



ON THE COVER:

Ketamine, used for more than 60 yr as a sedative, analgesic, and anesthetic, is now being explored as a rapidly acting antidepressant. An article in this month's issue highlights the metabolites which may be responsible for this rapid antidepressant effect. (Illustration by A. Johnson, Vivo Visuals.)

- van Velzen and Dahan: Ketamine Metabolomics in the Treatment of Major Depression, p. 4
- Paul *et al.*: (R,S)-Ketamine Metabolites (R,S)-norketamine and (2S,6S)-hydroxynorketamine Increase the Mammalian Target of Rapamycin Function, p. 149

◆ THIS MONTH IN ANESTHESIOLOGY

3A

■ SCIENCE, MEDICINE, AND THE ANESTHESIOLOGIST

19A

■ INFOGRAPHICS IN ANESTHESIOLOGY

21A

◆ EDITORIAL VIEWS

Untangling the Triple Low: Causal Inference in Anesthesia Research

P.S. Myles

1

Ketamine Metabolomics in the Treatment of Major Depression

M. van Velzen and A. Dahan

4

Data, Data, On the Server: Challenges in Applying Data Analysis to Operating Room Management

J.A. Sanford and A. Macario

6

■ SPECIAL ARTICLES

Epidural Catheter Design: History, Innovations, and Clinical Implications

R.D. Toledano and L.C. Tsen

9

Modifications in catheter materials, tip design, and orifice number and arrangement have been introduced over the past several decades in an attempt to improve analgesic and anesthetic outcomes.

■ PERIOPERATIVE MEDICINE

CLINICAL SCIENCE

◆◆ Cumulative Duration of “Triple Low” State of Low Blood Pressure, Low Bispectral Index, and Low Minimum Alveolar Concentration of Volatile Anesthesia Is Not Associated with Increased Mortality

M.D. Kertai, W.D. White, and T.J. Gan

18

In a review of over 16,000 patients, there was no association between duration of triple low state intraoperatively and either perioperative or intermediate-term mortality.

◆ Refers to This Month in Anesthesiology

◆ Refers to Editorial Views

🌐 See Supplemental Digital Content

CME CME Article

- ◇ **Predictors of Patient Medication Compliance on the Day of Surgery and the Effects of Providing Patients with Standardized yet Simplified Medication Instructions** 29
T.R. Vetter, M.E. Downing, S.C. Vanlandingham, K.M. Noles, and A.M. Boudreaux
 In over 1,000 patients in a case-control study design, use of a simple, multicolored Preoperative Patient Medication Instruction sheet improved compliance with instructions.
- Economic Trends from 2003 to 2010 for Perioperative Myocardial Infarction: A Retrospective, Cohort Study** 36
B.L. Udeh, J.E. Dalton, J.S. Hata, C.I. Udeh, and D.I. Sessler
 Charges for patients with perioperative myocardial infarction were about \$100,000 greater than in patients without infarctions. However, mortality remained nearly unchanged over the 8-yr period, and incremental costs decreased slightly.
- Intra- and Interrater Reliability of Ultrasound Assessment of Gastric Volume** 46
R. Kruisselbrink, C. Arzola, R. Endersby, C. Tse, V. Chan, and A. Perlas
 Gastric sonography can provide information about the volume of the stomach. Ultrasound assessment of gastric volume by clinical anesthesiologists is highly reproducible with high intrarater and interrater reliability.
- ◇ **Aspiration Induced by Remifentanyl: A Double-blind, Randomized, Crossover Study in Healthy Volunteers** 52
J. Savilampi, R. Ahlstrand, A. Magnuson, H. Geijer, and M. Wattwil
 Using randomized crossover study design, continuous slow infusion of radionuclide tracer into the pharynx in 26 healthy volunteers revealed incidence of pulmonary aspiration, directly determined by the tracer in the lung field, during remifentanyl (48%) than during placebo infusion (12%). Subjective symptoms such as swallowing difficulty and hand grip strength were not associated with the aspiration.
- Efficacy of Sugammadex for the Reversal of Moderate and Deep Rocuronium-induced Neuromuscular Block in Patients Pretreated with Intravenous Magnesium: A Randomized Controlled Trial** 59
C. Czarnetzki, E. Tassonyi, C. Lysakowski, N. Elia, and M.R. Tramèr
 A 60 mg/kg intravenous dose of magnesium sulfate administered before induction of anesthesia had no effect on the ability of recommended doses of sugammadex to reverse neuromuscular blockade produced by an intubating dose of rocuronium after spontaneous recovery to moderate and deep levels of blockade.
- BASIC SCIENCE**
- Fast-spiking Cell to Pyramidal Cell Connections Are the Most Sensitive to Propofol-induced Facilitation of GABAergic Currents in Rat Insular Cortex** 68
Y. Koyanagi, Y. Oi, K. Yamamoto, N. Koshikawa, and M. Kobayashi
 In brain slices from the insular cortex, propofol preferentially enhanced fast spiking GABAergic interneuron connections to pyramidal neurons. This suppresses excitatory output from the cortex.
- Disruption of Hippocampal Neuregulin 1–ErbB4 Signaling Contributes to the Hippocampus-dependent Cognitive Impairment Induced by Isoflurane in Aged Mice** 79
X.-M. Li, F. Su, M.-H. Ji, G.-F. Zhang, L.-L. Qiu, M. Jia, J. Gao, Z. Xie, and J.-J. Yang
 Isoflurane in 100% oxygen significantly impaired the hippocampus-dependent cognitive function assessed at 48 h by the fear conditioning test in mice. This effect was mediated at least in part via disruption of the neurotrophic factor-dependent NRG1–ErbB4 signaling in the parvalbumin-positive interneurons.

