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Volume 132

Issue 5

May 2020

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 An Introduction to Causal Diagrams for Anesthesiology Research <i>A. L. Gaskell, J. W. Sleight</i>	951
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This article reviews some basic principles of causal inference and the use of causal diagrams to understand and address different forms of bias in anesthesia research.

Perioperative Medicine

CLINICAL SCIENCE

  Machine Learning Prediction of Postoperative Emergency Department Hospital Readmission <i>V. V. Mišić, E. Gabel, I. Hofer, K. Rajaram, A. Mahajan</i>	968
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Hospital-specific 30-day surgical readmission models using machine learning techniques provide clinically usable predictions when applied to future patients. A parsimonious approach limiting which data elements are considered performs as well as more comprehensive models. SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT

  Hydromorphone Unit Dose Affects Intraoperative Dosing: An Observational Study <i>B. D. Ershoff, T. Grogan, J. C. Hong, P. A. Chia, E. Gabel, M. Cannesson</i>	981
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The investigators used a natural experiment in which their institution switched from 2-mg vials of hydromorphone to 1-mg vials, and then back to 2-mg vials. Using a sophisticated segmented regression analysis, they show that patients were far more likely to be given 1 mg hydromorphone when smaller vials were provided. The contents of single-patient-use vials influences drug use and might be used to guide practice.

  Multimodal Analgesic Regimen for Spine Surgery: A Randomized Placebo-controlled Trial <i>K. Maheshwari, R. Avitsian, D. I. Sessler, N. Makarova, M. Tanios, S. Raza, D. Traul, S. Rajan, M. Manlapaz, S. Machado, A. Krishnaney, A. Machado, R. Rosenquist, A. Kurz</i>	992
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Adult spine surgery patients were randomized to placebo or to the combination of acetaminophen, gabapentin, ketamine, and lidocaine. The Quality of Recovery was similar in each group, as were pain scores and opioid consumption. SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT

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ON THE COVER: Various multimodal analgesic approaches have been proposed for spine surgery, but none of these approaches have been carefully evaluated. In this issue of ANESTHESIOLOGY, Maheshwari *et al.* evaluated the effect of using a combination of four nonopioid analgesics *versus* placebo on Quality of Recovery, postoperative opioid consumption, and pain scores. They found that an analgesic pathway based on preoperative acetaminophen and gabapentin, combined with intraoperative infusions of lidocaine and ketamine, did not improve recovery in patients who had multilevel spine surgery. Cover Illustration: A. Johnson, Vivo Visuals.


• Maheshwari *et al.*: Multimodal Analgesic Regimen for Spine Surgery: A Randomized Placebo-controlled Trial, p. 992

-  **Spectral and Entropic Features Are Altered by Age in the Electroencephalogram in Patients under Sevoflurane Anesthesia**
M. Kreuzer, M. A. Stern, D. Hight, S. Berger, G. Schneider, J. W. Sleight, P. S. García1003

Older age is associated with a shift to a less predictable electroencephalogram, which could inform intraoperative monitoring approaches. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

-  **Source-level Cortical Power Changes for Xenon and Nitrous Oxide–induced Reductions in Consciousness in Healthy Male Volunteers**
A. Pelentritou, L. Kuhlmann, J. Cormack, S. McGuigan, W. Woods, S. Muthukumaraswamy, D. Liley1017


Magnetoencephalography and electroencephalography recordings at increasing equivalent dose of xenon and nitrous oxide show distinct effects of these two drugs on neural activity. While xenon increased low-frequency delta and theta activity, nitrous oxide induced alpha power depression. These observations suggest that, despite their high affinity to the *N*-methyl-D-aspartate receptor, xenon and nitrous oxide are acting via distinct mechanisms to modulate neural activity. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

-  **Sevoflurane and Parkinson's Disease: Subthalamic Nucleus Neuronal Activity and Clinical Outcome of Deep Brain Stimulation**
S.-T. Tsai, G.-F. Tseng, C.-C. Kuo, T.-Y. Chen, S.-Y. Chen1034

