

ON THE COVER:

Many modalities including peripheral nerve block, periarticular infiltration, and epidural analgesia have been used to provide analgesia after total knee arthroplasty, but their relative efficacy remains unknown. In this issue of *ANESTHESIOLOGY*, *Terkawi et al.* conducted a network meta-analysis of 170 trials (12,530 patients) assessing 17 treatment modalities and concluded that blocking multiple nerves was preferable to blocking any single nerve, periarticular infiltration, or epidural analgesia. In an accompanying Editorial View, *Ilfeld and McCartney* discuss the importance of looking beyond pain scores and analgesic consumption to consider the priorities of all stakeholders when choosing among available options for providing analgesia after surgery.

- *Terkawi et al.*: Pain Management Modalities after Total Knee Arthroplasty: A Network Meta-analysis of 170 Randomized Controlled Trials, p. 923
- *Ilfeld and McCartney*: Searching for the Optimal Pain Management Technique after Knee Arthroplasty: Analgesia Is Just the Tip of the Iceberg, p. 768

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◆ Early Development, Identification of Mode of Action, and Use of Dantrolene Sodium: The Role of Keith Ellis, Ph.D.

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A history of the role and work of Keith Osbourne Ellis, Ph.D., in the early investigations into and development of dantrolene sodium.

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D. H. Chestnut

Physician professionalism is a core competency that requires character and lifelong learning, commitment, and practice.

■ PERIOPERATIVE MEDICINE

CLINICAL SCIENCE

- ◇ ◆ **Long-term Effects of Remote Ischemic Preconditioning on Kidney Function in High-risk Cardiac Surgery Patients: Follow-up Results from the RenalRIP Trial** 787
A. Zarbock, J. A. Kellum, H. Van Aken, C. Schmidt, M. Küllmar, P. Rosenberger, S. Martens, D. Görlich, and M. Meersch

Remote ischemic preconditioning significantly reduced the 3-month incidence of a composite endpoint major adverse kidney event consisting of mortality, need for renal replacement therapy, and persistent renal dysfunction in high-risk patients undergoing cardiac surgery.

- ◇ **Lack of Association between Preoperative Statin Use and Respiratory and Neurologic Complications after Cardiac Surgery** 799
R. Komatsu, H. O. Yilmaz, J. You, C. A. Bashour, S. Rajan, E. G. Soltesz, D. I. Sessler, and A. Turan

Preoperative statin use did not reduce pulmonary or neurologic complications after cardiac surgery.

- 🌐 **Ischemic Optic Neuropathy in Cardiac Surgery: Incidence and Risk Factors in the United States from the National Inpatient Sample 1998 to 2013** 810
D. S. Rubin, M. M. Matsumoto, H. E. Moss, C. E. Joslin, A. Tung, and S. Roth

Development of ischemic optic neuropathy after cardiac surgery is associated with carotid artery stenosis, stroke, and degenerative eye conditions. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

- ◇ **Clinical Effectiveness and Safety of Intraoperative Methadone in Patients Undergoing Posterior Spinal Fusion Surgery: A Randomized, Double-blinded, Controlled Trial** 822
G. S. Murphy, J. W. Szokol, M. J. Avram, S. B. Greenberg, T. D. Shear, M. A. Deshur, J. S. Vender, J. Benson, and R. L. Newmark

In patients undergoing posterior spinal fusion surgery (averaging two levels), intravenous methadone (0.2 mg/kg) given at induction compared with intravenous hydromorphone (2 mg at surgical closure) resulted in decreased postoperative intravenous and oral opioid requirements and also diminished pain scores and improved patient satisfaction. There were no differences between the methadone and hydromorphone groups in opioid-related or other adverse events.

- 🌐 ***In Vivo* Cysteinyl Leukotriene Release in Allergic and Nonallergic Immediate Hypersensitivity Reactions during Anesthesia** 834
D. Laroche, P. Léturgie, D. Mariotte, Y. Ollivier, J.-L. Hanouz, B. Le Mauff, and J.-J. Parienti

Cysteinyl leukotriene concentrations are highly increased during at least 24 h in allergic and nonallergic immediate hypersensitivity reactions. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

BASIC SCIENCE

- Hypoxia Induces Internalization of κ -Opioid Receptor** 842
C. Xi, X. Liang, C. Chen, H. Babazada, T. Li, and R. Liu

While most κ -opioid receptors are located on the cell membrane of mouse Neuro2A neuroblastoma cells, oxygen–glucose deprivation induced significant internalization of them. Oxygen–glucose deprivation-induced internalization of κ -opioid receptors can be blocked by specific κ -opioid receptor antagonists or a dynamin inhibitor and can be reversed by reoxygenation.

- K-Cl Cotransporter 2–mediated Cl⁻ Extrusion Determines Developmental Stage–dependent Impact of Propofol Anesthesia on Dendritic Spines** 855
M. Puskarjov, H. Fiumelli, A. Briner, T. Bodogan, K. Demeter, C.-M. Laco, M. Mavrovic, P. Blaesse, K. Kaila, and L. Vutskits

The reduction in cortical dendritic spine number induced by propofol sedation of neonatal rats could be prevented by premature expression of potassium-chloride cotransporter 2 (KCC2) and the consequent increase in γ -aminobutyric acid–mediated inhibition. The age-dependent reduction in dendritic spine number induced by propofol is controlled by expression of KCC2 that determines γ -aminobutyric acid receptor type A–mediated inhibition, a novel mechanism for anesthetic effects on synaptic plasticity.

