



ON THE COVER:

Management of perioperative fluid impacts gastrointestinal function. In this issue of ANESTHESIOLOGY, Gómez-Izquierdo *et al.* randomized patients undergoing laparoscopic colorectal surgery within an Enhanced Recovery After Surgery program to receive intraoperative goal-directed fluid therapy or fluid therapy based on traditional principles and assessed the impact on postoperative ileus. Intraoperative goal-directed fluid therapy did not reduce postoperative ileus, suggesting that previously demonstrated benefits might have been offset by advancements in perioperative care.

- Gómez-Izquierdo *et al.*: Goal-directed Fluid Therapy Does Not Reduce Primary Postoperative Ileus after Elective Laparoscopic Colorectal Surgery: A Randomized Controlled Trial, p. 36

◆ THIS MONTH IN ANESTHESIOLOGY	1A
■ SCIENCE, MEDICINE, AND THE ANESTHESIOLOGIST	13A
■ INFOGRAPHICS IN ANESTHESIOLOGY	15A
◆ EDITORIAL VIEWS	
<p>Editor's Note: ANESTHESIOLOGY 2017: Expanding the Richness and Reach E. D. Kharasch</p> <p>Raising the Alarm on Brain Attacks in Surgical Patients: Are We Doing Enough to Prevent and Treat Postoperative Strokes? L. G. Glance and R. G. Holloway</p> <p>Understanding Potential Drug Side Effects: Can We Translate Molecular Mechanisms to Clinical Applications? A. Koster and J. H. Levy</p>	<p>1</p> <p>3</p> <p>6</p>
■ PERIOPERATIVE MEDICINE	

CLINICAL SCIENCE

- ◆ ◆  **Risks of Cardiovascular Adverse Events and Death in Patients with Previous Stroke Undergoing Emergency Noncardiac, Nonintracranial Surgery: The Importance of Operative Timing** 9
-  M. N. Christiansen, C. Andersson, G. H. Gislason, C. Torp-Pedersen, R. D. Sanders, P. Føge Jensen, and M. E. Jørgensen

After emergency noncardiac nonintracranial surgery, risks of 30-day major adverse cardiovascular events (acute myocardial infarction, ischemic stroke, or cardiovascular death) were high for patients with stroke less than 3 months before surgery (odds ratio [OR] = 4.7), 3 to 9 months (OR = 1.9), and more than 9 months (OR = 1.6) compared with no previous stroke. Risks of death (1.6, 1.2, and 1.2) in the same period were also increased. Risk of major adverse cardiovascular events was significantly lower after immediate (1 to 3 days after stroke) compared with early surgery (4 to 14 days). These patterns were similar to that observed in poststroke patients having elective surgery. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

◆ Refers to This Month in Anesthesiology

◆ Refers to Editorial Views

 This article has an Audio Podcast

 This is a Coagulation 2016 article

 See Supplemental Digital Content

 CME Article

 This article has a Video Abstract

- 

A Phase 1, Single-center, Double-blind, Placebo-controlled Study in Healthy Subjects to Assess the Safety, Tolerability, Clinical Effects, and Pharmacokinetics–Pharmacodynamics of Intravenous Cyclopropyl-methoxycarbonylmetomidate (ABP-700) after a Single Ascending Bolus Dose 20
- M. M. R. F. Struys, B. I. Valk, D. J. Eleveld, A. R. Absalom, P. Meyer, S. Meier, I. den Daas, T. Chou, K. van Amsterdam, J. A. Campagna, and S. P. Sweeney*
- In a first-in-human study, cyclopropyl-methoxycarbonylmetomidate (ABP-700) was safe and well tolerated up to a maximum tolerated bolus dose of 1.0 mg/kg. Onset of hypnosis after bolus administration was rapid as was recovery. APB-700 did not cause cardiovascular depression, centrally induced respiratory depression, or suppression of the physiologic response of the adrenal axis to adrenocorticotrophic hormone stimulation. Involuntary muscle movements were observed at doses of 0.175 mg/kg and greater. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*
- 