CONTENTS

■ CRITICAL CARE MEDICINE

CLINICAL SCIENCE

Lysis Onset Time as Diagnostic Rotational Thromboelastometry Parameter for Fast Detection of Hyperfibrinolysis 89

S.E. Dekker, V.A. Viersen, A. Duvekot, M. de Jong, C.E. van den Brom, P.M. van de Ven, P. Schober, and C. Boer

In an *in vitro* assay, this study investigated which thromboelastometric hemostatic parameters could be valuable for fast diagnosis of the severity of hyperfibrinolysis, and then confirmed the findings in a patient population with hyperfibrinolysis.

BASIC SCIENCE

Obesity-induced Hyperleptinemia Improves Survival and Immune Response in a Murine Model of Sepsis 98

D. Siegl, T. Annecke, B.L. Johnson III, C. Schlag, A. Martignoni, N. Huber, P. Conzen, C.C. Caldwell, and J. Tschöp

The relative hyperleptinemia of class 1 obesity or exogenous leptin administration was protective in experimental sepsis. This suggests leptin is a possible novel therapy for sepsis.

Inhibition of the Ubiquitin-Proteasome Pathway Does Not Protect against Ventilator-induced Accelerated Proteolysis or Atrophy in the Diaphragm 115

A.J. Smuder, W.B. Nelson, M.B. Hudson, A.N. Kavazis, and S.K. Powers

Pharmacologic inhibition of the ubiquitin-proteasome pathway, using epoxomicin, did not protect the diaphragm against oxidative stress or atrophy in anesthetized, mechanically ventilated rats.

■ PAIN MEDICINE

CLINICAL SCIENCE

Proteinase-activated Receptor 1 Contributed to Up-regulation of Enkephalin in Keratinocytes of Patients with Obstructive Jaundice 127

K.-M. Tao, Y. Tao, C.-Y. Chen, L.-Q. Yang, Z.-J. Lu, Y.-M. Sun, S.-D. Huang, and W.-F. Yu

In patients with cholestasis who were scheduled to surgery, postoperative morphine consumption was decreased. In skin biopsies, expression of enkephalin was significantly increased. In a parallel rodent study, in rats with experimentally induced cholestasis, skin enkephalin expression and nociceptive thresholds were increased. The administration of protease-activated receptors-1 antagonist reduced skin enkephalin expression. Protease activated receptors-1 receptor activation increases skin enkephalin expression and may serve as a novel therapeutic option for treatment of postoperative pain.

Polymorphism in the *ADRB2* Gene Explains a Small Portion of Intersubject Variability in Pain Relative to Cervical Dilatation in the First Stage of Labor 140

A.S. Terkawi, W.M. Jackson, S. Hansoti, R. Tabassum, and P. Flood

In modeling hourly labor pain as a function of cervical dilatation in approximately 200 women through the course of labor, *ADRB2* explained less than 1% of intersubject variance, considerably less than that of induction of labor.

