



ON THE COVER:

An analysis of malpractice claims associated with massive hemorrhage from the Anesthesia Closed Claims Project appears in this issue of ANESTHESIOLOGY. Hemorrhage claims were most common in obstetrics and spine surgery. Lack of timely diagnosis, transfusion, and return to the operating room were common factors among these claims. (Cover photo: J.P. Rathmell; cover illustration: A. Johnson, Vivo Visuals.)

- Scavone and Tung: The Transfusion Dilemma: More, Less, or More Organized?, p. 439
- Dutton *et al.*: Massive Hemorrhage: A Report from the Anesthesia Closed Claims Project, p. 450

◆ THIS MONTH IN ANESTHESIOLOGY

3A

■ SCIENCE, MEDICINE, AND THE ANESTHESIOLOGIST

21A

■ INFOGRAPHICS IN ANESTHESIOLOGY

23A

◆ EDITORIAL VIEWS

The Transfusion Dilemma: More, Less, or More Organized?

439

B.M. Scavone and A. Tung

The Latest Pharmacologic Ventilator

442

J.F. Cotten

Still Looking for Best PEEP

445

R.D. Hubmayr and A. Malhotra

Diaphragmatic Electrical Activity: A New Tool to Assess Lung Hyperinflation?

447

E.L.V. Costa and M.F. Vidal Melo

■ PERIOPERATIVE MEDICINE

CLINICAL SCIENCE

◆ ◆ **Massive Hemorrhage: A Report from the Anesthesia Closed Claims Project**

450

R.P. Dutton, L.A. Lee, L.S. Stephens, K.L. Posner, J.M. Davies, and K.B. Domino

In a review of the past 2 decades of closed anesthesia malpractice claims, two areas (obstetrics and spinal surgery) were overrepresented. Common to many cases were lack of timely diagnosis, timely transfusion, and reoperation, often reflecting poor team communication.

◆ Refers to This Month in Anesthesiology

◆ Refers to Editorial Views

🌐 See Supplemental Digital Content

CME CME Article

- ◆ ◆ **Two Studies on Reversal of Opioid-induced Respiratory Depression by BK-channel Blocker GAL021 in Human Volunteers** 459
M. Roozkrans, R. van der Schrier, P. Okkerse, J. Hay, J.F. McLeod, and A. Dahan
 In a double-blind, randomized, placebo-controlled crossover study, GAL021 stimulated ventilation in male volunteers with alfentanil-induced respiratory depression at a clamped and elevated end-tidal carbon dioxide partial pressure, increasing both tidal volume and respiratory rate. GAL021 also stimulated poikilocapnic ventilation during alfentanil administration, without affecting sedation, antinociception, hemodynamics, or safety parameters.
- ◆ **Early Effect of Tidal Volume on Lung Injury Biomarkers in Surgical Patients with Healthy Lungs** 469
A. Fernandez-Bustamante, J. Klawitter, J.E. Repine, A. Agazio, A.J. Janocha, C. Shah, M. Moss, I.S. Douglas, Z.V. Tran, S.C. Erzurum, U. Christians, and T. Seres
 Tidal volumes of 6 versus 10 ml/kg of ideal body weight in patients with normal lungs were prospectively and randomly compared in terms of markers of lung injury. A significant increase in plasma levels of neutrophil elastase in the V_T6 group and Clara cell protein 16 in the V_T10 group was observed, which may represent the effect of atelectrauma and increased alveolar distention, respectively.
- ◆ **Predictors of Functional Outcome after Intraoperative Cardiac Arrest** 482
A.-L. Constant, C. Montlahuc, D. Grimaldi, N. Pichon, N. Mongardon, L. Bordenave, A. Soummer, B. Sauneuf, S. Ricome, B. Misset, D. Schnell, E. Dubuisson, J. Brunet, S. Lasocki, P. Cronier, B. Bouhemad, J.-F. Loriferne, E. Begot, B. Vandembunder, G. Dhonneur, J.-P. Bedos, P. Jullien, M. Resche-Rigon, and S. Legriel
 The main causes of survived intraoperative arrest were preoperative complications (33%), anesthetic complications (28%), and surgical complications (26%). The initial recorded rhythms were asystole (57%), pulseless electrical activity (31%), and ventricular fibrillation (16%). By day 90, 44% of the survivors had a good functional outcome. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*
- ◆ **Effects of Dexamethasone on Cognitive Decline after Cardiac Surgery: A Randomized Clinical Trial** 492
T.H. Ottens, J.M. Dieleman, A.-M.C. Sauër, L.M. Peelen, A.P. Nierich, W.J. de Groot, H.M. Nathoe, M.P. Buijsrogge, C.J. Kalkman, and D. van Dijk
 In a preplanned secondary analysis of 291 cardiac surgical patients randomized to receive perioperative dexamethasone or placebo, the treatment groups did not differ in the incidence of postoperative cognitive decline 1 or 12 months after surgery. These results fail to support the use of dexamethasone to prevent postoperative cognitive decline in heart surgery patients. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*
- ◆ **Reducing Unnecessary Preoperative Blood Orders and Costs by Implementing an Updated Institution-specific Maximum Surgical Blood Order Schedule and a Remote Electronic Blood Release System** 501
S.M. Frank, M.J. Oleyar, P.M. Ness, and A.A.R. Tobian
 Use of a Maximum Surgical Blood Order Schedule in a tertiary hospital reduced blood over-ordering from 40 to 25% of patients. Emergency release of uncrossmatched blood increased from 0.22 to 0.31%. Combining the Maximum Surgical Blood Order Schedule with electronic crossmatching reduced costs by \$6 per patient. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