Goal-directed Fluid Therapy Does Not Reduce Primary Postoperative Ileus after Elective Laparoscopic Colorectal Surgery: A Randomized Controlled Trial 36
- 
J. C. Gómez-Izquierdo, A. Trainito, D. Mirzakandov, B. L. Stein, S. Liberman, P. Charlebois, N. Pecorelli, L. S. Feldman, F. Carli, and G. Baldini
- This randomized blinded trial assessed effects of goal-directed fluid therapy on primary postoperative ileus after laparoscopic colorectal surgery, within a well-established Enhanced Recovery After Surgery program. The incidence of primary postoperative ileus was identical (22%) in the goal-directed fluid therapy control groups. Previous benefits of goal-directed fluid therapy may have been offset by subsequent improvements in perioperative and surgical care. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*
- 
Epidural Neostigmine *versus* Fentanyl to Decrease Bupivacaine Use in Patient-controlled Epidural Analgesia during Labor: A Randomized, Double-blind, Controlled Study 50
- J. L. Booth, V. H. Ross, K. E. Nelson, L. Harris, J. C. Eisenach, and P. H. Pan*
- Adding neostigmine (2, 4, or 8 µg/ml) to bupivacaine for patient-controlled epidural analgesia during labor did not reduce bupivacaine requirement compared with bupivacaine plus fentanyl.
- 

Neurophysiologic Correlates of Ketamine Sedation and Anesthesia: A High-density Electroencephalography Study in Healthy Volunteers 58
- 
P. E. Vlisides, T. Bel-Bahar, U. Lee, D. Li, H. Kim, E. Janke, V. Tarnal, A. B. Pichurko, A. M. McKinney, B. S. Kunkler, P. Picton, and G. A. Mashour
- Ketamine had dose-dependent effects on spectral power, functional connectivity, and directed connectivity. Anesthetic doses of ketamine resulted in markedly increased theta power across the cortex as well as increased gamma and delta power. Increased anterior-posterior connectivity in the theta bandwidth and decreased connectivity in the alpha bandwidth were specific for ketamine anesthesia. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*
- GNAQ TT(-695/-694)GC Polymorphism Is Associated with Increased Gq Expression, Vascular Reactivity, and Myocardial Injury after Coronary Artery Bypass Surgery** 70
- U. H. Frey, S. Klenke, A. Mitchell, T. Knüfermann, H. Jakob, M. Thielmann, W. Siffert, and J. Peters*
- The GC/GC genotype of the TT(-695/-694)GC polymorphism is associated with increased Gq protein expression, augmented angiotensin II receptor type 1–related vasoconstriction, and increased myocardial injury after coronary artery bypass grafting.
- 
A Systematic Review and Meta-analysis Examining the Impact of Incident Postoperative Delirium on Mortality 78
- G. M. Hamilton, K. Wheeler, J. Di Michele, M. M. Lalu, and D. I. McIsaac*
- Patients who develop delirium are at increased risk of death. However, in the studies with reduced bias and adequate control for confounding, an independent association between delirium and mortality was not apparent. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

BASIC SCIENCE

◆ **High Concentrations of Tranexamic Acid Inhibit Ionotropic Glutamate Receptors** 89

🔴 *I. Lecker, D.-S. Wang, K. Kaneshwaran, C. D. Mazer, and B. A. Orser*

Tranexamic acid inhibits *N*-methyl-D-aspartate receptors likely by reducing the binding of the co-agonist glycine and also inhibits other ionotropic glutamate receptors. Receptor blockade only occurs at high concentrations, similar to those that occur after topical application to peripheral tissues. Inhibition of glutamate receptors in peripheral tissues may contribute to adverse effects observed at high concentrations.

