasoconstriction matches lung perfusion to ventilation in patients with lung disease and during one-lung ventilation. This review describes its physiology, factors affecting its activity, and how the reflex impacts on clinical anesthesiology.

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*O. Hung*

- The ASA 4 Patient at the VA Hospital** 950  
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*J. E. Chelly*

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