BASIC SCIENCE

- ◆ **Sevoflurane Induces Tau Phosphorylation and Glycogen Synthase Kinase 3 β Activation in Young Mice** 510
G. Tao, J. Zhang, L. Zhang, Y. Dong, B. Yu, G. Crosby, D.J. Culley, Y. Zhang, and Z. Xie
 Sevoflurane induced Tau phosphorylation and GSK3 β activation and led to cognitive impairment 3 weeks after exposure in 6-day-old mice. The simultaneous administration of the GSK3 β inhibitor lithium prevented the cognitive impairment. Increased Tau phosphorylation may contribute to the anesthesia-induced cognitive impairment in neonatal animals, and GSK3 β may serve as a therapeutic target for the prevention of this impairment.

General Anesthetic Isoflurane Modulates Inositol 1,4,5-Trisphosphate Receptor Calcium Channel Opening 528

J.D. Joseph, Y. Peng, D.-O.D. Mak, K.-H. Cheung, H. Vais, J.K. Foskett, and H. Wei

At a dose of 1 minimum alveolar concentration, isoflurane activated InsP_3R , and this activation was accompanied by an increase in intracellular calcium. Moreover, cell death was increased by isoflurane. The data support the premise that isoflurane modulates InsP_3R calcium-release channel and this activity may underlie a variety of effects of isoflurane, including neurotoxicity.

Cardioprotective Trafficking of Caveolin to Mitochondria Is G_i -protein Dependent 538

J. Wang, J.M. Schilling, I.R. Niesman, J.P. Headrick, J.C. Finley, E. Kwan, P.M. Patel, B.P. Head, D.M. Roth, Y. Yue, and H.H. Patel

In mice, cardiac preconditioning from isoflurane involved increased caveolin levels in mitochondria and their associated improved respiratory function. These effects were blocked by pretreatment with G_i inhibitors, suggesting that agents that target G_i and caveolin trafficking may serve as cardioprotective agents.