BASIC SCIENCE

◆◆ (R,S)-Ketamine Metabolites (R,S)-norketamine and (2S,6S)-hydroxynorketamine Increase the Mammalian Target of Rapamycin Function 149

R.K. Paul, N.S. Singh, M. Khadeer, R. Moaddel, M. Sanghvi, C.E. Green, K. O'Loughlin, M.C. Torjman, M. Bernier, and I.W. Wainer

Antidepressant effects of subanesthetic doses of (R,S)-ketamine may be due to a combination of interrelated effects at the α_7 -nicotinic acetylcholine receptor (α_7 -nAChR) produced by (R,S)-ketamine and its metabolites. One effect is increased protein expression *via* the mammalian target of rapamycin signaling pathway, which is initiated by antagonism of α_7 -nAChR and is reflected by increased monomeric serine racemase expression. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

CONTENTS

- 🌐 **Long-term Application of Glycine Transporter Inhibitors Acts Antineuropathic and Modulates Spinal *N*-methyl-D-aspartate Receptor Subunit NR-1 Expression in Rats** 160
F. Barthel, A. Urban, L. Schlösser, V. Eulenburg, R. Werdehausen, T. Brandenburger, C. Aragon, I. Bauer, and H. Hermanns

The long-term inhibition of glycine transporters GlyT1 and GlyT2 reduces neuropathic pain-related behavior in a rat model without neuromotor or respiratory side effects. The modulation of spinal *N*-methyl-D-aspartate receptors seems to contribute to this effect. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

■ EDUCATION

IMAGES IN ANESTHESIOLOGY

- ◇ **Endoluminal Computed Tomography: A Novel Technology for Assessment of Large Airway Pathologies** 170
S. Agarwal, W.B. Bates, and M.R. Castresana

ORIGINAL INVESTIGATIONS IN EDUCATION

- ◆◆ **Predicting Case Volume from the Accumulating Elective Operating Room Schedule Facilitates Staffing Improvements** 171
V. Tiwari, W.R. Furman, and W.S. Sandberg

In a review of 146 consecutive surgical days at one academic medical center, case volume could be predicted with high accuracy 1 to 2 weeks in advance, allowing a closer match of staffing to demand.

CLINICAL CONCEPTS AND COMMENTARY

- ◇ **Lung-protective Ventilation in the Operating Room: Time to Implement?** 184
N.M. Goldenberg, B.E. Steinberg, W.L. Lee, D.N. Wijeyesundera, and B.P. Kavanagh

Recent data suggest that adopting a lung protective ventilation strategy will benefit healthy surgical patients. The authors examine the data, and suggest exercising caution prior to implementing a practice change that will affect a massive population.

REVIEW ARTICLE

- 📄◇ **Mechanical Ventilation-associated Lung Fibrosis in Acute Respiratory Distress Syndrome: A Significant Contributor to Poor Outcome** 189
N.E. Cabrera-Benitez, J.G. Laffey, M. Parotto, P.M. Spieth, J. Villar, H. Zhang, and A.S. Slutsky

Mechanical ventilation may be a major contributor to pulmonary fibrosis in patients with the acute respiratory distress syndrome.

MIND TO MIND

- A Flash of Humanity** 199
M.J. Lenart

■ CORRESPONDENCE

- Factors Affecting Survival and Neurologic Outcome of Patient with Perioperative Cardiac Arrest** 201
F.-S. Xue, R.-P. Li, and S.-Y. Wang

Data on the Anesthetic Procedure or Surgical Risk Are Still Necessary
C.L. Errando

In Reply
S.K. Ramachandran

CONTENTS

“Big Data” Has Not Come to Pediatric Anesthesia 204

D.M. Fisher

In Reply

R.S. Litman

■ ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Guaranteed by Gas: Neiman’s Advertising Bookmark 3

George S. Bause

“Hands-On” Teaching by Chevalier Jackson 139

George S. Bause

Wrenching Experiences from the Heidbrink Company 188

George S. Bause

■ REVIEWS OF EDUCATIONAL MATERIAL

206

■ CAREERS & EVENTS

26A

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.lww.com/advertisingratecards/>). 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: bclaim@lwwis.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.