When compared to local anesthesia, sevoflurane-based general anesthesia decreased beta-frequency oscillations and induced coherent lower frequency oscillations in the subthalamic nucleus of patients with Parkinson's disease undergoing electrode placement for deep brain stimulation. These sevoflurane-induced changes in electrical activity patterns did not reduce electrode placement accuracy or clinical outcome. These observations suggest that electrode placement for deep brain stimulation under sevoflurane anesthesia is a feasible clinical option. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*


- Prophylactic Intrathecal Morphine and Prevention of Post–Dural Puncture Headache: A Randomized Double-blind Trial**
F. M. Peralta, C. A. Wong, N. Higgins, P. Toledo, M. J. Jones, R. J. McCarthy1045

In a single-center, randomized, double-blind study, there was no evidence that intrathecal morphine prevented post–dural puncture headache.


-  **Mild Acute Kidney Injury after Noncardiac Surgery Is Associated with Long-term Renal Dysfunction: A Retrospective Cohort Study**
A. Turan, B. Cohen, J. Adegboye, N. Makarova, L. Liu, E. J. Mascha, Y. Qiu, S. Irefin, B. J. Wakefield, K. Ruetzler, D. I. Sessler1053

Patients with mild postoperative kidney injury (stage I) after noncardiac surgery had estimated 2.4 times higher odds of having long-term renal dysfunction compared with patients without postoperative kidney injury. A quarter of patients who had stage I acute kidney injury postoperatively still had stage I kidney injury 1 to 2 yr later, and an additional 11% had even worse renal function. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

BASIC SCIENCE

-  **Dantrolene Ameliorates Impaired Neurogenesis and Synaptogenesis in Induced Pluripotent Stem Cell Lines Derived from Patients with Alzheimer's Disease**
Y. Wang, G. Liang, S. Liang, R. Mund, Y. Shi, H. Wei1062

Survival, proliferation, and differentiation of neuronal progenitors derived from patients with Alzheimer's disease are impaired when compared with healthy counterparts. Chronic exposure of induced pluripotent stem cells, derived from patients with Alzheimer's disease, to dantrolene improves the survival, proliferation, and differentiation of these cells. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

-  **Desflurane Anesthesia Alters Cortical Layer–specific Hierarchical Interactions in Rat Cerebral Cortex**
A. G. Hudetz, S. Pillay, S. Wang, H. Lee1080

In vivo intracortical electrophysiologic recordings from the visual cortices of male rats reveal that desflurane disrupts cortical layer–specific neuronal interactions in local brain circuits. These observations suggest that neuronal connectivity changes in local cortical circuits may contribute to large-scale cortical functional disintegration as a mechanism of anesthetic-induced unconsciousness. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

Comparison of Neonatal and Adult Fibrin Clot Properties between Porcine and Human Plasma

K. A. Nellenbach, S. Nandi, A. Kyu, S. Sivadanam,
N. A. Guzzetta, A. C. Brown 1091

Fibrinogen concentration and functionality in plasma collected from piglets paralleled those observed in plasma collected from human neonates. Fibrin network structure was highly aligned in both neonatal species and highly branched in adults of both species. Fibrin network stiffness and degradation patterns in both neonatal species were substantially similar as they were in adults of both species. The *ex vivo* addition of several procoagulant therapies augmented fibrin network properties of diluted piglet plasma.
SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT

Critical Care Medicine

CLINICAL SCIENCE

Myocardial Function during Low versus Intermediate Tidal Volume Ventilation in Patients without Acute Respiratory Distress Syndrome

T. G. V. Cherpanath, F. D. Simonis, B. J. Bouma, R. H. de Bruin-Bon,
R. M. Determann, N. P. Juffermans, M. Gama de Abreu, P. Pelosi,
A. S. Neto, J. A. B. Groeneveld, M. J. Schultz, W. K. Lagrand 1102

What is not known is if lower versus intermediate tidal volume mechanical ventilation is also associated with improved systolic and diastolic left ventricular and right ventricular myocardial function. This study of 42 mechanically-ventilated patients who did not have acute respiratory distress syndrome found that lower tidal volume mechanical ventilation was associated with increased right and left ventricular systolic function but not improved diastolic function.