Inhibition of N-myc Downstream-regulated Gene-2 Is Involved in an Astrocyte-specific Neuroprotection Induced by Sevoflurane Preconditioning 549

X. Li, P. Luo, F. Wang, Q. Yang, Y. Li, M. Zhao, S. Wang, Q. Wang, and L. Xiong

Using *in vivo* and *in vitro* models of ischemia, sevoflurane preconditioning reduced astrocytic NDRG2 expression and neuronal apoptosis, which was counteracted by NDRG2 overexpression. Reduction of astrocytic NDRG2 expression by sevoflurane preconditioning is a novel astrocyte-mediated mechanism for anesthetic neuroprotection.

■ CRITICAL CARE MEDICINE

CLINICAL SCIENCE

◆ Clinical Assessment of Auto-positive End-expiratory Pressure by Diaphragmatic Electrical Activity during Pressure Support and Neurally Adjusted Ventilatory Assist 563

G. Bellani, A. Coppadoro, N. Patroniti, M. Turella, S. Arrigoni Marocco, G. Grasselli, T. Mauri, and A. Pesenti

In 10 patients with auto-positive end-expiratory pressure (auto-PEEP), neurally adjusted ventilator assist (NAVA) ventilation and pressure support ventilation (PSV) were compared during PEEP trials. The pressures required to overcome auto-PEEP were significantly less with NAVA than with PSV and could be reliably assessed by diaphragmatic electrical activity (EAdi) monitoring in comparison with esophageal pressure.

◆◆🌐 Compressive Forces and Computed Tomography-derived Positive End-expiratory Pressure in Acute Respiratory Distress Syndrome 572

M. Cressoni, D. Chiumello, E. Carlesso, C. Chiurazzi, M. Amini, M. Brioni, P. Cadringer, M. Quintel, and L. Gattinoni

Lung recruitability and computed tomography scan-derived positive end-expiratory pressure are unrelated. The positive end-expiratory pressure required in patients who had more recruitment and less recruitment were similar. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

Erythropoietin and Protection of Renal Function in Cardiac Surgery (the EPRICS Trial) 582

A. Dardashti, P. Ederoth, L. Algotsson, B. Brondén, E. Grins, M. Larsson, S. Nozohoor, G. Zinko, and H. Bjursten

In a double-blind, randomized, placebo-controlled study of patients with preexisting impaired renal function undergoing coronary artery bypass grafting, preoperative administration of a high dose of recombinant human erythropoietin had no renal protective effects.

CONTENTS

■ PAIN MEDICINE

CLINICAL SCIENCE

- ◇ **Antidepressant Drugs for Prevention of Acute and Chronic Postsurgical Pain: Early Evidence and Recommended Future Directions** 591
K. Wong, R. Phelan, E. Kalso, I. Galvin, D. Goldstein, S. Raja, and I. Gilron

In a systematic review of 15 studies including approximately 1,000 patients, heterogeneity in drug, dose, timing, and outcome measure as well as general low quality precludes definitive conclusions although a majority of studies reported positive outcomes. There is insufficient evidence to support the routine use of antidepressants for analgesia in the perioperative period.

BASIC SCIENCE

- Down-regulation of Stargazin Inhibits the Enhanced Surface Delivery of α -Amino-3-hydroxy-5-methyl-4-isoxazole Propionate Receptor GluR1 Subunit in Rat Dorsal Horn and Ameliorates Postoperative Pain** 609
R. Guo, Y. Zhao, M. Zhang, Y. Wang, R. Shi, Y. Liu, J. Xu, A. Wu, Y. Yue, J. Wu, Y. Guan, and Y. Wang

Knockdown of the GluR1-interacting protein stargazin by intrathecal small interfering RNA reduced both postoperative pain and membrane GluR1 levels in a rat plantar incision model. Targeting the stargazin–GluR1 subunit interaction could provide a novel analgesic approach for postoperative pain.

