



## ON THE COVER:

Some investigators have speculated that increased homocysteine concentrations from nitrous oxide exposure might lead to myocardial ischemia and infarction. This issue includes an important clinical trial investigating the genetic and environmental influences on nitrous oxide-induced homocysteine in a high-risk patient population.

- Myles: Nitrous Oxide: Deep in the Zone of Uncertainty, p. 1
- Nagele *et al.*: Influence of Nitrous Oxide Anesthesia, B-Vitamins, and *MTHFR* Gene Polymorphisms on Perioperative Cardiac Events: The Vitamins in Nitrous Oxide (VINO) Randomized Trial, p. 19

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### Nitrous Oxide: Deep in the Zone of Uncertainty

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### Assessing Competence for Reentry: What Matters Most?

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## PERIOPERATIVE MEDICINE



### Influence of Nitrous Oxide Anesthesia, B-Vitamins, and *MTHFR* Gene Polymorphisms on Perioperative Cardiac Events: The Vitamins in Nitrous Oxide (VINO) Randomized Trial

Peter Nagele, Frank Brown, Amber Francis, Mitchell G. Scott, Brian F. Gage, and J. Philip Miller; for the VINO Study Team

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In 500 patients with cardiac risk factors undergoing noncardiac surgery with nitrous oxide, methylenetetrahydrofolate reductase gene variant did not alter homocysteine concentration or the incidence of cardiac injury. Vitamin B<sub>12</sub>, although decreasing homocysteine concentration, did not alter the incidence of cardiac injury. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

◇ Refers to This Month in Anesthesiology

◆ Refers to Editorial Views

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**CME** CME Article

- ◆ **Application of the Continual Reassessment Method to Dose-finding Studies in Regional Anesthesia: An Estimate of the ED<sub>95</sub> Dose for 0.5% Bupivacaine for Ultrasound-guided Supraclavicular Block** 29  
*Abhinav Kant, Pawan Kumar Gupta, Sarah Zohar, Sylvie Chevret, and Philip M. Hopkins*  
 Applying a different design, the continual reassessment method, to determine the ED<sub>95</sub> for local anesthetic dose needed for supraclavicular block resulted in a tight estimate (95% CIs of <10%) after the study of only 48 patients. This study design might be widely applied for ED<sub>95</sub> estimates in the specialty.
- ◆ **Reversal of Neuromuscular Blockade with Sugammadex at the Reappearance of Four Twitches to Train-of-four Stimulation** 36  
*Adrienn Pongrácz, Szilárd Szatmári, Réka Nemes, Béla Fülesdi, and Edömér Tassonyi*  
 Residual rocuronium-induced neuromuscular blockade at the reappearance of the fourth twitch in response to train-of-four stimulation can be reversed within 5 min by 1.0 and 2.0 mg/kg sugammadex. A sugammadex dose of 0.5 mg/kg can reverse such residual neuromuscular blockade in less than 10 min.
- 🌐 **Racial Disparities in Operative Procedure Time: The Influence of Obesity** 43  
*Jeffrey H. Silber, Paul R. Rosenbaum, Richard N. Ross, Orit Even-Shoshan, Rachel R. Kelz, Mark D. Neuman, Caroline E. Reinke, Justin M. Ludwig, Fabienne A. Kyle, Dale W. Bratzler, and Lee A. Fleisher*  
 White patients with similar body mass index undergoing general or orthopedic surgery were matched to comparable black patients within the same hospitals. After matching, blacks had induction-to-recovery room duration 7 min longer than whites ( $P = 0.0019$ ), 6 min reflect cut-to-close time ( $P = 0.0032$ ). *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*
- Effects of Anesthetic Isoflurane and Desflurane on Human Cerebrospinal Fluid A $\beta$  and  $\tau$  Level** 52  
*Bin Zhang, Ming Tian, Hui Zheng, Yu Zhen, Yun Yue, Tianzuo Li, Shuren Li, Edward R. Marcantonio, and Zhongcong Xie*  
 In 106 patients randomized to receive spinal anesthesia for surgery without general anesthetics or with isoflurane or desflurane, isoflurane was associated with an increase in cerebrospinal fluid concentrations of A $\beta$ 40 and desflurane with a decrease in A $\beta$ 42. This clinical work parallels observations in animals, but its relevance to cognition after surgery remains uncertain.
- ◇ **Effects of Volatile Anesthetic Choice on Hospital Length-of-stay: A Retrospective Study and a Prospective Trial** 61  
*Tatyana Kopyeva, Daniel I. Sessler, Stephanie Weiss, Jarrod Dalton, Edward J. Mascha, Jae H. Lee, Ravi P. Kiran, Belinda Udeh, and Andrea Kurz*  
 The choice of potent volatile anesthetic may prolong hospitalization, increasing the cost of patient care. The hypothesis that duration of hospitalization is longer in patients anesthetized with isoflurane than in patients anesthetized with sevoflurane was tested first in a propensity-matched retrospective analysis and subsequently in a prospective alternating-intervention trial. The retrospective study, which included 2,898 triplets matched on anesthetic used, found the duration of hospitalization was shorter in patients anesthetized with sevoflurane or desflurane than in those anesthetized with isoflurane. However, the prospective trial, which included 1,584 operations, found no difference in length-of-stay between patients anesthetized with isoflurane and those anesthetized with sevoflurane. This illustrates the importance of testing the results of even a very robust retrospective analysis with an appropriately designed prospective study.
- 🌐 **Impact of Anesthesia and Surgery for Congenital Heart Disease on the Vitamin D Status of Infants and Children: A Prospective Longitudinal Study** 71  
*J. Dayre McNally, Kusum Menon, Pranesh Chakraborty, Lawrence Fisher, Kathryn A. Williams, Osama Y. Al-Dirbashi, Tara Girolamo, Gyaandeo Maharajh, and Dermot R. Doherty*  
 Most children are vitamin D deficient after congenital heart disease surgery, secondary to borderline preoperative levels and significant intraoperative decline. Lower vitamin D levels were associated with worse clinical outcome. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

