



## ON THE COVER:

Traditional local anesthetics, like lidocaine, bupivacaine, and tetracaine, produce neural blockade by binding deep within the central pore of the transmembrane sodium channel. Local anesthetics have a limited duration of action and their use is restricted by cardiac and central nervous system toxicity. In contrast, marine toxins like tetrodotoxin and the saxitoxins bind at a distinct location on the sodium channel and have varying affinities for cardiac sodium channels. In this issue of *ANESTHESIOLOGY*, Cravero, Berde and their colleagues show that when neosaxitoxin and bupivacaine are administered concomitantly, a prolonged-duration sensory block is created without evidence of added cardiac or central nervous system toxicity, demonstrating the potential for prolonged, but reversible, neural blockade.

- Lobo *et al.*: A Phase 1, Dose-escalation, Double-blind, Block-randomized, Controlled Trial of Safety and Efficacy of Neosaxitoxin Alone and in Combination with 0.2% Bupivacaine, with and without Epinephrine, for Cutaneous Anesthesia, p. 873
- Templin *et al.*: Neosaxitoxin in Rat Sciatic Block: Improved Therapeutic Index Using Combinations with Bupivacaine, with and without Epinephrine, p. 886
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### ■ PERIOPERATIVE MEDICINE

#### CLINICAL SCIENCE

- Influence of Ventilation Strategies and Anesthetic Techniques on Regional Cerebral Oximetry in the Beach Chair Position: A Prospective Interventional Study with a Randomized Comparison of Two Anesthetics** 765  
*P. Picton, A. Dering, A. Alexander, M. Neff, B. S. Miller, A. Shanks, M. Housey, and G. A. Mashour*
- Cerebral oxygenation desaturation in the beach chair position, as estimated by cerebral oximetry, may be attenuated by the combination of normobaric hyperoxia and moderate hypercarbia. This appears independent of anesthetic agent.
- ◆ **Concurrence of Intraoperative Hypotension, Low Minimum Alveolar Concentration, and Low Bispectral Index Is Associated with Postoperative Death** 775  
*M. D. Willingham, E. Karren, A. M. Shanks, M. F. O'Connor, E. Jacobsohn, S. Kheterpal, and M. S. Avidan*
- In a retrospective study of nearly 14,000 patients from three clinical trials, the likelihood of 30- and 90-day mortality was increased approximately 10% for every 15 cumulative minutes in the triple low state, after controlling for known confounders for perioperative death.

#### BASIC SCIENCE

- ◆ **MicroRNA-21 Mediates Isoflurane-induced Cardioprotection against Ischemia–Reperfusion Injury via Akt/Nitric Oxide Synthase/Mitochondrial Permeability Transition Pore Pathway** 786  
*S. Qiao, J. M. Olson, M. Paterson, Y. Yan, I. Zaja, Y. Liu, M. L. Riess, J. R. Kersten, M. Liang, D. C. Wartier, Z. J. Bosnjak, and Z.-D. Ge*
- Isoflurane protects mouse hearts from myocardial ischemia/reperfusion injury by a microRNA-21-dependent mechanism. The results of this article open a new area of investigation into epigenetic mechanisms of volatile anesthetic-induced cardiac protection.
- ◆ **Influence of Tracheal Obstruction on the Efficacy of Superimposed High-frequency Jet Ventilation and Single-frequency Jet Ventilation** 799  
*R. Sütterlin, A. LoMauro, S. Gandolfi, R. Priori, A. Aliverti, P. Frykholm, and A. Larsson*
- In a study of pigs with obstructed airway, superimposed high-frequency jet ventilation was superior over high-frequency jet ventilation in providing adequate oxygenation by increasing lung volume and carbon dioxide removal by increasing tidal volume even without increasing the risk of barotrauma. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*
- ◆ **Astrocytes Protect against Isoflurane Neurotoxicity by Buffering pro-brain–derived Neurotrophic Factor** 810  
*C. M. Stary, X. Sun, and R. G. Giffard*
- Using cultured mouse neurons and astroglia, coculture with astrocytes reduced the neurotoxicity of isoflurane by buffering increases in pro-brain–derived neurotrophic factor. Modulation of brain-derived neurotrophic factor signaling or astrocyte function is a potential approach to prevent anesthetic neurotoxicity.