🌐 **Triggering Receptor Expressed on Myeloid Cells 2, a Novel Regulator of Immunocyte Phenotypes, Confers Neuroprotection by Relieving Neuroinflammation** 98

🌐 *Q. Zhai, F. Li, X. Chen, J. Jia, S. Sun, D. Zhou, L. Ma, T. Jiang, F. Bai, L. Xiong, and Q. Wang*

In a mouse model of middle cerebral artery occlusion, activation and up-regulation of triggering receptor expressed on myeloid cells 2 (TREM2) promoted microglial switching from the detrimental M1 phenotype to the beneficial M2 phenotype. Administering a TREM2 agonist systemically or delivering TREM2 lentivirus directly into the cerebral ventricle caused neuroprotection in mice. TREM2 regulates microglial phenotype after stroke and may affect short-term outcome after stroke in mice. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

■ CRITICAL CARE MEDICINE

CLINICAL SCIENCE

🔴 **Management of Severe Bleeding in Patients Treated with Direct Oral Anticoagulants: An Observational Registry Analysis** 111

🔴 *P. Albaladejo, C.-M. Samama, P. Sié, S. Kauffmann, V. Mémier, P. Suchon, A. Viallon, J. S. David, Y. Gruel, L. Bellamy, E. de Maistre, P. Romegoux, S. Thoret, G. Pernod, and J.-L. Bosson, on behalf of the GIHP-NACO Study Group*

In a prospective cohort registry study of 732 patients treated with direct oral anticoagulants and hospitalized for severe bleeding, bleeding sites were gastrointestinal in 37% and intracranial in 24% of the cases. Activated or nonactivated prothrombin complex concentrates were administered in 38% of the cases with a day 30 mortality of 13.5% and varied according to bleeding sites but was similar to previous reports. Our report provides a detailed assessment of direct oral anticoagulant-treated patients managed in clinical settings.

BASIC SCIENCE

🌐 **Iron Loading Exaggerates the Inflammatory Response to the Toll-like Receptor 4 Ligand Lipopolysaccharide by Altering Mitochondrial Homeostasis** 121

🌐 *K. Hoefft, D. B. Bloch, J. A. Graw, R. Malhotra, F. Ichinose, and A. Bagchi*

In rodent and cellular models, iron loading potentiated inflammation caused by lipopolysaccharide. Iron loading in this model increased the production of mitochondrial superoxide and disrupted mitochondrial homeostasis. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

■ PAIN MEDICINE

CLINICAL SCIENCE

◆ **Pain Catastrophizing Moderates Relationships between Pain Intensity and Opioid Prescription: Nonlinear Sex Differences Revealed Using a Learning Health System** 136

◆ *Y. Sharifzadeh, M.-C. Kao, J. A. Sturgeon, T. J. Rico, S. Mackey, and B. D. Darnall*

A retrospective study of 1,794 patients with chronic pain seeking initial medical evaluation found a significant relationship between pain intensity and opioid prescription that was much stronger in women, especially those with high levels of pain catastrophizing. Although men and women had similar levels of catastrophizing and opioid prescription, opioid prescriptions were more common at lower levels of catastrophizing for women. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

BASIC SCIENCE

- 🌐 **DNA Hydroxymethylation by Ten-eleven Translocation Methylcytosine Dioxygenase 1 and 3 Regulates Nociceptive Sensitization in a Chronic Inflammatory Pain Model** 147
Z. Pan, Z.-Y. Xue, G.-F. Li, M.-L. Sun, M. Zhang, L.-Y. Hao, Q.-Q. Tang, L.-J. Zhu, and J.-L. Cao

The knockdown of key DNA demethylating enzyme ten-eleven translocation enzymes (TET1, TET3) reduces nociceptive sensitization induced by inflammation. The effects of TET1/TET3 knockdown may result from alterations in spinal signal transducer and activator of transcription 3 expression. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

■ EDUCATION

IMAGES IN ANESTHESIOLOGY

- Torus Palatinus and Airway Management** 164
J. Aron, S. J. Raithel, and A. J. Mannes
- Persistent Left Superior Vena Cava: Unusual Catheter Position on Chest X-ray Film** 165
R. Deshpande, M. Band, and V. Kurup

CLINICAL CONCEPTS AND COMMENTARY

- ◇ **Perioperative Steroid Management: Approaches Based on Current Evidence** 166
M. M. Liu, A. B. Reidy, S. Saatee, and C. D. Collard

Perioperative stress-dose steroid administration remains a controversial topic, with recent studies questioning its necessity. We discuss the current literature, largely published in nonanesthesiology journals, and suggest a practical approach to perioperative steroid management.