- ◆ **Effects of Volatile Anesthetic Agents on Cerebral Cortical Synchronization in Sheep** 81  
*Duan Li, Logan J. Voss, Jamie W. Sleight, and Xiaoli Li*  
 The effects of volatile anesthetics on synchronization between electrocorticogram recordings in sheep were analyzed. In contrast to global synchrony, local cortical synchrony increased during anesthesia, which might contribute to the loss of long-range synchrony and information integration critical to consciousness.
- Effect of Positive End-expiratory Pressure on Regional Ventilation Distribution during Mechanical Ventilation after Surfactant Depletion** 89  
*Sam Bayat, Liisa Porra, Gergely Albu, Heikki Suhonen, Satu Strengell, Pekka Suortti, Anssi Sovijärvi, Ferenc Peták, and Walid Habre*  
 Using a novel lung imaging technique that uses synchrotron radiation, the administration of positive end-expiratory pressure was shown to improve aeration in collapsed lung but not to eliminate overventilation of normal lung units in experimental lung injury.
- Comparison of Static End-expiratory and Effective Lung Volumes for Gas Exchange in Healthy and Surfactant-depleted Lungs** 101  
*Gergely Albu, Mats Wallin, Magnus Hallbäck, Per Emtell, Andrew Wolf, Per-Arne Lönnqvist, Sylvia Göthberg, Ferenc Peták, and Walid Habre*  
 The effective lung volume participating in gas exchange was estimated at the bedside by the differential Fick method and shown to be highly correlated with the end-expiratory lung volume, suggesting its use clinically.
- Skeletal Muscle Ryanodine Receptor Mutations Associated with Malignant Hyperthermia Showed Enhanced Intensity and Sensitivity to Triggering Drugs when Expressed in Human Embryonic Kidney Cells** 111  
*Keisaku Sato, Cornelia Roesl, Neil Pollock, and Kathryn M. Stowell*  
 Skeletal muscle ryanodine receptor proteins with a mutation associated with malignant hyperthermia were transiently expressed in human embryonic kidney cells. The authors could show enhanced sensitivity and intensity of the calcium mobilization response to specific pharmacologic stimulation of the ryanodine receptor of six mutant proteins compared with the wild type.
- Sevoflurane Preconditioning Attenuates the Fall in Adenosine Triphosphate Levels, but Does Not Alter the Changes in Sodium and Potassium Levels during Hypoxia in Rat Hippocampal Slices** 119  
*Brandon R. Esenther, Zhijun Ge, Fanli Meng, James E. Cottrell, and Ira S. Kass*  
 Using the acute hippocampal slice, the authors provide evidence that sevoflurane-induced preconditioning (4%, 60 min given before a 5-min period of hypoxia) attenuates the decrease in adenosine triphosphate stores, but not the changes in sodium and potassium levels. These results suggest that improved adenosine triphosphate content, but not Na<sup>+</sup> or K<sup>+</sup> levels, correlates with improved physiological recovery induced by sevoflurane preconditioning.
- In Vivo* Fluorescence-mediated Tomography Imaging Demonstrates Atorvastatin-mediated Reduction of Lesion Macrophages in ApoE<sup>-/-</sup> Mice** 129  
*Jan Larmann, Tim Frenzel, Martina Schmitz, Anke Hahnenkamp, Philipp Demmer, Stephan Immenschuh, Uwe J.F. Tietge, Christoph Bremer, and Gregor Theilmeier*  
 Acute statin treatment decreased macrophage infiltration of atherosclerotic lesions, as visualized with *in vivo* fluorescence-mediated tomography, in mice. The results suggested that short-term statin treatment may produce favorable effects to stabilize atherosclerotic plaques and decrease cardiovascular risk.
- Evaluation of Spinal Toxicity and Long-term Spinal Reflex Function after Intrathecal Levobupivacaine in the Neonatal Rat** 142  
*Emre Hamurtekin, Bethany L. Fitzsimmons, Veronica I. Shubayev, Marjorie R. Grafe, Ronald Deumens, Tony L. Yaksh, and Suellen M. Walker*  
 In 3- and 7-day-old rats, intrathecal injection of 0.5% levobupivacaine produced temporary spinal anesthesia, but did not increase apoptosis or result in histologic or behavioral neurotoxicity.