## ■ CRITICAL CARE MEDICINE

## CLINICAL SCIENCE

**Low Cerebral Oxygenation Levels during Resuscitation in Out-of-hospital Cardiac Arrest Are Associated with Hyperfibrinolysis** 820

A. Duvekot, V. A. Viersen, S. E. Dekker, L. M. G. Geeraedts, Jr., L. A. Schwarte, A. M. E. Spoelstra-Man, P. M. van de Ven, C. E. van den Brom, M. C. de Waard, S. A. Loer, and C. Boer

Activation of the fibrinolytic system is more common in out-of-hospital cardiopulmonary arrest patients with an initial cerebral tissue oxygenation value of 50% or less during resuscitation and is linked to increased levels of tissue plasminogen activator rather than involvement of protein C.

◆◆🌐 **Diagnostic Accuracy of Respiratory Distress Observation Scales as Surrogates of Dyspnea Self-report in Intensive Care Unit Patients** 830

R. Persichini, F. Gay, M. Schmidt, J. Mayaux, A. Demoule, C. Morélot-Panzini, and T. Similowski

In 220 intensive care unit patients able to communicate, an observational scale containing five nonverbal signs was derived and validated respective to dyspnea self-report. This should help better understand and manage mechanically ventilated patients in the future. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

## ■ PAIN MEDICINE

## CLINICAL SCIENCE

◆◆🌐 **Up-regulation of Cathepsin G in the Development of Chronic Postsurgical Pain: An Experimental and Clinical Genetic Study** 838

X. Liu, Y. Tian, Z. Meng, Y. Chen, I. H. T. Ho, K. W. Choy, P. Lichtner, S. H. Wong, J. Yu, T. Gin, W. K. K. Wu, C. H. K. Cheng, and M. T. V. Chan

Cathepsin G blockade reduced inflammation in the spinal cord and reduced pain behavior in rodents. In humans, two specific polymorphisms were associated with a lower risk for the development of chronic postsurgical pain. The data suggest that cathepsin G is a pronociceptive mediator in experimental subjects and humans; as such, it offers a potential therapeutic target for prevention of chronic postsurgical pain. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

◆ **Novel 10-kHz High-frequency Therapy (HF10 Therapy) Is Superior to Traditional Low-frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: The SENZA-RCT Randomized Controlled Trial** 851

L. Kapural, C. Yu, M. W. Doust, B. E. Gliner, R. Vallejo, B. T. Sitzman, K. Amirdelfan, D. M. Morgan, L. L. Brown, T. L. Yearwood, R. Bundschu, A. W. Burton, T. Yang, R. Benyamin, and A. H. Burgher

This randomized trial involving 198 participants demonstrated that high-frequency spinal cord stimulation was superior to conventional spinal cord stimulation for the treatment of back pain and leg pain. The effects of high-frequency stimulation relative to conventional stimulation persisted for 12 months.

◆ **H Psychiatric Comorbidity Is Associated Prospectively with Diminished Opioid Analgesia and Increased Opioid Misuse in Patients with Chronic Low Back Pain** 861

A. D. Wasan, E. Michna, R. R. Edwards, J. N. Katz, S. S. Nedeljkovic, A. J. Dolman, D. Janfaza, Z. Isaac, and R. N. Jamison

In 81 patients with chronic low back pain prospectively studied for 6½ months with placebo followed by opioids, those with high negative affect were prescribed larger average daily doses of opioids, had less improvement in pain, and had a greater rate of opioid misuse than those with low negative affect. These prospective data support previous cross-sectional data to suggest that negative affect presents an important risk factor in inadequate analgesia from opioids and opioid misuse.