REVIEW ARTICLE

- ◇ **Phrenic Nerve Palsy and Regional Anesthesia for Shoulder Surgery: Anatomical, Physiologic, and Clinical Considerations** 173
K. El-Boghdadly, K. J. Chin, and V. W. S. Chan

A review of the anatomical, physiologic, and clinical principles governing phrenic nerve palsy in the context of regional anesthesia for shoulder surgery and the strategies for reducing its incidence and impact.

MIND TO MIND

- Texting under Anesthesia** 192
D. Guardiola, M. Guardiola, and S. D. Cook-Sather

■ CORRESPONDENCE

- Should Neuromuscular Blocking Agents Always Be Reversed?** 194
M. J. Meyer and M. Eikermann
- Neuromuscular Blockade and Risk of Postoperative Pneumonia** 195
A. Cumberworth
- Accounting for Planned Postoperative Intubation** 195
T. M. Austin and H. Lam
- Risk of Postoperative Pneumonia with Neuromuscular Blockade: Keep It Simple!** 196
L. J. Caruso, H. Reed, and R. V. Zhang

Science or Fiction? Risk of Postoperative Pneumonia with Neuromuscular Blockade 197
R. V. Zhang, H. Reed, and L. J. Caruso

In Reply
C. M. Bulka and J. M. Ehrenfeld

In Reply
A. S. Kopman and G. S. Murphy

Assessing Success of Rescue Intubation Techniques after Failed Direct Laryngoscopy 198
F.-S. Xue, G.-Z. Yang, and H.-X. Li

Is Airway Management Better? 200
A. Maslow and S. Panaro

Apneic Intubation: Video Laryngoscopy Lacks the Continuous Ventilation Offered by Other Airway Management Techniques 201
S. T. Herway and J. L. Benumof

In Reply
M. F. Aziz, D. W. Healy, A. M. Brambrink, and S. Kheterpal

Calculating Ideal Body Weight: Keep It Simple 203
O. Moreault, Y. Lacasse, and J. S. Bussières

In Reply
G. Hedenstierna and L. Edmark

Evaluation of Nitrous Oxide in the Gas Mixture for Anesthesia II (ENIGMA II) Revisited: Patients Still Vomiting 204
E. C. K. Li, L. D. Balbuena, and J. J. Gamble

In Reply
P. S. Myles and J. Kasza

Promoting Sustainable Practices *via* Art 206
K. L. Zuegge, M. E. Warren, B. L. Muldowney, and A. T. B. Kron

■ **ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM**

Stamping Out Pain with Brandy Anesthesia: McDowell’s Cystolithotomy of Polk 8
George S. Bause

Clean Analgesia? A Civil War Tin for Pills of Opium...and Soap 35
George S. Bause

Laughing Gas in Baltimore, Hagerstown, and Smithsburg: Maryland’s Dr. D. W. Crowther 135
George S. Bause

William B. Quinn, M.D., Eclectic Physician and Occasional “Anaesthetist” 191
George S. Bause

CONTENTS

■ ERRATUM

208

■ CAREERS & EVENTS

17A

INSTRUCTIONS FOR AUTHORS

The most recently updated version of the Instructions for Authors is available at www.anesthesiology.org. Please refer to the Instructions for the preparation of any material for submission to ANESTHESIOLOGY.

Manuscripts submitted for consideration for publication must be submitted in electronic format. The preferred method is via the Journal's Web site (<http://www.anesthesiology.org>). Detailed directions for submissions and the most recent version of the Instructions for Authors can be found on the Web site (<http://www.anesthesiology.org>). Books and educational materials should be sent to Alan Jay Schwartz, M.D., M.S.Ed., Director of Education, Department of Anesthesiology and Critical Care Medicine, The Children's Hospital of Philadelphia, 34th Street and Civic Center Blvd., Room 9327, Philadelphia, Pennsylvania 19104-4399. Requests for permission to duplicate materials published in ANESTHESIOLOGY should be submitted in electronic format, to the Permissions Department (journalpermissions@lww.com). Advertising and related correspondence should be addressed to Advertising Manager, ANESTHESIOLOGY, Wolters Kluwer Health, Inc., Two Commerce Square, 2001 Market Street, Philadelphia, Pennsylvania 19103 (Web site: <http://www.wkadcenter.com/>). Publication of an advertisement in ANESTHESIOLOGY does not constitute endorsement by the Society or Wolters Kluwer Health, Inc. of the product or service described therein or of any representations made by the advertiser with respect to the product or service.