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*Mauro R. Tucci, Eduardo L. V. Costa, Tyler J. Wellman, Guido Musch, Tilo Winkler, R. Scott Harris, Jose G. Venegas, Marcelo B. P. Amato, and Marcos F. Vidal Melo*

In normal sheep lungs mechanically ventilated (over 16 h, 8 ml/kg, zero positive end-expiratory pressure), progressive derecruitment is associated with increased regional shunt, implying insufficient hypoxic pulmonary vasoconstriction, and incipient inflammation.

#### ◆ **Probiotic Administration Reduces Mortality and Improves Intestinal Epithelial Homeostasis in Experimental Sepsis**

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*Ludmila Khailova, Daniel N. Frank, Jessica A. Dominguez, and Paul E. Wischmeyer*

Administration of probiotics in septic mice decreased mortality and systemic bacteremia and led to decreased apoptosis of colonic epithelium, decreased colonic epithelial proliferation, and decreased systemic and colonic cytokine expression.

### ■ PAIN MEDICINE

#### **◆ Perioperative Systemic Magnesium to Minimize Postoperative Pain: A Meta-analysis of Randomized Controlled Trials**

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*Gildasio S. De Oliveira, Jr., Lucas J. Castro-Alves, Jamil H. Khan, and Robert J. McCarthy*

In this meta-analysis of data from more than 1,200 patients, systemically administered magnesium decreased postoperative pain a small, statistically significant amount; a reduction in morphine use was clearly evident. The reduction in both pain and morphine use indicates magnesium has some utility as an analgesic adjunct after surgery.

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*Riccardo Pincioli, Cristina Mietto, and Lorenzo Berra*

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##### **◆ Simulation-based Assessment and Retraining for the Anesthesiologist Seeking Reentry to Clinical Practice: A Case Series**

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*Samuel DeMaria, Jr., Stefan T. Samuelson, Andrew D. Schwartz, Alan J. Sim, and Adam I. Levine*

Over a 10-yr period, 20 anesthesiologists referred to one institution after hiatus from practice underwent a simulation-based reentry program. The group was heterogeneous, and simulation aided the assessors in making recommendations.

#### **CLINICAL CONCEPTS AND COMMENTARY**

##### **Perioperative Management of Coagulation in Nontraumatic Intracerebral Hemorrhage**

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*Vincent Degos, Erick M. Westbroek, Michael T. Lawton, J. Claude Hemphill III, Gregory J. del Zoppo, and William L. Young*

This commentary seeks to clarify the recommendations and highlight the debate regarding the perioperative management of hemostasis in intracerebral hemorrhage.

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