- ◆◆◆** **A Phase 1, Dose-escalation, Double-blind, Block-randomized, Controlled Trial of Safety and Efficacy of Neosaxitoxin Alone and in Combination with 0.2% Bupivacaine, with and without Epinephrine, for Cutaneous Anesthesia** **873**

*K. Lobo, C. Donado, L. Cornelissen, J. Kim, R. Ortiz, R. W. A. Peake, M. Kellogg, M. E. Alexander, D. Zurakowski, K. E. Kurgansky, J. Peyton, A. Bilge, K. Boretsky, M. E. McCann, C. B. Berde, and J. Cravero*

In a first-in-human Food and Drug Administration–regulated phase 1 safety study in 84 male volunteers, subcutaneous infiltration of Neosaxitoxin with bupivacaine produced long-lasting anesthesia but no serious adverse events although perioral numbness and tingling were noted at high doses. Addition of epinephrine reduced circulating Neosaxitoxin concentrations and perioral tingling and numbness and further prolonged sensory block. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

## BASIC SCIENCE

- ◆** **Neosaxitoxin in Rat Sciatic Block: Improved Therapeutic Index Using Combinations with Bupivacaine, with and without Epinephrine** **886**

*J. S. Templin, M. C. Wylie, J. D. Kim, K. E. Kurgansky, G. Gorski, J. Kheir, D. Zurakowski, G. Corfas, and C. Berde*

In rats, combination of Neosaxitoxin with bupivacaine for sciatic nerve block resulted in motor and sensory block, which was longer than either agent alone, and was up to 48 h when epinephrine was added. Histologic examination showed no evidence of neural toxicity, and intravenous injection of Neosaxitoxin resulted in cardiotoxicity with longer delays than bupivacaine.

- Impaired Pain-evoked Analgesia after Nerve Injury in Rats Reflects Altered Glutamate Regulation in the Locus Coeruleus** **899**

*M. Kimura, T. Suto, C. E. Morado-Urbina, C. M. Peters, J. C. Eisenach, and K.-I. Hayashida*

The authors investigated the circuitry for impaired noxious stimulation–induced analgesia in rats with neuropathic pain. The authors demonstrate glutamate dysregulation in the locus coeruleus, and the resulting impairment of descending inhibitory control contributes to the loss of noxious stimulation–induced analgesia in neuropathic pain.

- Neuropathic Allodynia Involves Spinal Neurexin-1 $\beta$ -dependent Neuroligin-1/ Postsynaptic Density-95/NR2B Cascade in Rats** **909**

*T.-B. Lin, C.-Y. Lai, M.-C. Hsieh, J.-L. Jiang, J.-K. Cheng, Y.-P. Chau, T. Ruan, G.-D. Chen, and H.-Y. Peng*

It was shown that the association of *N*-methyl-D-aspartate receptor NR2B subunits and postsynaptic density-95 scaffolding protein was enhanced in spinal cord dorsal horn neurons after nerve ligation in rats. The disruption of neurexin-1 $\beta$ –neuroligin-1 interaction reduced allodynia and NR2B–postsynaptic density-95 interactions in nerve-ligated rats.

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*D. O. Warner, K. Berge, H. Sun, A. Harman, A. Hanson, and D. R. Schroeder*

In a nested, matched case-cohort design of 384 anesthesia residents who developed substance use disorder (SUD) and 768 controls who did not, receiving medical education in the United States, but not anesthesia knowledge early in residency, was associated with risk of developing SUD. By the end of follow-up, 54 anesthesiology residents (14.1%) with SUD and 10 controls (1.3%) were dead. Those with SUD were 15-, 10-, and 7-fold more likely to not complete residency, to not become board certified, or have adverse medical licensure actions, respectively.

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*P. L. Purdon, A. Sampson, K. J. Pavone, and E. N. Brown*

The authors review the neurophysiology of the electroencephalogram signatures of the anesthetics: propofol, dexmedetomidine, ketamine, sevoflurane, isoflurane, desflurane, and nitrous oxide. These signatures provide a neurophysiologically based paradigm for brain state monitoring of patients receiving anesthesia care.

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