ANESTHESIOLOGY (ISSN 0003-3022) is published monthly by Wolters Kluwer Health, Inc., 14700 Citicorp Drive, Bldg 3, Hagerstown, MD 21742. Business office: Two Commerce Square, 2001 Market Street, Philadelphia, PA 19103. Periodicals postage paid at Hagerstown, MD, and at additional mailing offices. Copyright © 2017, the American Society of Anesthesiologists, Inc.

Annual Subscription Rates: *United States*—\$981 Individual, \$1876 Institution, \$354 In-training. *Rest of World*—\$930 Individual, \$2084 Institution, \$354 In-training. Single copy rate \$189. Subscriptions outside of North America must add \$54 for airfreight delivery. Add state sales tax, where applicable. The GST tax of 7% must be added to all orders shipped to Canada (Wolters Kluwer Health, Inc.'s GST Identification #895524239, Publications Mail Agreement #1119672). Indicate in-training status and name of institution. Institution rates apply to libraries, hospitals, corporations, and partnerships of three or more individuals. Subscription prices outside the United States must be prepaid. Prices subject to change without notice. Subscriptions will begin with currently available issue unless otherwise requested. Visit us online at www.lww.com.

Individual and in-training subscription rates include print and access to the online version. Online-only subscriptions for individuals (\$301) and persons in training (\$301) are available to nonmembers and may be ordered by downloading a copy of the Online Subscription FAXback Form from the Web site, completing the information requested, and faxing the completed form to 301-223-2400. Institutional rates are for print only; online subscriptions are available via Ovid. Institutions can choose to purchase a print and online subscription together for a discounted rate. Institutions that wish to purchase a print subscription, please contact Wolters Kluwer Health, Inc., 14700 Citicorp Drive, Bldg 3, Hagerstown, MD 21742; phone: 800-638-3030; fax: 301-223-2400. Institutions that wish to purchase an online

subscription or online with print, please contact the Ovid Regional Sales Office near you or visit www.ovid.com/site/index.jsp and select Contact and Locations.

Address for non-member subscription information, orders, or change of address (except Japan): Wolters Kluwer Health, Inc., 14700 Citicorp Drive, Bldg 3, Hagerstown, MD 21742; phone: 800-638-3030; fax: 301-223-2400. In Japan, contact Wolters Kluwer Health Japan Co., Ltd., Forecast Mita Building 5th floor, 1-3-31 Mita Minato-ku, Tokyo, Japan 108-0073; phone: +81 3 5427 1969; email: journal@wkjapan.co.jp.

Address for member subscription information, orders, or change of address: Members of the American Society of Anesthesiologists receive the print and online journal with their membership. To become a member or provide a change of address, please contact the American Society of Anesthesiologists, 1061 American Lane, Schaumburg, Illinois 60173-4973; phone: 847-825-5586; fax: 847-825-1692; email: membership@ASAhq.org. For all other membership inquiries, contact Wolters Kluwer Health, Inc., Customer Service Department, P.O. Box 1610, Hagerstown, MD 21740; phone: 800-638-3030; fax: 301-223-2400.

Postmaster: Send address changes to ANESTHESIOLOGY, P.O. BOX 1610, Hagerstown, MD 21740.

Advertising: Please contact Hilary Druker, Advertising Field Sales Representative, Health Learning, Research & Practice, Medical Journals, Wolters Kluwer Health, Inc.; phone: 609-304-9187; e-mail: Hilary.Druker@wolterskluwer.com. For classified advertising: Joe Anzuena, Recruitment Advertising Representative, Wolters Kluwer Health, Inc., Two Commerce Square, 2001 Market Street, Philadelphia, PA 19103; phone: 215-521-8532; fax: 215-701-2410; e-mail: Joe.Anzuena@wolterskluwer.com.