Usefulness of Parasternal Intercostal Muscle Ultrasound during Weaning from Mechanical Ventilation

M. Dres, B.-P. Dubé, E. Goligher, S. Vorona, S. Demiri, E. Morawiec,
J. Mayaux, L. Brochard, T. Similowski, A. Demoule 1114

Parasternal intercostal muscle thickness can be measured with ultrasound with good interobserver reproducibility. Parasternal intercostal muscle thickening was responsive to the level of ventilator assistance and significantly higher (*i.e.*, increased) in mechanically ventilated patients with diaphragm dysfunction. The pressure-generating capacity of the diaphragm, the diaphragm thickening fraction, and the parasternal intercostal muscle thickening fraction were all significantly associated with failure of a spontaneous breathing trial in mechanically ventilated patients.
SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT

BASIC SCIENCE

Does Iso-mechanical Power Lead to Iso-lung Damage? An Experimental Study in a Porcine Model

F. Vassalli, I. Pasticci, F. Romitti, E. Duscio, D. J. Abmann,
H. Grünhagen, F. Vasques, M. Bonifazi, M. Busana, M. M. Macri,
L. Giosa, V. Reupke, P. Herrmann, G. Hahn, O. Leopardi,
O. Moerer, M. Quintel, J. J. Marini, L. Gattinoni 1126

The authors studied 42 healthy sedated pigs ventilated in the prone position for 48 h, controlling anesthetic level, hemodynamics, and temperature. Three ventilatory strategies (high tidal volume, high respiratory rate, or high positive end-expiratory pressure [PEEP]) were studied at two levels of mechanical power (15 or 30 J/min, regulated by manipulating the other component variables). Measurements included hemodynamics, lung mechanics, gas exchange, lung histology, and lung weight. High PEEP, as expected, had the greatest adverse hemodynamic impact. For all strategies, similar degrees of histologic lung injury and extravascular lung water accumulation occurred by 48 h, despite different time courses. Paradoxically, a greater degree of alveolar edema occurred at lower mechanical power, perhaps explained by different hemodynamic patterns that favored or reduced extravascular fluid accumulation. These data suggest that over time, the integrated effects resulting from high tidal volume, high respiratory rate, or high PEEP are more important than the direct and immediate consequence of any one of them alone. Ventilator-induced lung injury should be considered holistically in the context of whole-body physiology rather than as an isolated effect on the lung alone.
SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT

Severe Hypoxemia Prevents Spontaneous and Naloxone-induced Breathing Recovery after Fentanyl Overdose in Awake and Sedated Rats

P. Haouzi, D. Guck, M. McCann, M. Sternick,
T. Sonobe, N. Tubbs 1138

The level of hypoxemia reached during fentanyl-induced apnea in unsedated rats affected their ability to "autoresuscitate" and to respond to naloxone. Fentanyl-induced apnea in urethane-anesthetized rats was not associated with spontaneous recovery when PaO_2 decreased below approximately 16 mmHg during apnea and could not be reversed with naloxone.
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Pain Medicine

CLINICAL SCIENCE

Drug Enforcement Agency 2014 Hydrocodone Rescheduling Rule and Opioid Dispensing after Surgery

M. D. Neuman, S. Hennessy, D. S. Small, C. Newcomb,
L. Gaskins, C. M. Brensinger, D. N. Wijesundera,
B. T. Bateman, H. Wunsch.....1151

Data derived from a large insurance database for a group of 10 common ambulatory orthopedic surgeries suggested that hydrocodone dispensing increased after rescheduling for the 30-day period after surgery. Data from the same source showed no difference in hydrocodone prescribing from 90 to 180 days after surgery. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*