- Neurosteroids Allopregnanolone Sulfate and Pregnanolone Sulfate Have Diverse Effect on the α Subunit of the Neuronal Voltage-gated Sodium Channels $\text{Na}_v1.2$, $\text{Na}_v1.6$, $\text{Na}_v1.7$, and $\text{Na}_v1.8$ Expressed in *Xenopus* Oocytes** 620
T. Horishita, N. Yanagihara, S. Ueno, Y. Sudo, Y. Uezono, D. Okura, T. Minami, T. Kawasaki, and T. Sata

The neurosteroids tested produced voltage and use-dependent block of all the subtypes tested, with more potent effects on $\text{Na}_v1.2$. Inhibition of $\text{Na}_v1.2$ in the spinal cord by allopregnanolone is a plausible mechanism for its analgesic effects if confirmed in neuronal preparations and pain models.

- 🌐 **Blocking the Mineralocorticoid Receptor Improves Effectiveness of Steroid Treatment for Low Back Pain in Rats** 632
L. Ye, W. Xie, J.A. Strong, and J.-M. Zhang

In rats, a mixed gluco- and mineralocorticoid agonist (6- α methylprednisolone) was less effective than a glucocorticoid-selective agonist in reducing behavioral sensory afferent hypersensitivity, and combination of 6- α methylprednisolone with a mineralocorticoid antagonist improved its efficacy. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

■ EDUCATION

CASE SCENARIO

- 📺 ◇ **A Patient on Dual Antiplatelet Therapy with an Intracranial Hemorrhage after Percutaneous Coronary Intervention** 644
B.I. Naik, E.C. Keeley, D.R. Gress, and Z. Zuo

IMAGES IN ANESTHESIOLOGY

- Unusual Access to Airway with Transorbital Intubation** 654
L.F. dos Reis Falcão, F. Negreiros, R.F. França, and J.L.G. Amaral

CLINICAL CONCEPTS AND COMMENTARY

- ◇ **This Is Not a Test! Misconceptions Surrounding the Maintenance of Certification in Anesthesiology Simulation Course** 655
M.B. Weinger, A.R. Burden, R.H. Steadman, and D.M. Gaba

Simulation-based training courses for maintenance of certification in anesthesiology have been very well received and have led to widespread reports of meaningful practice improvement.

CONTENTS

MIND TO MIND

- The Line** 660
C.S. Myler
- An Inquiry Concerning the Nature of the Clinical Efficacy of Propofol on the Soul** 661
D.L. Hester

■ CORRESPONDENCE

- About Acupuncture and Electroacupuncture** 662
J.B.G. Silva

In Reply
R. Zhang, L. Lao, K. Ren, and B.M. Berman

-
- The Potency of Different Propofol Formulations** 663
S. Goddon

In Reply
M. Le Guen and M. Fischler

-
- Practice Guidelines for the Perioperative Management of Patients with Obstructive Sleep Apnea: Navigating through Uncertainty** 664
R.M. Corso, C. Gregoretti, A. Braghiroli, F. Fanfulla, and G. Insalaco

Read the Fine Print: Updated Sleep Apnea Guidelines and Risk Stratification
K.P. Rothfield

Postoperative Continuous Positive Airway Pressure Treatment in Surgical Patients with Obstructive Sleep Apnea
M.S. Roesslein

In Reply
J.B. Gross, J.L. Apfelbaum, R.T. Connis, and D.G. Nickinovich

-
- Single-injection and Continuous Femoral Nerve Blocks Are Associated with Different Risks of Falling** 668
B.M. Ilfeld

In Reply
S.G. Memtsoudis and E.R. Mariano

■ ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

- Batchelder's "Anaesthesia" Trade Card** 527
George S. Bause
- Haller and the Movement of Blood** 590
George S. Bause
- Wood, Camphor, and an Antidote for Avertin Overdoses** 643
George S. Bause

CONTENTS

■ REVIEWS OF EDUCATIONAL MATERIAL

670

■ RETRACTION

Postoperative Neurocognitive Dysfunction in Elderly Patients after Xenon *versus* Propofol Anesthesia for Major Noncardiac Surgery: A Double-blinded Randomized Controlled Pilot Study: Retraction

672

■ ERRATUM

Comparison of the Potency of Different Propofol Formulations: A Randomized, Double-blind Trial Using Closed-loop Administration: Erratum

