



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

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◆ ◆ Massive Hemorrhage: A Report from the Anesthesia Closed Claims Project <i>R.P. Dutton, L.A. Lee, L.S. Stephens, K.L. Posner, J.M. Davies, and K.B. Domino</i>	450

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.

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◆ Refers to Editorial Views	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. Vandebunder, 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.

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CLINICAL SCIENCE

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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 $Na_v1.2$, $Na_v1.6$, $Na_v1.7$, and $Na_v1.8$ 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 $Na_v1.2$. Inhibition of $Na_v1.2$ 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*

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- ◇ **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.

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