Opioid Fills for Lumbar Facet Radiofrequency Ablation Associated with New Persistent Opioid Use

D. L. Southren, S. Moser, H. Abu-Amara, P. Lin, A. A. Schack,
V. Gunaseelan, J. F. Waljee, C. M. Brummett.....1165

More than one in five opioid-naïve patients filled a prescription for opioid after minimally painful procedures. Patients who filled opioid prescriptions had more than twice the odds of persistent opioid use. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

BASIC SCIENCE

A Central Amygdala–Ventrolateral Periaqueductal Gray Matter Pathway for Pain in a Mouse Model of Depression-like Behavior

 W. Yin, L. Mei, T. Sun, Y. Wang, J. Li, C. Chen, Z. Farzinpour,
Y. Mao, W. Tao, J. Li, W. Xie, Z. Zhang.....1175

Chemogenetic experiments in a mouse model of depression reveal the involvement of a neural circuitry between the central amygdala and the periaqueductal gray in nociception. In this mouse model, pathologically increased activity of inhibitory γ -aminobutyric acid–mediated neurons in the central amygdala will result in the inhibition of inhibitory γ -aminobutyric acid–mediated neurons in the periaqueductal gray. This, in turn, will lead to the activation of glutamatergic cells involved in periaqueductal gray–mediated nociception. These findings provide a framework for how the central amygdala–periaqueductal gray circuitry may play a role in coping with nociception in depressive states. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

Countering Opioid-induced Respiratory Depression in Male Rats with Nicotinic Acetylcholine Receptor Partial Agonists Varenicline and ABT 594

J. Ren, X. Ding, J. J. Greer.....1197

Pre- or coadministration of varenicline or ABT 594 with opioids markedly reduced the degree of respiratory depression they caused in rats. Varenicline and ABT 594 reversed moderate to severe respiratory depression produced by fentanyl without interfering with opioid-induced suppression of pain. Administration of ABT 594 and varenicline coadministered with a low dose of naloxone reversed respiratory depression and prevented death caused by a bolus lethal dose of fentanyl or the combination of fentanyl and diazepam.

Synaptic Dynamics of the Feed-forward Inhibitory Circuitry Gating Mechanical Allodynia in Mice

Q. Wang, X. Zhang, X. He, S. Du, Z. Jiang, P. Liu, L. Qi,
C. Liang, N. Gu, Y. Lu.....1212

Using the clustered regularly interspaced short palindromic repeats/clustered regularly interspaced short palindromic repeats-associated nuclease 9 technique, a novel mouse strain was created allowing study of a key set of spinal interneurons. The data suggest hyperexcitability of spinal protein kinase C γ expressing interneurons facilitates allodynia after nerve injury. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

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- ◇ **Sepsis-induced Coagulopathy and Disseminated Intravascular Coagulation**
T. Iba, J. H. Levy1238

Coagulopathy, a common complication with sepsis, contributes to vascular injury and organ dysfunction. Early detection using diagnostic criteria for sepsis-induced coagulopathy is important to consider for potential clinical management.

- ◇ **Ventilatory Mechanics in the Patient with Obesity**
L. Grassi, R. Kacmarek, L. Berra1246

A brief review of how central adiposity affects intrathoracic pressures and its effects on spontaneous breathing and artificial ventilation.

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- ◇ **Extracorporeal Membrane Oxygenation for Respiratory Failure**
M. Quintel, R. H. Bartlett, M. P. W. Grocott, A. Combes, M. V. Ranieri, M. Baiocchi, S. Nava, D. Brodie, L. Camporota, F. Vasques, M. Busana, J. J. Marini, L. Gattinoni1257

This review presents an overview of selected aspects of extracorporeal membrane oxygenation use in respiratory failure, including historical and technical development, relevant principles of gas exchange, clinical applications and indications, ethical considerations, and potential improvements for its optimal implementation.

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