672

■ CAREERS & EVENTS

25A

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 Michael J. Avram, Ph.D., Diplomate, ABCP, Associate Professor of Anesthesiology, Director, Mary Beth Donnelley Clinical Pharmacology Core Facility of the Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, 300 E. Superior Street, Tarry 4-735, Chicago, Illinois 60611. 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, Lippincott Williams & Wilkins, Two Commerce Square, 2001 Market Street, Philadelphia, Pennsylvania 19103 (Web site: <http://www.wkaddcenter.com/>). Publication of an advertisement in ANESTHESIOLOGY does not constitute endorsement by the Society or Lippincott Williams & Wilkins, 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 Lippincott Williams & Wilkins, 16522 Hunters Green Parkway, Hagerstown, MD 21740-2116. Business office: Two Commerce Square, 2001 Market Street, Philadelphia, PA 19103. Periodicals postage paid at Hagerstown, MD, and at additional mailing offices. Copyright © 2014, the American Society of Anesthesiologists, Inc.

Annual Subscription Rates: *United States*—\$758 Individual, \$1431 Institution, \$304 In-training. *Rest of World*—\$800 Individual, \$1589 Institution, \$304 In-training. Single copy rate \$132. Subscriptions outside of North America must add \$52 for airfreight delivery. Add state sales tax, where applicable. The GST tax of 7% must be added to all orders shipped to Canada (Lippincott Williams & Wilkins' 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 (\$257) and persons in training (\$257) 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 301-223-2400/44 (0) 20 7981 0535. 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 Lippincott Williams & Wilkins, 16522 Hunters Green Parkway, Hagerstown, MD 21740-2116; phone: 1-800-638-3030 (outside the United States 301-223-2300/44 (0) 20 7981 0525); fax: 301-223-2400/44 (0) 20 7981 0535. 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: Lippincott Williams & Wilkins, 16522 Hunters Green Parkway, Hagerstown, MD 21740-2116; phone: 1-800-638-3030 (outside the United States 301-223-2300/44 (0) 20 7981 0525); fax: 301-223-2400/44 (0) 20 7981 0535; email: customerservice@lww.com. In Japan, contact LWW Japan Ltd., 3-23-14 Hongo, Bunkyo-ku, Tokyo 113, Japan; phone: 81-3-5689-5400; fax: 81-3-5689-5402; email: bcclaim@lwws.co.jp. In Bangladesh, India, Nepal, Pakistan, and Sri Lanka, contact Globe Publications Pvt. Ltd., B-13 3rd Floor, A Block, Shopping Complex, Naraina, Vihar, Ring Road, New Delhi 110028, India; phone: 91-11-25770411; fax: 91-11-25778876; email: info@globepub.com.

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, 520 N. Northwest Highway, Park Ridge, IL 60068-2573; phone: 847-825-5586; fax: 847-825-1692; email: membership@ASAhq.org. For all other membership inquiries, contact Lippincott Williams & Wilkins Customer Service Department, P.O. Box 1580, Hagerstown, MD 21741-1580; phone: 1-800-638-3030 (outside the United States 301-223-2300/44 (0) 20 7981 0525); fax: 301-223-2400/44 (0) 20 7981 0535; email: memberservice@lww.com.

Postmaster: Send address changes to ANESTHESIOLOGY, P.O. BOX 1550, Hagerstown, MD 21740.

Advertising: Please contact Michelle Smith, Senior Account Manager, Advertising, Lippincott Williams & Wilkins, 333 Seventh Avenue, 19th Floor, New York, NY 10001; tel: (646) 674-6537, fax: (646) 607-5479, e-mail: Michelle.Smith@wolterskluwer.com. For classified advertising: Keida Spurlock, Recruitment Advertising Representative, Lippincott Williams & Wilkins, Two Commerce Square, 2001 Market Street, Philadelphia, PA 19103; tel: (215) 521-8501, fax: (215) 689-2453, e-mail: Keida.Spurlock@wolterskluwer.com.