- ◇ **Lidocaine Induces Apoptosis and Suppresses Tumor Growth in Human Hepatocellular Carcinoma Cells *In Vitro* and in a Xenograft Model *In Vivo*** 868
W. Xing, D.-T. Chen, J.-H. Pan, Y.-H. Chen, Y. Yan, Q. Li, R.-F. Xue, Y.-F. Yuan, and W.-A. Zeng


Either lidocaine (30 mg/kg intraperitoneally, twice a week) or cisplatin (3 mg/kg intraperitoneally, once a week) treatment alone markedly suppressed human hepatocellular carcinoma HepG2 xenograft tumor growth in male athymic nude mice compared with the control. The combination of lidocaine and cisplatin exerted a therapeutic effect that was significantly better than the effects in all the other experimental groups.

■ CRITICAL CARE MEDICINE

CLINICAL SCIENCE

- ◇ **Causes and Characteristics of Death in Intensive Care Units: A Prospective Multicenter Study** 882
J.-C. Orban, Y. Walrave, N. Mongardon, B. Allaouchiche, L. Argaud, F. Aubrun, G. Barjon, J.-M. Constantin, G. Dhonneur, J. Durand-Gasselin, H. Dupont, M. Genestal, C. Goguey, P. Goutorbe, B. Guidet, H. Hyvernat, S. Jaber, J.-Y. Lefrant, Y. Mallédant, J. Morel, A. Ouattara, N. Pichon, A.-M. G. Robardey, M. Sirodot, A. Theissen, S. Wiramus, L. Zieleskiewicz, M. Leone, and C. Ichai, for the AzuRéa Network

In a general intensive care unit population, the majority of patients present with at least one organ failure at the time of death. Compared to its anticipated counterpart, unexpected death occurred earlier and had fewer organ failures.

- ◇  **Nebulization of Antiinfective Agents in Invasively Mechanically Ventilated Adults: A Systematic Review and Meta-analysis** 890
C. Solé-Lleonart, J.-J. Rouby, S. Blot, G. Poulakou, J. Chastre, L. B. Palmer, M. Bassetti, C.-E. Luyt, J. M. Pereira, J. Riera, T. Felton, J. Dhanani, T. Welte, J. M. Garcia-Alamino, J. A. Roberts, and J. Rello

A systematic review reports that the data are sparse; however, nebulization may be more effective in cases of resistant organisms and less nephrotoxic (if replacing nephrotoxic systemic agents) but may compromise mechanical ventilation especially in hypoxemic patients.



BASIC SCIENCE

- ◆  **One-hit Models of Ventilator-induced Lung Injury: Benign Inflammation *versus* Inflammation as a By-product** 909
D. Lex and S. Uhlig

Murine ventilator-induced lung injury (single “hit”) is characterized by either mild inflammation with normal lung functions or—above a threshold plateau pressure—fulminant lung failure. In this latter condition, pretreatment with corticosteroid suggests that ventilator-induced inflammation may have a bystander rather than a pathogenic impact on lung injury. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

■ PAIN MEDICINE

CLINICAL SCIENCE

- ◆   **Pain Management Modalities after Total Knee Arthroplasty: A Network Meta-analysis of 170 Randomized Controlled Trials** 923
A. S. Terkawi, D. Mavridis, D. I. Sessler, M. S. Nunemaker, K. S. Doais, R. S. Terkawi, Y. S. Terkawi, M. Petropoulou, and E. C. Nemergut

Using a random-effects network meta-analysis technique, 170 trials were analyzed to identify the optimal analgesic modality that balances pain control, opioid use, and passive range of motion of the prosthetic joint. Although functional outcomes were suboptimally studied, the combination of femoral and sciatic nerve block was judged to be the overall best approach. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

- ◇  **A Prospective Study of Chronic Pain after Thoracic Surgery** 938
E. O. Bayman, K. R. Parekh, J. Keech, A. Selte, and T. J. Brennan

In a study of 107 patients undergoing thoracotomy and thoracoscopy, the incidence and severity of pain 6 months after surgery were similar. Acute postoperative pain was the strongest predictor of pain at 6 months. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

BASIC SCIENCE

- 1-(2,4-Dibromophenyl)-3,6,6-trimethyl-1,5,6,7-tetrahydro-4H-indazol-4-one: A Novel Opioid Receptor Agonist with Less Accompanying Gastrointestinal Dysfunction than Morphine** 952

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Compound 1 was further tested and found to be an agonist at μ -, δ -, and κ -opioid receptors but caused antinociception exclusively *via* μ -receptor activation. Compared with morphine, compound 1 caused greater antinociception but less gastrointestinal slowing.

- MicroRNA-182-5p Regulates Nerve Injury–induced Nociceptive Hypersensitivity by Targeting Ephrin Type-b Receptor 1** 967

X. Zhou, Chenjing Zhang, Congjuan Zhang, Y. Peng, Y. Wang, and H. Xu

After sciatic nerve injury in rats, microRNA-182-5p expression levels decreased in spinal cord tissue while ephrin type-b receptor 1 increased. The overexpression of microRNA-182-5p reduced ephrin type-b receptor expression and prevented nociceptive sensitization after nerve injury.

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